FDA Briefing Document

Arthritis Advisory Committee Meeting

April 23, 2018

NDA 207924
Baricitinib
Janus Kinase (JAK) inhibitor for RA

Eli Lilly and Company (Lilly)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the NDA for baricitinib with the Applicant's proposed indication to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Executive Summary

Thank you for your participation in the upcoming Arthritis Advisory Committee (AAC) meeting to be held on April 23, 2018. As members of FDA Advisory Committees (AC), we consider your expert scientific advice and recommendations to the FDA very important to our regulatory decision making processes. The objective of the upcoming meeting is to discuss the new drug application (NDA) 207924 submitted by Eli Lilly and Company (Lilly) for the new molecular entity (NME) baricitinib (proposed trade name Olumiant), an oral small molecule inhibitor of the Janus associated kinases (JAK) being 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). Lilly proposes two doses of baricitinib (2 mg or 4 mg) once daily for oral administration.

The original NDA for baricitinib was submitted on January 14, 2016. As described below and in the attached reviews, safety concerns were identified, including the risk of 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.

For transparency, this briefing document includes the complete reviews and interpretation of the data from the first review cycle by the primary review team (Cross-Discipline Team Leader review), the Division Director, and signatory Office Director. We note that some of the recommendations and overall conclusions differ between these reviews reflecting the respective reviewers' interpretation of the data. These differences in conclusions and benefit/risk assessments highlight the challenge of interpretation of data from this clinical program.

To address the CR letter deficiencies, the Applicant re-submitted the application on December 4, 2017. A Summary of Re-submission is included in the briefing document. The following is a brief introduction of the main issues for discussion, which are described in more detail in the attached reviews.

Dose Selection

Lilly conducted a large clinical program to evaluate the efficacy and safety of baricitinib. Phase 2 trials evaluated doses of baricitinib ranging from 1 mg to 10 mg. While there was some evidence that all doses of baricitinib were efficacious compared to placebo with respect to ACR20 response in patients with RA, Lilly chose to carry forward two doses of baricitinib (2 mg and 4 mg) into the phase 3 clinical program. As described in the attached reviews, there were four pivotal trials in the phase 3 program (JADV, JADW, JADX, JADZ). Since Lilly targeted 4 mg as the to-be-marketed dose, baricitinib 4 mg was included in all four pivotal trials, but the 2 mg dose was included in only two of the phase 3 clinical trials (JADW, JADX). This differential exposure of the 4 mg and 2 mg dose in the phase 3 program was an important issue that impacted the interpretation of the benefit/risk assessment of the baricitinib 2 mg dose as described below.

Efficacy
There was a general agreement by the FDA review team that the data submitted demonstrated the efficacy for baricitinib in RA at doses of 2 mg and 4 mg once daily for signs and symptoms assessed by ACR response, as well as for physical function assessed by HAQ-DI response. In trials that included both doses of baricitinib, the data were not consistent in showing a benefit of 4 mg over the 2 mg dose. The data on structural progression assessed by radiographic response showed consistent efficacy for the baricitinib 4 mg dose. Only one trial evaluated the impact of baricitinib 2 mg on radiographic progression. The data from this single trial were not as robust for baricitinib 2 mg and corroborating evidence from another trial was not available. Lilly has proposed 2 doses of baricitinib for marketing. Whether there is additional benefit of the 4 mg dose compared to the 2 mg dose of baricitinib is a topic for discussion. This is important because of the dose-related safety issues noted in the clinical program.

Safety
One of the challenges of the baricitinib clinical program is assessment of safety. As with other RA programs, there was a limited placebo control period and patients could escape and/or cross over to baricitinib 4 mg. When most of the safety data are from baricitinib treatment groups and there are limited control group data, interpretation of imbalance in adverse reactions between treatment groups is problematic. In addition, the fact that the baricitinib 2 mg dose was only included in 2 clinical trials complicated assessment of the safety of baricitinib 2 mg. To address some of these limitations, several strategies to combine the safety data were used (e.g. integrated phase 3 trials, integrated phase 2 and 3 trials, and integrated data from trials that included both baricitinib 2 and 4 mg doses). This is important to note when reviewing the safety analyses as there may be slightly different numbers of events, exposures, rates, and statistics, depending on the strategy for integrating safety data. The FDA reviews provide annotation and further contextual information where appropriate. These strategies, however, cannot overcome the limited placebo control data and limited safety database with the baricitinib 2 mg dose.

The FDA reviews identified a safety profile of baricitinib 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). Many of these adverse reactions appeared to be dose-dependent. 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. FDA considered a plausible mechanism related to JAK inhibition and platelet elevation as discussed in further detail in the Summary of Re-submission.

Benefit/Risk
Because the majority of the safety data are with the higher dose of baricitinib, the identified safety issues raised concern regarding the 4 mg dose of baricitinib. The limited safety database with the lower dose complicated the benefit/risk assessment of the 2 mg dose of bariticitinib. Whether the benefit/risk assessment is favorable for the 4 mg or the 2 mg dose of baricitinib for the treatment of RA is the main issue for discussion at the upcoming AC meeting.

Resubmission
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) which was ongoing at the time of the original submission. Of note, this study did not include the baricitinib 2 mg dose group and thus, did not contribute to the comparison of safety or efficacy between the two baricitinib doses. 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) with data cut-off April, 01, 2017. These analyses were consistent with the findings from the first review cycle. The Applicant 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. We have addressed this information in the Summary of Re-submission; however, we note limitations of these data sources. Therefore, we intend to focus our benefit/risk assessment for baricitinib on the data from the clinical development program.

In the re-submission, Lilly proposed a different dosing strategy for baricitinib. The change in dosing recommendations is shown in the table below. The proposed dosing strategy in the re-submission is more complicated and deviates from labeling for other non-biologic DMARD RA products. This is also problematic, given that the clinical development program was not designed to support the proposed dosing strategy. While Lilly submitted a rationale for the dosing recommendations, it is primarily based on post-hoc analyses which do not provide convincing evidence that the relative benefit of the two doses differs according to degree of prior DMARD use, or that the 4 mg dose provides meaningful added benefit over 2 mg in the proposed subpopulation of patients with an inadequate response or intolerance to two or more DMARDs. This is discussed in more detail in the Summary of Re-submission. Therefore, to avoid being distracted with nuances of the proposed dosage and administration of baricitinib, we ask the AC panel to consider the benefit/risk assessment of each proposed dose of baricitinib for the treatment of adult patients with RA who have had an inadequate response or intolerance to methotrexate (MTX).

Lilly's Proposed Dosage and Administration for Baricitinib		
	Baricitinib 2 mg	Baricitinib 4 mg
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.

Draft Points to Consider

On April 23, 2018, the Committee will discuss the new drug application (NDA) 207924, for baricitinib (proposed trade name Olumiant), submitted by Eli Lilly, for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. The Agency is seeking input from the Committee on issues related to efficacy, safety, including the risk of thromboembolic adverse events, dose selection, and overall benefit-risk considerations.

The following are draft points to consider for discussion at the upcoming AC.

- Discuss the efficacy of 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.

- Discuss if the data provide substantial evidence of the efficacy of 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).
    a) Baricitinib 4 mg
        - If no, what data are needed?
    b) Baricitinib 2 mg
        - If no, what data are needed?

- 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). Please address the following issues in your discussion:
    a) Adequacy of safety database for the 2 mg dose of baricitinib
    b) Safety issues of interest and whether data suggest a dose response
        - Thromboembolic events
        - Malignancy
        - Serious infections, opportunistic infections, H. zoster, tuberculosis
        - Abnormal laboratory parameters, specifically platelet count elevations
    c) Overall safety profile of the 2 mg dose and the 4 mg dose, and whether the data are more favorable for one dose versus the other

- Discuss if the safety profile of baricitinib is adequate to support approval of 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).
    a) Baricitinib 4 mg
        - If no, what data are needed?
    b) Baricitinib 2 mg
        - If no, what data are needed?

- Discuss if the benefit-risk is adequate to support approval of baricitinib 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).
    a) Baricitinib 4 mg
        - If no, what data are needed?
    b) Baricitinib 2 mg
        - If no, what data are needed?

Cross-Discipline Team Leader Review

Date	January 5, 2017
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 207924
Applicant	Eli Lilly and Company (Lilly)
Date of Submission	January 15, 2016
PDUFA Goal Date	January 15, 2017
Proprietary Name / Non-Proprietary Name	Olumiant / Baricitinib
Dosage form(s) / Strength(s)	4 mg and 2 mg tablets
Applicant Proposed Indication(s)/Population(s)	Adult patients with moderately to severely active rheumatoid arthritis
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.*

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Rheumatoid arthritis (RA) is a serious disease that can cause pain, stiffness, and functional impairment. The majority of patients with RA have a chronic, progressive disease that is associated with increased morbidity and mortality. There are multiple approved drugs to treat RA, but another oral therapy would add an additional therapeutic option for RA.

Baricitinib is an oral small molecule inhibitor of the Janus associated kinases (JAK). The efficacy of baricitinib (2 mg and 4 mg) was established in 4 adequate and well-controlled phase 3 studies in patients with RA. The trials provided evidence of the efficacy of baricitinib for reducing signs and symptoms

of RA based on the proportion of patients experiencing and American College of Rheumatology (ACR) response and improvement in physical function, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI). For some endpoints in some studies, there was a suggestion of higher responses for the baricitinib 4 mg dose compared to the 2 mg dose. The effect of baricitinib on structural damage progression was assessed by x-rays in three studies. The data provide evidence of efficacy of baricitinib 4 mg on structural damage progression, however there is some uncertainty regarding the 2 mg dose.

The safety profile of baricitinib is well-characterized within the clinical trials. The major toxicities of concern with baricitinib are related to immunosuppression and are similar to tofacitinib, which is also a JAK inhibitor. Baricitinib was associated with infections, including opportunistic infections and tuberculosis. Additional risks included laboratory abnormalities, such as decreases in lymphocytes and increases in lipid parameters, malignancy, gastrointestinal perforations, and thrombosis. Many of the identified safety signals, such as laboratory abnormalities, opportunistic infections, and venous thrombosis, occurred at a slightly higher incidence 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 and we therefore have limited ability to rule out increases in risk based on the currently available data. A postmarketing requirement is recommended to evaluate these adverse events of special interest.

Based on the data in this submission and the seriousness of RA, the benefit/risk profile of baricitinib is adequately favorable to support the 4 mg dose, with the 2 mg dose as an option for some patients. Compared to the 2 mg dose, the 4 mg dose demonstrated numerical trends suggesting additional benefit on some clinical endpoints. In addition, there is evidence of inhibition of radiographic progression for the 4 mg dose, but not the 2 mg dose. While there were some dose-related safety signals, the safety profile of both doses is acceptable given the severity of the disease and the demonstrated benefits.

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 pathways	There are multiple current treatment options for patients with RA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	can be used. • Tofacitinib is approved for the treatment of RA and is a Janus kinase inhibitor, similar to baricitinib.	
Benefit	• Baricitinib is proposed for treatment of adult patients with moderately to severely active RA. The efficacy of baricitinib was established in four randomized, double-blind trials (JADX, JADW, JADV, and JADZ). • The primary endpoint in the trials was the proportion of patients who achieved an ACR20 response at Week 12 (JADX, JADW, and JADV) or Week 24 (JADZ). • The ACR20 response is calculated as a >20% improvement in tender joint count and swollen joint count and 3 of the 5 remaining ACR core set measures: patient global assessment of arthritis, physician global assessment of arthritis, patient assessment of pain, patient assessment of physical function, and acute phase reactant. 50% and 70% improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement. • In all studies, patients treated with either 2 mg or 4 mg of baricitinib daily had higher ACR20, ACR50, and ACR70 response rates versus placebo-treated patients at Week 12 and Week 24. • All studies demonstrated that patients receiving baricitinib 2 mg or 4 mg daily had greater improvement from baseline in physical function, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) compared to placebo. • Results from studies JADV and JADZ demonstrated that, compared to placebo, baricitinib 4 mg inhibited radiographic progression. One study, JADX, evaluated the impact of baricitinib 2 mg on radiographic progression and did not establish that baricitinib 2 mg inhibits radiographic progression. • While not consistent across all studies and endpoints, there were numerically higher results for some endpoints for the 4 mg dose compared to the 2 mg dose.	The baricitinib clinical trials were adequate and well-controlled. Baricitinib 2 mg and 4 mg were both effective in reducing signs and symptoms in patients with RA. There is evidence that 4 mg inhibits radiographic progression in RA, but there is uncertainty regarding the 2 mg dose. Without effective treatment of RA, joint damage progresses chronically and irreversibly and results in impaired physical function and disability. Thus, effective therapies are needed for RA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• A total of 3,464 patients with RA were exposed to baricitinib in RA studies. The drug exposure data are considered adequate. • Major safety concerns: • Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving baricitinib. • Laboratory abnormalities: Baricitinib treatment is associated with neutropenia, lymphopenia, decreases in hemoglobin, and increases in liver enzymes and lipids. • Malignancy: Malignancies were observed in clinical studies with baricitinib. • Gastrointestinal perforations: Events of gastrointestinal perforation have been reported in clinical trials with baricitinib. • Thrombosis: Arterial and venous thromboses were observed in association with baricitinib.	The main safety concerns with baricitinib are immunosuppression and laboratory abnormalities, including lipid parameter elevations. Overall, the risks observed are deemed acceptable with proper labeling and warnings.
Risk Management	• The safety concerns with baricitinib are well-characterized. Healthcare providers are familiar with treatments for RA associated with immunosuppression and lipid elevations.	These risks can be communicated to healthcare professionals through labeling (including a Medication Guide). The labeling will include a boxed warning for serious infections. A boxed warning for malignancy is recommended. In addition, the labeling will contain Warnings and Precautions for the major safety signals. A postmarketing requirement is recommended for additional safety data related to the major risks.

2. Background

Eli Lilly and Company (Lilly) submitted new drug application (NDA) 207924 on January 15, 2016, for the new molecular entity (NME) baricitinib, an oral small molecule inhibitor of the Janus associated kinases (JAK) being proposed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The product is being proposed as tablets for oral administration in 2 and 4 mg dosage strengths. Lilly proposes a recommended dose of 4 mg once daily, with an added notation that a dose of 2 mg once daily may be acceptable.

If approved, baricitinib would be the second JAK inhibitor for rheumatoid arthritis (RA). Tofacitinib (Xeljanz®, NDA 20321), another JAK inhibitor, was approved for RA on November 6, 2012. Subsequently, tofacitinib extended release (XR) tablets (Xeljanz XR, NDA 208246) were approved for RA on February 23, 2016. Both Xeljanz and Xeljanz XR are approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Thus, the proposed indication for baricitinib is broader than that currently approved for Xeljanz. Another JAK inhibitor, ruxolitinib (Jakafi™, NDA 202192), has been approved since November 2011 for myelofibrosis indications.

RA is a chronic, symmetric inflammatory polyarthritis that primarily involves synovial joints. In RA, synovial tissues become inflamed and proliferate, forming pannus that invades bone, cartilage, and ligament and leads to joint damage and deformities. Destruction of synovial joints can lead to severe disability and premature mortality.[1,2]

RA affects approximately 1% of the adult population in North America and Northern Europe.[3] The disease is three times more frequent in women than men. Prevalence rises with age and is highest in woman older than 65 years.

While there is heterogeneity in the natural history of RA, it is generally a chronic, progressive disease. Patients can develop joint destruction, severe physical disability and multiple co-morbidities. In contrast to clinical symptoms, structural damage is irreversible and cumulative.[4]

All patients diagnosed with RA are generally treated with disease-modifying antirheumatic drugs (DMARDs). A variety of non-biologic DMARDs are approved for RA, including corticosteroids, various nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, auranofin, methotrexate (MTX), azathioprine, penicillamine, cyclosporine, and leflunomide.

[1] Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.
[2] Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706-14.
[3] Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11(3):229.
[4] Scott DL. Radiographic progression in established rheumatoid arthritis. *J Rheumatol Suppl* 2004;69:55-65.

Non-biologic DMARDs, such as MTX, are the first line of therapy for RA.[5] Treatment with a tumor necrosis factor-alpha (TNF-α) antagonist is generally the next line of treatment for patients with ongoing disease activity. Currently approved TNF-α antagonists include etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab pegol (CIMZIA), golimumab IV (SIMPONI ARIA), infliximab-dyyb (INFLECTRA), etanercept-szzs (ERELZI) and adalimumab-atto (AMJEVITA). Between 30% and 40% of patients fail to respond or become intolerant to anti-TNF-α therapy.[6] For patients with ongoing disease activity, the therapeutic strategy usually involves trying another TNF-α antagonist or switching to a medication with a different mechanism of action. Approved alternative therapies include an orally bioavailable Janus kinase (JAK) inhibitor (tofacitinib/XELJANZ OR XELJANZ XR), and biological DMARDs targeting the B-cell antigen CD-20 (rituximab/RITUXAN), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; abatacept/ORENCIA), and the pro-inflammatory cytokines IL-1 (anakinra/KINERET) and IL-6 (tocilizumab/ACTEMRA).

The long-term goal of treatment is prevention of irreversible joint destruction and functional impairment given the significant impact on patients and public health. The short-term goal of treatment is improvement in signs, symptoms, and functional status.

Key Regulatory Interactions
Key regulatory interactions are listed below by date. The development program for baricitinib occurred under IND 102204. The IND was opened in May 2008.

June 26, 2012 – End of Phase 2 Meeting

Concerns were raised regarding linear extrapolation of radiographic data and the applicant was told not to impute radiographic progression in the statistical analysis plan. The sponsor was encouraged to study two doses in phase 3 and to explore twice daily dosing given the pharmacokinetic profile of the product. It was noted that controlled data would be needed to evaluate a step-down regimen and the sponsor's proposal to evaluate step-down dosing based on patients achieving Clinical Disease Activity Index (CDAI) remission was not optimal. FDA stated that duration of morning stiffness, severity of morning joint stiffness, worst tiredness, and worst pain were endpoints that represent overlapping and ancillary benefits with respect to the core outcome measures currently used to support RA labeling claims. The anticipated safety database was felt to be reasonable as long as there were no other safety signals that would require further characterization.

September 23, 2013 – Type C Written Responses Only

[5] Katchamart W, et al. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev 2010;4:CD008495.
[6] Smolen JS, et al. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015;11(5):276-89.

The sponsor's rationale for studying once daily, rather than twice daily dosing was felt to be generally reasonable, but it was noted that if there was a serious safety concern at both 2 mg and 4 mg, than there would be questions of whether BID dosing would have allowed for a lower total daily dose with similar efficacy and a better safety profile.

October 30, 2013 – End of Phase 2 CMC Only Meeting

There was discussion and agreement on several CMC topics, including the starting material and control strategy used in the synthesis of the drug substance, stability protocol design, and batch identification.

October 10, 2014 – Type C Written Responses Only

Lilly's proposal to assess duration of morning stiffness was noted to be acceptable given prior precedent in labeling. It was noted that the prior precedent is for duration of morning stiffness, rather than severity, of morning stiffness. Formal validation of this PRO and assessment of a responder definition were not felt to be necessary.

September 2, 2015 – pre-NDA meeting

At the pre-NDA meeting, there was general agreement between the Agency and Lilly on the content and format of the NDA submission. The statistical team, noted the importance of evaluating the potential effect of missing data on the reliability of efficacy results. Lilly was informed that tipping point analyses should be performed and the appropriate procedure for these analyses was discussed.

3. Product Quality

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	II/Division of New Drug API
Drug Product	Art Shaw	IV/DNDPII
Process	Ted Chang	IV/DPAII
Microbiology	Ted Chang	IV/DPAII
Facility	Rebecca Dombrowski	II/DIA
Biopharmaceutics	Kalpana Paudel	II/DB
Regulatory Business Process Manager	Florence Aisida	I/Division I
Appl. Technical Lead	Craig M. Bertha	IV/DNDPII
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue, Jr.	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Analysis	N/A	

- **General product quality considerations**

The drug substance manufacturing process uses (b) (4)

The drug product is available as oblong (2 mg) and round (4 mg), debossed, film-coated, immediate-release tablets. The tablets are differentiated by shape and color and will be commercially supplied in blister and bottle packaging in various global markets. The 2 mg tablets are light pink with "Lilly" on one side and "2" on the other side. The 4 mg tablets are medium pink with "Lilly on one side and "4" on the other side. The immediate release tablet drug product is manufactured using (b) (4) and film coating. The dosage forms are prepared with common compendial grade excipients.

The stability information submitted to the NDA supports a 24 months expiration dating period for the drug product under the labeled storage conditions (store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

The biopharmaceutics team has found the applicant's dissolution method to be discriminating, and the specification acceptance criterion for dissolution to be acceptable, from a quality control perspective.

- **Facilities review/inspection**

The synthesis of the new molecular entity, baricitinib, is convergent and is performed by Lilly in Ireland. The drug product manufacturing site is in Carolina, Puerto Rico and the final packaging site is in Indianapolis, IN. Based on file review and pre-approval inspections, there are no outstanding facilities issues and all sites are found to be acceptable.

- **Other notable issues (resolved or outstanding)**

From a Chemistry, Manufacturing, and Controls (CMC) perspective, the application is recommended for approval. Associated manufacturing and testing sites supporting this NDA are deemed acceptable by the Office of Process and Facilities (OPF) as of October 24, 2016.

4. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: Matthew Whittaker, PhD; Supervisor/Team Leader: Timothy Robison, PhD

- **General nonclinical pharmacology/toxicology considerations**

Baricitinib inhibits JAK enzyme function in in vitro assays with IC_{50} values generally in the low nanomolar range. Increased selectivity for JAK1 and JAK2 relative to JAK3 and TYK2 was demonstrated in cell-free isolated enzyme assays. These effects were not recapitulated in cell-based assays conducted in human leukocyte preparations. The most appropriate Established Pharmacologic Classification (EPC) for baricitinib was determined to be Janus kinase (JAK) inhibitor, identical to the EPC used for the approved pan-JAK inhibitor tofacitinib.

Chronic toxicology studies with baricitinib were conducted in rats (26 weeks) and dogs (39 weeks). Immunosuppressant effects were the major treatment-related toxicities observed in rats and dogs. Lymphoid organs including bone marrow, spleen, and lymph nodes were target organs of toxicity in both species. Dose limiting toxicities in the GI tract (inflammation, infiltrates) and liver (infiltrates/inflammation, bile duct hyperplasia) were observed in male and female dogs at ≥ 3 mg/kg/day. The dog is the more sensitive nonclinical species, with an $AUC_{0\text{-}24h}$ of 1.21 μM*hr at the limit dose. This exposure supports the clinical baricitinib exposure at the maximum recommended human dose (MRHD) of 4 mg/day.

- **Carcinogenicity**

Baricitinib was negative in a standard battery of genotoxicity assays. There was no evidence of tumorigenic potential in a 2 year carcinogenicity study conducted in rats or in a 26 week carcinogenicity study in Tg.rasH2 mice.

- **Reproductive toxicology**

Fertility (based upon achievement of pregnancy) was reduced in male and female rats that received baricitinib at oral doses of 50 and 100 mg/kg/day, respectively. Fertility was unaffected in male and female rats at oral doses of 15 and 25 mg/kg/day. However, maintenance of pregnancy was adversely affected at these doses as evidenced by increased post-implantation losses and decreased number of mean viable embryos per litter.

In embryofetal development studies, baricitinib was teratogenic (skeletal malformations including bent limb bones and rib anomalies) in both rats and rabbits. In a pre- and post-natal development study, treatment of pregnant rats with baricitinib at 25 mg/kg/day from gestation day 6 – lactation day 20 resulted in multiple adverse findings in F1 offspring in the absence of maternal toxicity. These included decreased survival from birth to postnatal day 4 (due to increased stillbirths and early neonatal deaths), decreased mean birth weight, decreased body weight gain during the pre-weaning phase, increased incidence of malrotated forelimbs, and immune suppression (decreased cytotoxic T cells on PND 35 with evidence of recovery by PND 65).

- **Other notable issues (resolved or outstanding)**

From the nonclinical perspective, the application is recommended for approval. There are no outstanding nonclinical issues.

5. Clinical Pharmacology

Clinical pharmacology reviewer team: Yunzhao Ren, MD, PhD, Yuching Yang, PhD, Ping Zhao, PhD, Jingyu Yu, PhD, and Marathe Anshu, PhD; Division Director: Chandrahas Sahajwalla, PhD

- **General clinical pharmacology considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

Baricitinib exposure increases approximately linearly proportional to dose from 1 mg to 20 mg following single oral dose administration in healthy subjects. The median baricitinib t_{max} following 8 mg oral administration in healthy subjects is 1 hour. The mean absolute bioavailability of baricitinib following 4 mg oral administration in healthy subjects is 79%. A high-fat meal slightly increases baricitinib AUC and C_{max} by 11% and 18%, respectively.

The volume of distribution of baricitinib is 76 L following IV administration. Baricitinib is approximately 50% bound to plasma proteins and 45% bound to serum proteins. Baricitinib is a substrate of the Pgp, BCRP, OAT3 and MATE2-K transporters, which play roles in drug absorption, distribution, and elimination.

The typical clearance of baricitinib is 8.9 L/h in patients with RA as estimated by population PK analysis. The elimination half-life in patients with RA is approximately 12 hours. Steady state is reached following 2 daily doses with minimal accumulation.

Approximately 6% of the orally administered baricitinib dose is identified as metabolites (three from urine and one from feces). CYP3A4 is identified as one of the major metabolizing enzymes. None of baricitinib metabolites were quantifiable in plasma.

Renal elimination is the principal clearance mechanism for baricitinib. In a mass balance study, approximately 75% of the administered dose was excreted in the urine, while about 20% of the dose was eliminated in the feces. Baricitinib was excreted predominately as unchanged drug in urine (69% of the dose) and feces (15% of the dose).

In a dedicated renal impairment study (Study JADL), the geometric mean $AUC_{0\text{-}inf}$ of baricitinib was estimated to be 1.4-, 2.2-fold, and 4.1-fold higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function following single dose administration of 10 mg baricitinib. A dose reduction to 2 mg is proposed for patients with moderate renal impairment. In addition, baricitinib is not recommended for use in patients with severe renal impairment.

- **Intrinsic factors potentially affecting elimination**

In a dedicated renal impairment study (Study JADL), the geometric mean $AUC_{0\text{-}inf}$ of baricitinib was estimated to be 1.4-, 2.2-fold, and 4.1-fold higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function following single dose administration of 10 mg baricitinib. A dose reduction to 2 mg is proposed

for patients with moderate renal impairment. In addition, baricitinib is not recommended for use in patients with severe renal impairment.

In a dedicated hepatic impairment study, the geometric mean $AUC_{0\text{-}inf}$ and C_{max} in subjects with moderate hepatic impairment was 19% and 8% higher than subjects with normal hepatic function. No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Since baricitinib has not been studied in patients with severe hepatic impairment, it use is not recommended in this setting.

- **Extrinsic factors potentially affecting elimination**

Dose, formulation (commercial tablet vs. non-commercial tablet/capsule), patients' previous DMARDS treatment history, concomitant medications (corticoids, MTX, diclofenac, ibuprofen, NSAIDS, bDMARDs, HCQ, LEF, and SSZ) were evaluated in the model and none of them was identified as significant covariate.

- **Drug-drug interactions**

In a dedicated drug-interaction study, concomitant probenecid (a strong OAT3 inhibitor) increased $AUC_{0\text{-}inf}$ of baricitinib 2-fold. Physiologically-based pharmacokinetic (PBPK) modeling predicted that the OAT3 moderate inhibitors ibuprofen and diclofenac are unlikely to increase the AUC of baricitinib by more than 1.25-fold. Therefore, a dose reduction to 2 mg once daily is recommended for patients taking strong OAT3 inhibitor, such as probenecid. There is no clinically relevant effect of other drugs on baricitinib exposure, nor is there a clinically relevant effect of baricitinib on other drugs' exposure.

- **Demographic interactions/special populations**

In population PK analyses, modification of diet in renal disease (MDRD)-eGFR, body weight, and baseline erythrocyte sediment rate (bESR) were identified as significant covariates for baricitinib CLr/F in the final model. Patients with body weight of 52 kg (median body weight of 1st quartile of body weight) and 96 Kg (median body weight of 4th quartile of body weight) were estimated to have 12% decrease and 17% increase of CL/F compared to patients weighing 70 kg (median body weight of all patients), respectively. Patients with bESR of 19 mm/hr (median value of 1st quartile of bESR) and 75 mm/hr (median value of 4th quartile of bESR) were estimated to have 3.4% decrease and 5.4% increase of CL/F compared to patients with bESR of 40 mm/hr (median bESR of all patients), respectively. Age, sex, liver function tests (ALT, AST, bilirubin), race, and duration of RA were evaluated in the model and not identified as significant covariates.

- **Thorough QT study**

Baricitinib is a low-potency blocker of the hERG channel (IC50=60 μg/mL). No significant QTc prolongation effect of 40 mg single dose baricitinib was detected in a dedicated TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between baricitinib and

placebo was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

- **Other notable issues (resolved or outstanding)**

The Office of Clinical Pharmacology has determined the information in NDA 207924 is approvable from a clinical pharmacology perspective. No outstanding issues have been identified.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Clinical primary reviewer: Raj Nair, MD
Statistical Reviewer: Robert Abugov, PhD, Statistical Team Leader: Gregory Levin, PhD

Overview of the clinical program

Four placebo-controlled phase 3 trials (JADV, JADW, JADX, and JADZ) have been submitted as the primary evidence of efficacy and safety of baricitinib for RA, as summarized below (Table 2). In addition, three phase 2 trials (JADC, JADA, and JADN) were performed (Table 1). Patients completing JADZ, JADV, JADX, JADW, JADA, and JAGS could enroll in the long term safety study (JADY, Table 3) which is discussed in Section 8. Of note, JAGS is ongoing, and safety data have not been included in this submission.

Table 1: Summary of Phase 2 Studies in RA Submitted for the NDA

Study (# on proposed label) *Date* Duration	Patient Population	Overview	Treatment arms	Number per arm	Primary endpoint	Regions and Countries
Phase 2						
JADC *May 2009-July 2010* 24 weeks	MTX/cDMARD-IR (previous biologics allowed)	MC, R, DB, PC, dose-ranging study. 12-week controlled study followed by 12-week open label period	B4 B7 B10 PBO (to B7 or B10 at 12 wk)	32 32 32 31 Total: 127	ACR20 at 12 weeks	USA (74%); Czech Republic (26%)
JADA *Nov 2010-March 2014* 128 weeks	MTX/cDMARD-IR (no previous biologics allowed)	MC, R, DB, PG study in 4 parts: **Part A (Wk 0 to 12):** DB, PC, R evaluation of baricitinib or PBO QD for 12 weeks **Part B (Wk 12 to 24):** DB, R evaluation of baricitinib BID or QD for 12 additional weeks **Part C (Wk 24 to 76):** 52 wk OLE **Part D (Wk 76 to 128):** 52 wk OLE	**Part A:** B1 B2 B4 B8 PBO **Part B:** B1→B2 BID or B4 QD B2 B4 B8 **Part C:** B2 QD or BID→B4 B4 (NR increase to B8 at wk 28 or 32) B8 **Part D:** B4	**Part A:** 49 52 52 50 98 Total: 301	ACR20 at 12 weeks	Europe (39%); USA (32%); Mexico (16%); India (14%)
JADN *Nov 2011-Dec 2011* 64 weeks	MTX/cDMARD-IR (previous biologics allowed)	R, PC, dose-ranging study of baricitinib in Japanese patients **Part A:** 12-week DB **Part B:** 52-week SB	**Part A:** B1 B2 B4 B8 PBO **Part B:** B4	**Part A:** 24 24 24 24 49 Total: 145 **Part B:** 142	ACR20 at 12 weeks	Japan (100%)

Dose for renally (<60mL/min/1.73m^2) impaired patients randomized or rescued to baricitinib is B2 for all studies in this submission.
Abbreviations: MTX=methotrexate; cDMARD=conventional disease modifying antirheumatic drugs; MC=multicenter; R=randomized; PC=placebo controlled; ACR=American College of Rheumatology; PG=parallel group; Wk=week; QD=daily; BID=twice daily; B=baricitinib; PBO=placebo; NR=non-response

Table 2: Summary of Phase 3 Studies in RA Submitted for the NDA

Study (# on proposed label) *Date* Duration	Overview Patient Population	Treatment arms	Number per arm	Primary endpoint	Regions and Countries
Phase 3					
JADV (RA-BEAM; II) *Oct 2012-Sept 2015* 52 weeks	R, DB, PC and AC MTX-IR (no previous biologics allowed)	B4+MTX ADA+MTX PBO+MTX (to B4 at 24 wks) Rescue: Every 4 weeks starting at Week 16. At Week 16, rescue to B4 was given for lack of at least 20% improvement in both tender and swollen joint counts at Weeks 14 and 16. After Week 16, rescue therapy offered to patients based on investigator discretion.	488 330 487 Total: 1307	ACR20 at 12 weeks	Central & S. America (30%); Japan (19%); E. Europe (18%); N. America (8%); W. Europe (6%); Asia ex Japan (10%); ROW (10%)
JADX (RA-BUILD; III) *Jan 2013-Dec 2014* 24 weeks	R, DB, PC cDMARD-IR (no previous biologics allowed)	B2+cDMARD B4+cDMARD PBO+cDMARD Rescue: At Week 16 and Week 20. At Week 16, rescue to B4 was given for lack of at least 20% improvement in both tender and swollen joint counts at Weeks 14 and 16. At Week 20, rescue therapy with B4 offered to patients based on investigator discretion.	229 227 228 Total: 684	ACR20 at 12 weeks	N. America (30%); Asia (18%); E. Europe (16%); S. and Central America & Mexico (12%); W. Europe (11%); ROW (14%)
JADW (RA-BEACON; IV) *Jan 2013-Sept 2014* 24 weeks	R, DB, PC TNF-IR	B2+cDMARD B4+cDMARD PBO+cDMARD Rescue: At Week 16 and Week 20. At Week 16, rescue to B4 was given for lack of at least 20% improvement in both tender and swollen joint counts at Weeks 14 and 16. At Week 20, rescue therapy with B4 offered to patients based on investigator discretion.	174 177 178 Total: 527	ACR20 at 12 weeks	N. America (44%); Europe (30%); S. & Central America & Mexico (10%); Asia (6%) ROW (10%)
JADZ (RA-BEGIN; I) *Jan 2013-Aug 2015* 52 weeks	R, DB, AC study; MTX was titrated up to 20 mg weekly Treatment naïve/early RA	MTX B4 B4+MTX Rescue: every 8 weeks starting at Week 24, all patients could initiate B4+MTX if lack of improvement of at least 20% in both TJC and SJC at Week 24 compared to baseline.	213 160 215 Total: 588	ACR20 at 24 weeks	N. America (20%); Europe (15%); S. and Central America & Mexico (29%); Japan (17%); ROW (19%)

Baricitinib dose for renally (<60mL/min/1.73m^2) impaired patients randomized or rescued to baricitinib is B2 for all studies in this submission.
Abbreviations: RA=rheumatoid arthritis; MTX=methotrexate; cDMARD=conventional disease modifying antirheumatic drugs; MC=multicenter; R=randomized; PC=placebo controlled; AC=active controlled; IR=inadequate response; TNF=tumor necrosis factor; ACR=American College of Rheumatology; PG=parallel group; Wk=week; QD=daily; BID=twice daily; B=baricitinib; PBO=placebo; NR=non-response; ROW=rest of world

Table 3: Summary of Long-term Study (JADY) in RA Submitted for the NDA

Study (# on proposed label) *Date* Duration	Overview	Treatment arms	Total N
JADY (RA-BEYOND) *June 2013-current* 48 months	LTE study for patients from JADA, JADZ, JADV, JADX, JADW, and JAGS	B2 (patients from JADX and JADW) B4 Rescue: JADV, JADW, JADX: CDAI≤10 for ≥12 weeks in study JADY JADZ CDAI ≤2.8 for ≥12 weeks in study JADY	2539
Baricitinib dose for renally (<60mL/min/1.73m^2) impaired patients randomized or rescued to baricitinib is B2 for all studies in this submission. Abbreviations: B=baricitinib; CDAI=clinical disease activity index			

The primary evidence of efficacy is from studies JADZ, JADV, JADX, and JADW. All of the studies were double-blind, placebo or active-controlled in patients with moderately to severely active RA and provided rescue therapy for patients with inadequate response to double-blind treatment. Study JADV was conducted in patients with inadequate response to MTX, JADX in patients with inadequate response to cDMARDs, JADW in patients with inadequate response to TNF inhibitors, and JADZ in patients naïve to DMARDs.

JADV (Figure 1) was a parallel group, double-blind, double-dummy, placebo controlled trial randomizing 1,260 patients with RA who were biologic naïve, had inadequate response to MTX, and evidence of erosive joint damage to B4, adalimumab, or placebo. All patients continued background MTX therapy. Rescue therapy was offered every 4 weeks starting at Week 16. At Week 16, rescue to baricitinib 4 mg was given for lack of at least 20% improvement in both tender and swollen joint counts at Weeks 14 and 16. After Week 16, rescue therapy was offered to patients based on investigator discretion. The primary endpoint was ACR20 at Week 12.

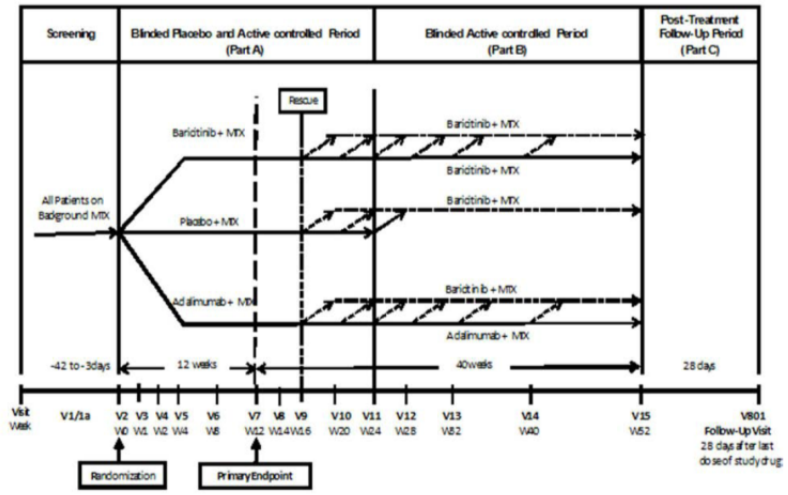
JADX (Figure 2) was a parallel group, double-blind, double-dummy, placebo controlled trial randomizing 660 patients to baricitinib 4 mg, baricitinib 2 mg, or placebo. All patients continued background cDMARDs. The placebo group was continued until Week 24, with the possibility of rescue to baricitinib 4 mg offered at Week 16 to patients in the placebo and baricitinib 2 mg trial arms. The primary endpoint was ACR20 at Week 12.

JADW (Figure 3) had an identical design to JADX in terms of study arms, background therapy, duration, and primary endpoint. The only differences between the studies were related to patient population and stratification factors. JADW randomized 525 patients with RA to baricitinib 4 mg, baricitinib 2 mg, or placebo.

JADZ (Figure 3) was a parallel group, double-blind, double-dummy, active controlled trial randomizing 500 adult patients to baricitinib 4 mg, baricitinib 4 mg with MTX, or MTX. MTX was up-titrated to 20 mg weekly. All treatment groups continued to Week 52, with rescue to baricitinib 4 mg with MTX offered to baricitinib 4 mg and MTX patients at Week 24. The primary endpoint evaluated noninferioirty of baricitinib 4 mg to MTX alone for ACR20 at Week 24.

JADY is an ongoing, long-term extension study evaluating the safety of baricitinib 2 mg and 4 mg. All patients from JADZ, JADV, JADA, and JAGS received baricitinib 4 mg in JADY. These patients were not blinded to their dose. Non-rescued patients from studies JADX and JADW continued receiving baricitinib 2 mg or 4 mg in JADY in a blinded manner. Patients with low disease activity (defined as CDAI≤10 for studies JADV, JADX, and JADW) or remission (CDAI<2.8 for study JADZ) and randomized to baricitinib 4 mg were eligible for a step-down study. All patients remained on the add-on medications from their respective studies, with half re-randomized to receive a reduction in dose from baricitinib 4 mg to baricitinib 2 mg. The study was parallel group, double-blind, and double dummy. Rescue was allowed after step down in this extension study. Patients re-randomized to baricitinib 2 mg who originated from studies JADV, JADW, and JADX were eligible for rescue to baricitinib 4 mg at or after 12 weeks following enrollment into JADY. For patients enrolled from study JADZ, rescue via increases in MTX or other cDMARDs was allowed.

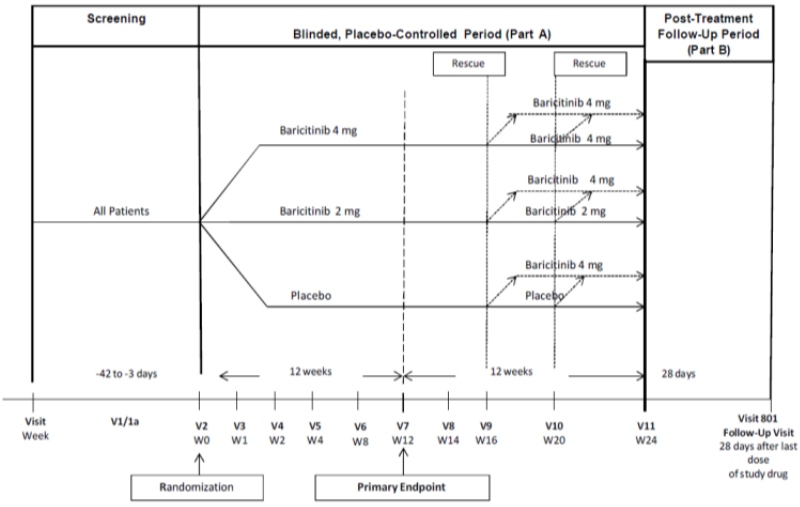
Figure 1: JADV Study Design



Note: Diagonal dashed arrows indicate an option for rescue therapy. The diagonal solid arrow indicates a mandatory change to baricitinib treatment (at Week 24 for placebo-treated patients).
Abbreviations: V = visit; W = week.

Source: JADV complete study report, page 112

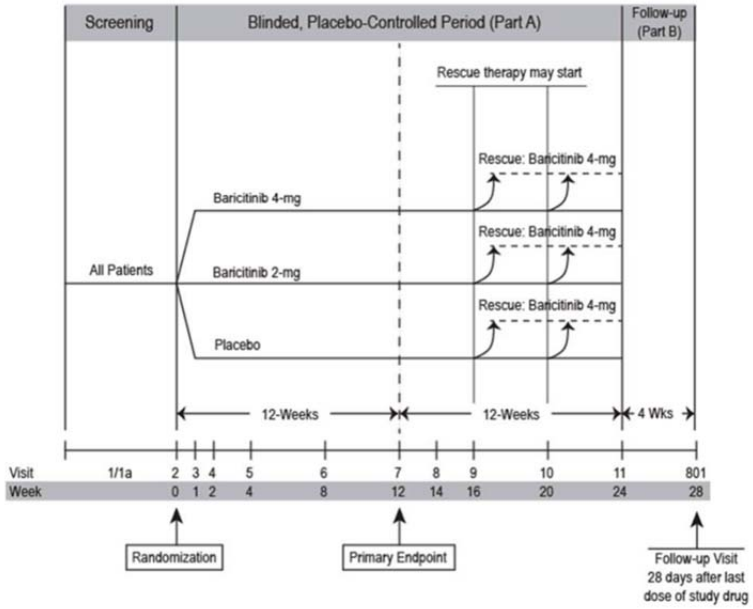
Figure 2: JADX Study Design



Abbreviations: V = study visit; W = study week. Diagonal dashed arrows indicate an option for rescue therapy.

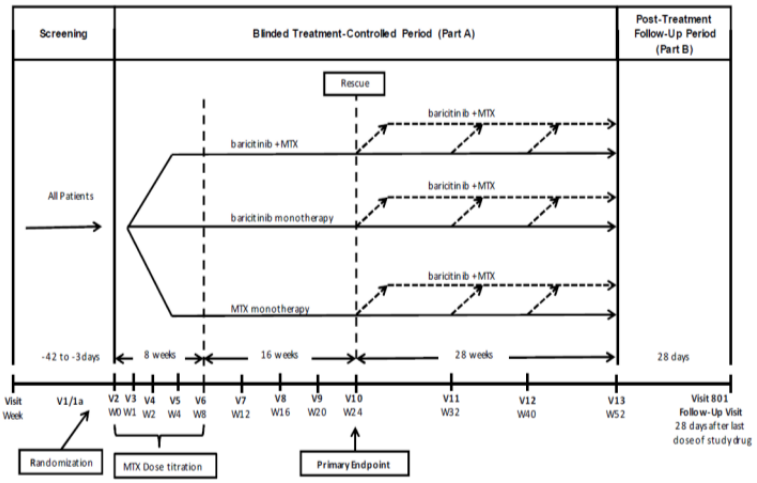
Source: JADX complete study report, page 85

Figure 3: JADW Study Design



Source: JADW complete study report, page 78

Figure 4: JADZ Study Design



Abbreviations: MTX = methotrexate; V = study visit; W = study week.
Note: Diagonal dashed arrows indicate an option for rescue therapy.

Source: JADZ complete study report, page 102

Brief Description of Efficacy Endpoints

- *ACR Response Rates*

In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in RA, which have since been used in drug development trials to demonstrate evidence of efficacy for signs and symptoms of RA.[7] The ACR20 response is calculated as a >20% improvement in:

- tender joint count (of 68 joints) and
- swollen joint count (of 66 joints) and
- 3 of the 5 remaining ACR core set measures
    - Patient Global Assessment of Arthritis on a visual analog scale (VAS)
    - Physician Global Assessment of Arthritis on a VAS
    - Patient Assessment of Pain on a VAS
    - Patient Assessment of Physical Function (e.g. Health Assessment Questionnaire)
    - Acute Phase Reactant (Erythrocyte Sedimentation Rate or C-reactive protein)

Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

The Agency has historically recognized a distinct claim in RA for "improvement in physical function" based on outcome measures such as the HAQ-DI.[8] This instrument assesses a patient's level of functional ability and includes questions pertaining to fine movements of the upper extremity, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients respond on a four-level difficulty scale ranging from zero (no difficulty) to three (unable to do). The 8 category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to 3 (completely disabled). The most widely accepted figure on the minimal clinically important difference in the HAQ-DI score is an improvement (decrease) of at least 0.22 units.

- *Disease Activity Score (DAS)-28*

The DAS28 is a composite index of RA disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and erythrocyte sedimentation rate (ESR) results.[9] An alternative equation

[7] DT Felson, et al. Arthritis Rheum 1995. June, 38(6):727-735.
[8] B Bruce and JF Fries, "The Health Assessment Questionnaire (HAQ)." Clin Exp Rheumatol 2005; 23 (Suppl 39):S14-S18.
[9] J Fransen and PLCM van Riel, "The Disease Activity Score and the EULAR Response Criteria." Clin Exp Rheumatol 2005; 23 (Suppl 39): S93-S99.

is available for use with c-reactive protein (CRP) results. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. Comparing the DAS28 and the ACR response criteria, beyond the differences in number of maximum tender or swollen joints counted (e.g. DAS28 does not include the joints of the feet), additional variables of physician global assessment, patient pain, and HAQ score are incorporated into the ACR response criteria. The DAS28 has additional utility in measuring the level of disease activity at a given time point, whereas the ACR response criteria are calculated as improvement in the variables over a set period of time. A DAS28 score >5.1 is indicative of high disease activity, and <3.2 of low disease activity. A score of <2.6 has been used to describe an even lower threshold of disease activity.

- *Radiographic Outcome: Van der Heijde modified Sharp Score*

The Van der Heijde-modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet.[10] The scores for each feature for the individual joints are summed. Erosions are assessed at 16 locations in each hand and wrists and 12 locations in each foot, using a 6-point scale from 0 to 5. Scores are derived based on the number and size of discrete erosions in each location, but are summed to a maximum of 5. Thus, the maximum erosion score for the hands/wrists is 160, and the maximum erosion score for the feet is 120, for a maximum total erosion score of 280. JSN scores are based on 15 locations in each hand and wrist and 6 locations in each foot, scored using a 5-point scale from 0 to 4: 0 = normal; 1 = focal or minimal and generalized narrowing; 2 = generalized narrowing <50%; 3 = generalized narrowing >50% or subluxation; and 4 = ankylosis or complete dislocation. The maximum total JSN for the hands/wrists is 120, and the maximum total JSN for the feet is 48, for a maximum total JSN score of 168. Therefore, the theoretical maximum modified total Sharp Score (mTSS) is 448, although the actual clinical range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage.

- *SF-36*

The medical outcome short form health survey (SF-36) is an instrument used to measure health-related quality of life or general health status. It consists of 8 subscales that are scored individually: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items). Two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed.

- *Simplified Disease Activity Index (SDAI)*

[10] S Boini and F Guillemin, "Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages." Ann Rheum Dis 2001; 60:817-827.

The SDAI integrates measures of the physical examination, acute phase response, patient self-assessment, and evaluator assessment.[11] Disease remission has been defined as an SDAI score ≤3.3[12] and low disease activity has been considered as an SDAI score ≤11. SDAI is calculated by adding the scores from the following assessments:

- number of tender joints (0 to 28)
- number of swollen joints (0 to 28)
- hsCRP in mg/dL (0.1 to 10.0)
- Patient's Global Assessment of Disease Activity VAS (0 to 10.0 cm)
- Physician's Global Assessment of Disease Activity VAS (0 to 10.0 cm)

Thus, the SDAI ranges from 0.1 to 86.

- *Clinical Disease Activity Index (CDAI)*

This measure is similar to the SDAI, but it allows for immediate scoring in the clinic because it does not include a laboratory result. Disease remission has been considered as a CDAI score ≤2.8 (Felson et al. 2011). CDAI is calculated by adding the scores from the following assessments:

- number of tender joints (0 to 28)
- number of swollen joints (0 to 28)
- Patient's Global Assessment of Disease Activity VAS (0 to 10.0 cm)
- Physician's Global Assessment of Disease Activity VAS (0 to 10.0 cm)

Thus, the CDAI ranges from 0 to 76.

Dose selection

The proposed recommended dose is 4 mg once daily. For some patients, a dose of 2 mg once daily may be acceptable. Lilly performed three phase 2 studies (JADC, JADA, and JADN), but noted that the selected baricitinib doses of 2 and 4 mg daily were based on dose-ranging safety and efficacy data from studies JADC and JADA because data from JADN were analyzed after the start of the phase 3 program. Each phase 2 study was a randomized, double-blind, placebo-controlled 12-week evaluation of baricitinib administered with concomitant MTX in patients with active RA. Patients were randomized to placebo or baricitinib (4 mg, 7 mg, or 10 mg daily in JADC or 1 mg, 2 mg, 4 mg, or 8 mg in JADA and JADN).

JADC and JADA were conducted in 428 patients with active RA and an inadequate response to cDMARDs. The key results for the American College of Rheumatology (ACR) Responses are summarized in Table 4 and Figure 5, which demonstrate a dose-response for efficacy. In

[11] Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): A review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23(5 Suppl 39):S100-8.
[12] Felson DT, et al. American College of Rheumatology/European League against Rheumatism Preliminary Definition of Remission in Rheumatoid Arthritis. Arthritis Rheum 2011;63(3):573-586.

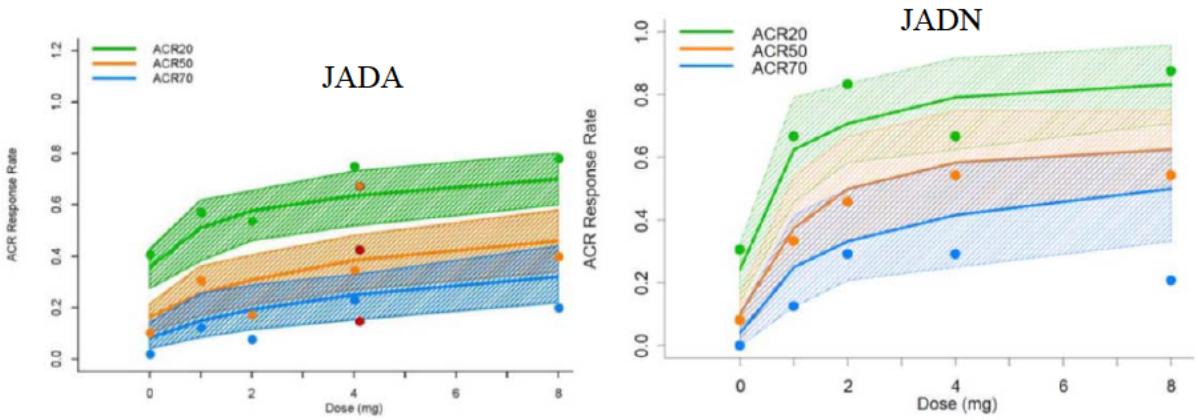
general, the dose-response curve is flat for ACR20/50/70 from 2 mg to 8 mg, which supports the dose selection of 2 mg and 4 mg in phase 3 studies. Exposure-response analyses for safety were performed to help consider dose selection. Due to the overall small change in hemoglobin level and absolute neutrophil count over about a 6-fold of Cavg,ss range, PK/PD models were not developed for hemoglobin concentration and absolute neutrophil count. Therefore, the lack of significant exposure-response results for these two lab parameters supports the dose selection for phase 3 studies.

Table 4: Primary Efficacy Results from Three Phase 2 Dose-Ranging Studies

Study ID	Patient Population	ACR20 Response at Week 12*				
		Placebo Group	Baricitinib Groups			
JADC	Active RA patients inadequately controlled with at least one DMARD	32% (10/31)	4 mg[1]	7 mg[1]	10 mg[1]	
			52% (16/31) p=0.1978	59% (19/32) p=0.0437	53% (16/30) p=0.1236	
JADA	Active RA patients with use of MTX for at least 12 weeks	41% (40/98)	1 mg[2]	2 mg[2]	4 mg[2]	8 mg[2]
			57% (28/49) p=0.045	54% (28/52) p=0.088	75% (39/52) p<0.001	78% (39/50) p<0.001
JADN	Active Japanese RA patients with use of MTX for at least 12 weeks	31% (15/49)	1 mg[2]	2 mg[2]	4 mg[2]	8 mg[2]
			67% (16/24) p=0.004	83% (20/24) p<0.001	67% (16/24) p=0.004	88% (21/24) p<0.001

* listed as response rate (%) calculated by response patient number/total patient number
[1] as primary objective
[2] as secondary objective
Source: CSR JADC, page 80, Table 10; CSR JADA, page 190, Table 11.2; CSR JADN, page 104, Table 11.6
Source: Clinical Pharmacology Review, Table 1, page 10

Figure 5: Observed and Estimated Dose Response Relationship for the ACR20/50/70 Response Rate after 12 Weeks of Baricitinib Treatment in Study JADA (left) and JADN (right)



Lines are modeled curves with corresponding 90% prediction intervals; green, orange, and blue symbols are for observed ACR20, ACR50, and ACR70, respectively; red symbols are for observed BID dosing (Part B of Study JADA). (Source: CSR JADA page 301, Figure 11.46 and CDR JADN page 138, Figure 11.7)

Source: Clinical Pharmacology Review, Figure 1, page 11

Statistical considerations

Efficacy analyses were generally conducted on the modified-intent-to-treat (mITT) population, defined as patients receiving at least one dose of the study drug. An exception was the analysis for radiographic progression, in which analyzed patients not only had to receive one dose of the study drug, but also were required to have non-missing baseline measurement as well as at least one non-missing post baseline measurement. Type 1 error rates in the face of multiple endpoints and doses, was controlled at the 0.05 level of significance using analysis hierarchies defined graphically as in Bretz et al.[13] See Dr. Abugov's statistical review for details of the analysis hierarchies particular to each study. The specific hierarchies are included in Figure 6, Figure 7, Figure 8, and Figure 9.

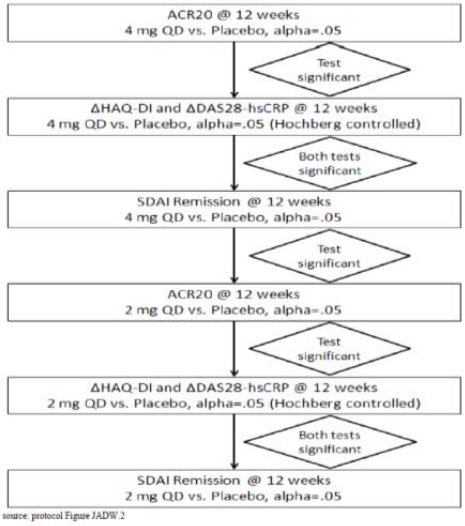
Lilly and the statistical reviewer performed multiple sensitivity analyses, including tipping point analyses, to assess the impact of missing data on the primary endpoints and multiple secondary endpoints.

Non-response was recorded for binary response data missing or collected after permanent discontinuation or escape. Therefore, these variables were considered composite endpoints defined by remaining on randomized treatment through the time point of interest and meeting the binary response criteria at the time point of interest. For key secondary endpoints, missing continuous data was imputed using modified baseline observation carried forward (mBOCF), with BOCF used after patients discontinued the study or study treatment due to an adverse event, and last observation carried forward (LOCF) used after patients who discontinued the study or study treatment due to other reasons. Radiographic data missing or collected after treatment discontinuation or escape was imputed using linear extrapolation, with analysis via ANCOVA for the time point of interest.

The initial submission failed to address multiple statistical issues, such estimands for time points after rescue and documentation of analysis datasets. After multiple information requests, adequate information was obtained from Lilly.

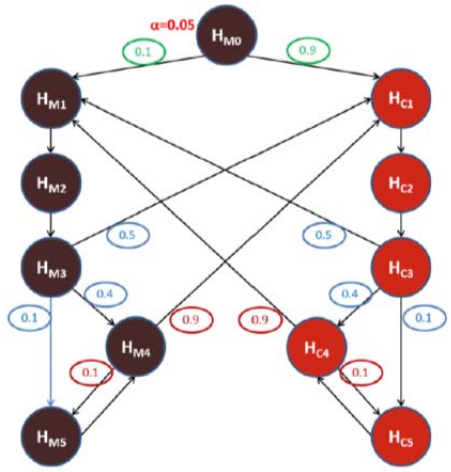
[13] Bretz, F. Maurer, W, Brannath, W, and Posch, M (2009). A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 28 (4), 586-604.

Figure 6: Multiple Test Procedure, Study JADW



source: protocol Figure JADW.2

Figure 7: Multiple Test Procedure, Study JADZ



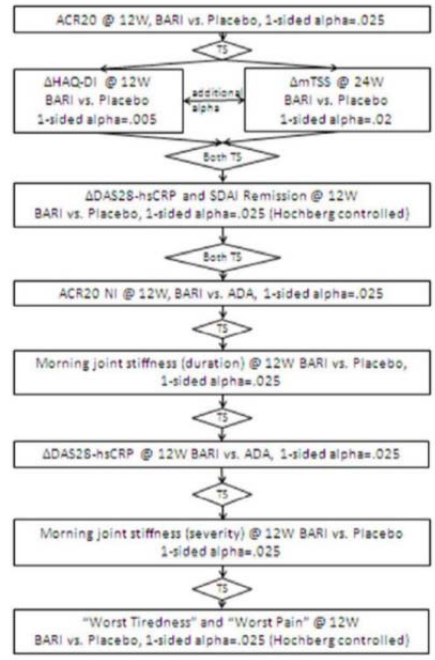
source: Figure JADZ.9.2 of CSR

- **HM0**: Proportion of patients who achieved ACR20 at Week 24, noninferiority of baricitinib monotherapy to MTX monotherapy
- **HM1**: Proportion of patients who achieved ACR20 at Week 24, superiority of baricitinib monotherapy to MTX monotherapy
- **HM2**: Mean change from baseline in DAS28-hsCRP at Week 24, baricitinib monotherapy vs MTX monotherapy

ortion of patients who achieved SDAI ≤3.3 at Week 24, baricitinib monotherapy vs MTX monotherapy

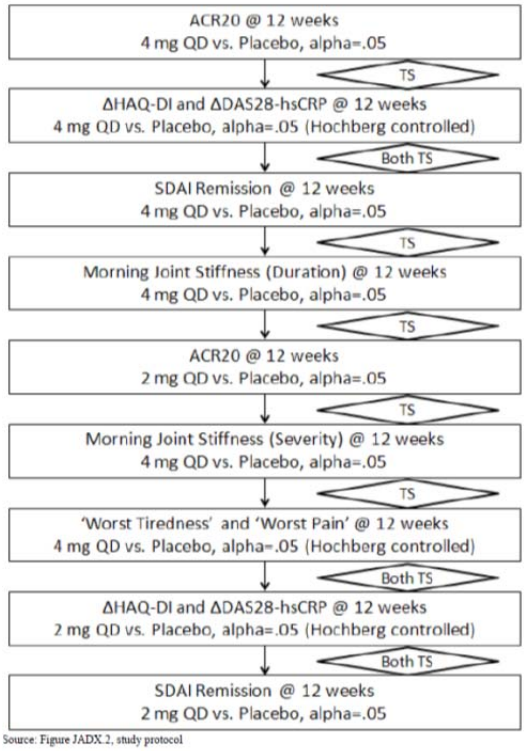
- **HM3**: Mean change from baseline in HAQ-DI at Week 24, baricitinib monotherapy vs MTX monotherapy
- **HM4**: Mean change from baseline in mTSS at Week 24, baricitinib monotherapy vs MTX monotherapy
- **HM5**: Proportion of patients who achieved SDAI ≤3.3 at Week 24, baricitinib monotherapy vs MTX monotherapy
- **HC1**: Proportion of patients who achieved ACR20 at Week 24, baricitinib plus MTX vs MTX monotherapy
- **HC2**: Mean change in DAS28-hsCRP at Week 24, baricitinib plus MTX vs MTX monotherapy
- **HC3**: Mean change in HAQ-DI at Week 24, baricitinib plus MTX vs MTX monotherapy
- **HC4**: Mean change in mTSS at Week 24, baricitinib plus MTX vs MTX monotherapy
- **HC5**: Proportion of patients who achieved SDAI ≤3.3 at Week 24, baricitinib plus MTX vs MTX monotherapy

Figure 8: Multiple Test Procedure, Study JADV



source: Figure JADV.2, Study Protocol

Figure 9: Multiple Test Procedure, Study JADX



Source: Figure JADX.2, study protocol

Patient disposition, demographics, and baseline characteristics

Treatment groups in the studies were generally balanced with respect to demographics and baseline characteristics. The mean age of patients in the treatment arms in these studies ranged from 49 to 56 years, and a majority were female and white or Asian. Overall completion rates were in the 50 to 97% range for active and control groups. Dropout rates due to adverse events tended to be higher or similar in the baricitinib treatment groups (0-11%) compared to the placebo control groups (1-4%). Dropout rates due to lack of efficacy tended to be somewhat higher in the placebo groups of the studies (0-3% with baricitinib, 2-9% with placebo). This pattern and amount of missing data is consistent with other RA clinical development programs.

Efficacy findings

- *ACR Response Rates*

The primary endpoint for all four phase 3 trials was the proportion of patients experiencing an ACR20 response at 12 weeks (JADX, JADV, and JADW) or 24 weeks (JADZ). Statistically significant differences between baricitinib 4 mg and 2 mg versus placebo were seen at 12 weeks in studies JADV, JADW, and JADX (Table 5). For ACR20, there was no consistent trend favoring baricitinib 2 mg or baricitinib 4 mg. In JADZ, baricitinib 4 mg monotherapy was superior to MTX monotherapy for ACR20 response. The ACR20 response for baricitinib 4 mg monotherapy and baricitinib 4 mg+MTX was similar.

Table 5: Summary of ACR20 Response Rates (Primary Endpoint) in Phase 3 RA Studies (JADV, JADX, JADW, and JADZ)

Study	% Responders (Responders/Total)			Odds Ratio (p-value)		
	B4	B2	Pbo	B4:Pbo	B2:Pbo	B4:B2
At week 12						
JADV	70 (339/487)	--	40 (196/488)	3.6 (<0.001)	--	--
JADW	55 (98/177)	49 (85/174)	27 (48/176)	3.4 (<0.001)	2.7 (0.001)	1.3 (0.3)
JADX	62 (140/227)	66 (151/229)	39 (90/228)	2.5 (<0.001)	3 (<0.001)	0.8 (0.4)
At week 24						
	B4MTX	B4	MTX	B4MTX:MTX	B4:MTX	B4MTX:B4
JADZ	78 (168/215)	77 (122/159)	62 (130/210)	2.2 (0.001)	2.0 (0.003)	1.1 (0.7)

Abbreviations: B4=baricitinib 4 mg; B2=baricitinib 2mg; Pbo=placebo; MTX=methotrexate
Source: Table 14 and Table 17 of Dr. Abugov's statistical review dated 11/17/16

Consistent with the primary endpoint results, the proportion of patients experiencing ACR50 and ACR70 levels of improvement were higher in the baricitinib groups compared to the placebo or active control groups. In general, the results did not consistently favor 4 mg versus 2 mg.

In JADV, baricitinib was statistically superior to adalimumab at Week 12 for ACR20, ACR50, and ACR70 (Table 6). Similar results were seen at Week 24.

Table 6: Summary of ACR20/50/70 Response Rates for Baricitinib vs. Adalimumab (JADV)

At Week 12	% Responders (Responders/Total)			Odds Ratio (p-value)		
	B4	Adalimumab	Pbo	B4:Pbo	Adalimumab:Pbo	B4:Adalimumab
ACR20	70 (339/487)	61 (202/330)	40 (196/488)	3.6 (<0.001)	2.4 (<0.001)	1.5 (0.01)
ACR50	45 (219/487)	35 (115/330)	17 (82/488)	4.2 (<0.001)	2.7 (<0.001)	1.5 (0.005)
ACR70	19 (92/487)	13 (42/330)	5 (23/488)	4.9 (<0.001)	3 (<0.001)	1.6 (0.02)

Abbreviations: B4=baricitinib 4 mg; B2=baricitinib 2mg; Pbo=placebo
Source: Tables 20, 21, and 22 of Dr. Abugov's statistical review dated 11/17/16

Analysis of the ACR components demonstrated that no one component appeared to drive the overall efficacy results. When comparing the two doses studied in JADW, results for the ACR components, including changes in hsCRP, HAQ-DI, pain, patient global assessment, physician global assessment, tender joint count, and swollen joint count generally favored baricitinib 4 mg over baricitinib 2 mg. When comparing the two doses studied in JADX, there was not a consistent trend favoring one dose at Week 12.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

All phase 3 trials assessed the treatment effect of baricitinib on HAQ-DI (Table 7). The change in HAQ-DI score was assessed as part of the statistical hierarchy from baseline to Week 12 in studies JADW, JADV, and JADX and Week 24 in study JADZ. Baricitinib treatment was associated with a statistically significant improvement (decrease) in HAQ-DI (mean change from baseline) compared to placebo. In JADZ, baricitinib monotherapy was superior to methotrexate for mean change in HAQ-DI. In JADV, baricitinib was superior to adalimumab for mean change in HAQ-DI. In one of the two phase 3 studies with the 2 mg and 4 mg doses (JADW), the 4mg dose group appeared to be associated with slightly greater improvement in HAQ-DI. In the other phase 3 study with both doses (JADX), results for HAQ-DI were similar for the two doses.

Table 7: Summary of Mean Change from Baseline in HAQ-DI in Phase 3 RA Studies (JADV, JADX, JADW, and JADZ)

Study	Mean Change from Baseline (N)			Difference (p-value)		
At week 12						
	B4	A	Pbo	B4-Pbo	A-Pbo	B4-A
JADV	-0.66 (482)	-0.56 (327)	-0.34 (484)	-0.32 (<0.001)	-0.22 (<0.001)	-0.1 (0.004)
	B4	B2	Pbo	B4-Pbo	B2-Pbo	B4-B2
JADW	-0.41 (175)	-0.37 (172)	-0.17 (171)	-0.24 (<0.001)	-0.2 (<0.001)	-0.03 (0.51)
JADX	-0.56 (222)	-0.57 (228)	-0.36 (220)	-0.19 (<0.001)	-0.21 (<0.001)	0.01 (0.76)
At week 24						
	B4MTX	B4	MTX	B4MTX:MTX	B4:MTX	B4MTX:B4
JADZ	-1.03 (209)	-1.04 (159)	-0.74 (204)	0.01 (0.83)	-0.29 (<0.001)	-0.3 (<0.001)

Abbreviations: B4=baricitinib 4 mg; B2=baricitinib 2mg; Pbo=placebo; MTX=methotrexate; A: adalimumab
Source: Tables 23, 24, 25, and 26 of Dr. Abugov's statistical review dated 11/17/16

- *Disease Activity Score (DAS)28-hsCRP<2.6*

The proportion of patients achieving a DAS28-hsCRP<2.6 was assessed at week 12 in studies JADV, JADW, and JADX and Week 24 in study JADZ. In all studies, the proportion of patients

achieving a DAS28-hsCRP<2.6 was significantly higher for baricitinib 2 mg and 4 mg versus placebo (Table 8). In the two studies with both doses studies, baricitinib 4 mg was numerically superior to 2 mg at week 24. Similar results favoring 4 mg over 2 mg were seen in JADW at week 12, but the two doses had a similar response at week 12 in JADX. In study JADZ, baricitinib 4 mg was significantly superior to MTX and baricitinib 4mg+MTX was superior to MTX alone. In patients on baricitinib in JADZ, the proportion of responders was the same with or without methotrexate.

Table 8: Summary of DAS28-hsCRP≤2.6 in Phase 3 RA Studies (JADV, JADX, JADW, and JADZ)

Study	% Responders (Responders/Total)			Odds Ratio (p-value)		
At week 12						
	B4	**A**	**Pbo**	**B4:Pbo**	**A:Pbo**	**B4:A**
JADV	24 (119/487)	19 (63/330)	4 (21/488)	7.6 (<0.001)	5.5 (<0.001)	1.4 (0.077)
	B4	**B2**	**Pbo**	**B4:Pbo**	**B2:Pbo**	**B4:B2**
JADW	16 (29/177)	11 (19/174)	4 (7/176)	4.8 (<0.001)	3 (0.02)	1.6 (0.2)
JADX	26 (58/227)	26 (59/229)	9 (20/228)	3.7 (<0.001)	3.7 (<0.001)	1 (0.97)
At week 24						
	B4	**B2**	**Pbo**	**B4:Pbo**	**B2:Pbo**	**B4:B2**
JADW	21 (38/177)	11 (19/174)	6 (11/176)	4.2 (<0.001)	1.9 (0.11)	2.2 (0.01)
JADX	33 (75/227)	31 (70/229)	11 (24/228)	4.2 (<0.001)	3.8 (<0.001)	1.1 (0.6)
	B4MTX	**B4**	**MTX**	**B4MTX:MTX**	**B4:MTX**	**B4MTX:B4**
JADZ	40 (87/215)	40 (64/159)	24 (50/210)	2.2 (<0.001)	2.2 (<0.001)	1 (0.97)

Abbreviations: B4=baricitinib 4 mg; B2=baricitinib 2mg; Pbo=placebo; MTX=methotrexate; A: adalimumab
Source: Tables 28 and 30 of Dr. Abugov's statistical review dated 11/17/16

- *Radiographic Outcomes: Van der Heijde Modified Total Sharp Score*

The effect of baricitinib on radiographic progression was evaluated in studies JADV, JADZ, and JADX. Only one of these studies, JADX, evaluated the impact of baricitinib 2 mg on radiographic progression. Lilly emphasized analyses utilizing linear extrapolation to impute missing radiographic data and radiographic data after escape to baricitinib, despite several pre-submission interactions at which the Agency advised against this because it relies on unverifiable assumptions. Thus, the review team focused on supportive analyses utilizing all observed data and tipping point analyses. These analyses showed that linear extrapolation may exaggerate the effects of baricitinib.

Study JADV showed statistically significant differences between baricitinib 4 mg and placebo in mTSS at weeks 24 and 52 in analyses using linear extrapolation of missing data and data post-escape and in analyses of all observed data, including data collected after treatment discontinuation and escape to baricitinib (Table 9). Tipping point analyses supported these findings at week 24, but not at week 52. Differences between baricitinib 4 mg and adalimumab in this study were not statistically significant and there was a trend toward slightly less radiographic progression with adalimumab than baricitinib (Table 9).

In JADX, compared to placebo, baricitinib 4 mg reduced mTSS at week 24 in an analysis using linear extrapolation of missing and post-escape data, and an analysis including all observed data, including data collected after treatment discontinuation and escape to baricitinib (Table 9).

Results were not as consistent for baricitinib 2 mg, with lack of evidence of an effect in the analyses based on only observed data. Tipping point analyses comparing baricitinib 4 mg and 2 mg to placebo showed lack of statistical significance under some plausible alternative missing data assumptions.

In JADZ, baricitinib 4 mg was not significantly superior to methotrexate alone at week 24, but baricitinib with methotrexate was superior to methotrexate monotherapy at week 24. Tipping point analyses weakly supported superiority of baricitinib 4 mg with methotrexate to methotrexate monotherapy.

Table 9: Summary of Mean Change from Baseline in mTSS in Studies JADV, JADX, and JADZ

	mTSS Mean Change from Baseline (N)			Difference (p-value)		
At week 24	**B4**	**A**	**Pbo**	**B4-Pbo**	**A-Pbo**	**B4-A**
JADV (Linear extrap.)	0.41 (470)	0.33 (312)	0.90 (452)	-0.49 (<0.001)	-0.56 (<0.001)	0.07 (0.6)
JADV (All observed data)	0.36 (444)	0.30 (299)	0.8 (426)	-0.43 (<0.001)	-0.5 (<0.001)	0.07 (0.6)
	B4	**B2**	**Pbo**	**B4-Pbo**	**B2-Pbo**	**B4-B2**
JADX (Linear extrap.)	0.15 (198)	0.33 (208)	0.7 (190)	-0.55 (0.003)	-0.38 (0.04)	-0.18 (0.3
JADX (All observed data)	0.19 (184)	0.34 (188)	0.49 (167)	-0.3 (0.03)	-0.15 (0.3)	-0.15 (0.3)
	B4MTX	**B4**	**MTX**	**B4MTX:MTX**	**B4:MTX**	**B4MTX:B4**
JADZ (All observed data), week 24	0.31 (177)	0.38 (138)	0.65 (172)	-0.34 (0.03)	-0.27 (0.1)	-0.07 (0.7)
JADZ (All observed data), week 52	0.31 (174)	0.62 (135)	1.09 (160)	-0.78 (<0.001)	-0.47 (0.04)	-0.31 (0.2)

Abbreviations: B4=baricitinib 4 mg; B2=baricitinib 2mg; Pbo=placebo; MTX=methotrexate; A: adalimumab; extrap=extrapolation
Source: Tables 35, 37, 41, 43, 48 of Dr. Abugov's statistical review dated 11/17/16

In JADV, the proportion of patients without radiographic progression (Δmean TSS$\leq$0) was significantly higher for baricitinib 4 mg compared to placebo. In JADV, there was no statistically significant difference between baricitinib 4 mg and adalimumab. In JADX, there was not statistically significant difference between baricitinib 4 mg or 2 mg and placebo. There was a numerically higher proportion of patients without radiographic progression with baricitinib 4 mg (80%) than baricitinib 2 mg (71%). In JADZ, baricitinib 4 mg with methotrexate was superior to methotrexate at 24 and 52 weeks. However, the difference between baricitinib 4 mg and methotrexate and baricitinib 4 mg with methotrexate and baricitinib 4 mg were not significant at week 24.

Table 10: Proportion of Patients without Radiographic Progression, Studies JADV, JADX, and JADZ (All Recorded Data)

	Proportion without radiographic progression			Odds ratio (p-value)		
At week 24	**B4**	**A**	**Pbo**	**B4:Pbo**	**A:Pbo**	**B4:A**
JADV	81 (361/444)	82 (246/299)	70 (300/426)	1.8 (<0.001)	1.9 (<0.001)	0.9 (0.7)
	B4	**B2**	**Pbo**	**B4:Pbo**	**B2:Pbo**	**B4-B2**
JADX	80 (144/181)	71 (131/184)	76 (118/156)	1.3 (0.3)	0.8 (0.4)	0.6 (0.05)
	B4MTX	**B4**	**MTX**	**B4MTX:MTX**	**B4:MTX**	**B4MTX:B4**
JADZ	80 (142/177)	75 (104/138)	66 (113/172)	2.2 (0.002)	1.3 (0.3)	1.6 (0.06)

Abbreviations: B4=baricitinib 4 mg; B2=baricitinib 2mg; Pbo=placebo; MTX=methotrexate; A: adalimumab
Source: Tables 51, 53, and 55 of Dr. Abugov's statistical review dated 11/17/16

In summary, studies JADV and JADZ provide evidence of the effect of baricitinib 4 mg on inhibition of radiographic progression. Only one study, JADX, evaluated the impact of baricitinib 2 mg on radiographic progression and this study did not show a statistically significant impact of baricitinib 2 mg compared to placebo in analyses including all observed data. Thus, there is not convincing evidence of efficacy of baricitinib 2 mg for inhibition of radiographic progression.

- *Additional PROs*

Baricitinib 2 mg and 4 mg significantly reduced median duration and severity of morning joint stiffness (Table 11). While duration of morning stiffness has been included in other RA product labels, there is no precedent for inclusion of severity of morning stiffness in labeling.

Worst tiredness was measured on an 11 point scale, with 0 representing no tiredness and 10 'as bad as you can imagine.' Baricitinib significantly reduced worst tiredness at week 12, with differences between baricitinib and placebo ranging from 0.4 to 0.8 (Table 11).

SF-36 was assessed as a measure of general health status. In three studies (JADV, JADW, and JADX), baricitinib provided statistically significant improvements in physical component score, physical function, role physical, bodily pain, vitality, and general health at week 12, with no statistically significant effects for mental component score, and mixed results for role emotional, mental health, and social functioning. These findings are consistent with several other RA programs, in which patients tend to have less impairment on the mental component score than the physical component score and thus it is more difficult to demonstrate efficacy on these domains. See the statistical review for the numerical results.

Table 11: Summary of Morning Stiffness Duration and Severity, Worst Tiredness, and Worst Joint Pain in Studies JADV and JADX

Study	Δ Minutes (N)/ Δ Severity (N)			Median Difference (p-value)		
Median change from baseline to week 12						
JADV	**B4**	**A**	**Pbo**	**B4-Pbo**	**A-Pbo**	**B4:A**
Morning stiff duration	-30 (277)	-13 (190)	-2 (276)	-30 (0.001)	-10 (0.02)	-10 (0.3)
Morning stiff severity	-2.46 (478)	-1.97 (320)	-1.38 (476)	-1.08 (<0.001)	-0.6 (<0.001)	-0.49 (0.001)
Worst tiredness	-2.02 (478)	-1.7 (320)	-1.24 (476)	-0.78 (<0.0001)	-0.45 (0.002)	-0.32 (0.03)
Worst joint pain	-2.47 (478)	-1.83 (320)	-1.29 (476)	-1.19 (<0.0001)	-0.54 (<0.001)	-0.65 (<0.0001)
JADX	**B4**	**B2**	**Pbo**	**B4:Pbo**	**B2:Pbo**	**B4:B2**
Morning stiff duration	-20 (222)	-30 (223)	-9 (221)	-14 (0.2)	-21 (0.004)	4 (0.5)
Morning stiff severity	-2.07 (219)	-1.95 (223)	-1.32 (220)	-0.75 (<0.001)	-0.63 (0.002)	-0.12 (0.6)
Worst tiredness	-1.68 (219)	-1.63 (223)	-1.23 (220)	-0.45 (0.03)	-0.40 (0.049)	-0.05 (0.8)
Worst joint pain	-1.97 (219)	-1.99 (223)	-1.09 (220)	-0.89 (<0.0001)	-0.91 (<0.0001)	0.02 (0.9)

Abbreviations: B4=baricitinib 4 mg; B2=baricitinib 2mg; Pbo=placebo; MTX=methotrexate; A: adalimumab; stiff=stiffness
Source: Tables 56-63 of Dr. Abugov's statistical review dated 11/17/16

- *Step-down dosing*

In JADY, Lilly performed a randomized step-down in dosage from baricitinib 4 mg to 2 mg. There are limitations to these analyses given that JADY did not control type 1 error over multiple endpoints. Despite limitations, the numerical differences between baricitinib 4 mg and 2 mg tended to favor 4 mg on certain endpoints, such as the ACR components and DAS28-CRP. A randomized comparison of step-up dosing from 2 mg to 4 mg was not performed in Lilly's clinical program.

- *Subgroup analyses*

Impacts of gender, age, race, ethnicity, and country on the effects of baricitinib compared to placebo were evaluated in studies JADV, X, W, and Z. With the exception of race in study JADV, no statistically significant impacts of subgroups on treatment efficacy were seen. Given the results of other studies, this was most likely a chance finding.

- *Integrated efficacy analyses*

On June 24, 2016, the statistical review team with concurrence of the clinical review team asked Lilly to conduct integrated efficacy analyses of studies JADA, JADN, JADX, and JADW to explore comparative efficacy between the 4 mg and 2 mg doses. These four studies were selected by the review teams because these studies had the 4 mg and 2 mg doses in the same study. Lilly submitted the results of the integrated analyses on July 21, 2016. Results showed that ACR20 response was superior for the 4 mg dose versus the 2 mg dose up to, but not including Week 12 (nominal p-value of 0.04 at Week 8). Further results are included as an Appendix to this review. These integrated efficacy analyses were supportive of other efficacy trends, such as with the ACR20 components in the individual studies, but we do not typically rely on integrated efficacy analyses and they were not a key driver of my risk/benefit conclusions for the doses.

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions and ways that any disagreements were addressed**

The clinical and statistical review teams are in agreement that baricitinib at both 2 mg and 4 mg doses is efficacious for signs and symptoms (ACR responses, DAS28) as well as for physical function (HAQ-DI). There is convincing evidence of inhibition of radiographic progression for baricitinib 4 mg, but not 2 mg. For ACR20, there was no consistent trend favoring baricitinib 2 mg or baricitinib 4 mg. For continuous endpoints, such as the components of the ACR20 response, there generally appeared to be some greater efficacy of the 4 mg dose compared to the 2 mg dose in study JADW.

- **Discussion of notable efficacy issues both resolved and outstanding**

There are no unresolved issues.

8. Safety

- **Studies contributing to integrated safety analyses and Lilly's pooling and attribution strategies**

A summary of the studies contributing to the primary integrated analyses may be found in Table 1, Table 2, and Table 3. These included 4 phase 3 studies, 3 phase 2 studies in RA, and 1 long-term extension study (JADY). JADY enrolled patients who completed active treatment in one of the following studies: JADA, JADZ, JADV, JADX, JADW, or JAGS. JAGS is ongoing and data from this study are not included in this submission. In some integrated analyses, safety information from 1 phase 1 study in RA (JADB) and other indications besides RA, including diabetic kidney disease and plaque psoriasis, were included. JADB was a phase 1 open label study of baricitinib 5 mg, 10 mg, and 15 mg daily in a total of 53 RA patients. JAGQ was a randomized, double-blind, placebo-controlled study of baricitinib 0.75 mg, 1.5 mg, and 4 mg once daily and 0.75 mg bid versus placebo in a total of 129 patients. JADP was a randomized, double-blind, placebo-controlled study of baricitinib (2 mg, 4 mg, 8 mg, and 10 mg daily) versus placebo in a total of 271 patients with plaque psoriasis.

As noted in Table 1 and Table 2, placebo-controlled periods (without the option for rescue) were limited to 12 to 24 weeks. There was heterogeneity in the study design. Studies JADC and JADN were placebo controlled for 12 weeks. JADA was placebo controlled for 12 weeks and then had a blinded extension for 12 weeks. JADZ compared baricitinib (with or without methotrexate) to optimized methotrexate for 52 weeks, with the option for rescue at 24 weeks. JADV was placebo controlled for 24 weeks and adalimumab controlled for 52 weeks with an option for rescue starting at Week 16. After Week 24, all patients originally randomized to placebo received baricitinib. Studies JADX and JADW offered rescue to patients beginning at Week 16. Non-responders were defined based on assessment of swollen and tender joints. There were two active comparator studies (JADV-adalimumab and JADZ-methotrexate).

The aforementioned design features of the phase 2 and phase 3 studies complicate the comparison of baricitinib to control group and between the 2 mg and 4 mg dose groups. The integrated safety analysis sets used to assess safety across the program are described in Table 12. Of note, JADZ was not included in the integrated analyses with the phase 2/3 studies because it was an active comparator study with optimized methotrexate, unlike the other studies. JADZ was included in the All BARI RA and All BARI analysis sets.

Table 12: Studies Contributing Data to the Integrated Analysis Sets

Analysis Set	Designation	Studies Included	Treatment Groups Included in the Analysis Set[a]
BARI 4-mg RA PC	Primary	JADA, JADC, JADN, JADV, JADW, JADX	PBO, BARI 4-mg
BARI 2-mg vs 4-mg RA	Secondary	JADA, JADN, JADW, JADX	BARI: 2-mg, 4-mg
Ext BARI 2-mg vs 4-mg RA	Secondary	JADA/JADY, JADN, JADW/JADY, JADX/JADY	BARI: 2-mg, 4-mg
All BARI RA	-	JADA/JADY, JADB, JADC, JADN, JADV/JADY, JADW/JADY, JADX/JADY, JADZ/JADY	BARI: 1-mg, 2-mg, 2-mg BID, 4-mg, 5-mg BID, 7-mg, 8-mg, 10-mg, 15-mg,
All BARI	-	**All BARI RA** and JADP[b], JAGQ[b]	**All BARI RA** and BARI: 0.75-mg, 0.75-mg BID, 1.5-mg
BARI 2-mg RA PC	-	JADA, JADN, JADW, JADX	PBO, BARI 2-mg
BARI 2-mg/4-mg RA PC	-	JADA, JADC, JADN, JADV, JADW, JADX	PBO, BARI 2-mg, BARI 4-mg

Abbreviations: BID = twice daily; Ext = Extended; PC = placebo-controlled; RA = rheumatoid arthritis.
[a] Baricitinib doses have been administered once daily, unless stated otherwise. Patients with renal function impairment who were randomized to BARI 4-mg but treated with the 2-mg dose were analyzed in the BARI 4-mg group.
[b] JADP is a study in psoriasis. JAGQ is a study in diabetic kidney disease.

Source: Clinical Summary of Safety, Table 2.7.4.1, page 18

Given the complexities of the study design, including differences in study duration, duration of placebo-controlled periods, time of rescue, and comparator and background therapy, additional analyses were requested. To better characterize adverse events during the pre-rescue/pre-switch period (16 weeks in the phase 3 studies and 12 weeks in the phase 2 studies), FDA requested Lilly estimate incidence rates for adverse events of special interest from the 6 controlled phase 2 and 3 studies (**BARI 2 mg/4 mg PC**: JADA, JADC, JADN, JADV, JADW, and JADX). The goal of these analyses was to utilize all available randomized, controlled data to provide the most reliable evaluation of (potentially rare) adverse events of special interest. The data were analyzed in a model that accounted for study differences to help reduce the potential for confounding by study. These analyses had advantages over those proposed by Lilly because they used all available pre-rescue data and allowed for comparisons between the 4 mg and 2 mg dose groups.

Additional analyses were needed to better characterize the long-term safety of baricitinib and to compare the 2 mg and 4 mg dose groups, with a focus on adverse events of special interest. FDA requested Lilly generate a new dataset utilizing 6 studies (**Ext BARI 2 mg/4 mg PC**: JADA/JADY, JADC, JADN, JADV/JADY, JADW/JADY, and JADX/JADY) rather than the existing "Ext BARI 2 mg vs. 4 mg" dataset given that many adverse events of special interest are relatively rare and the requested dataset utilized 6 studies, rather than 4 studies in Lilly's analyses. FDA requested 2 analytical methodologies: method 1 and method 2. Method 1 included analyses from all time on the initially randomized treatment arm and method 2 included safety data after escape in patients who transitioned from placebo to baricitinib during studies included in the analysis dataset. Lilly noted limitations in these analyses given that for both

methods 1 and 2, the placebo and baricitinib 2 mg dose groups were censored at rescue, while the baricitinib 4 mg dose group is not. This approach to censoring creates an inherent imbalance in the risk of comorbidities between the baricitinib groups. FDA acknowledged these limitations, but noted that the analyses try to pool additional data to provide larger treatment groups for evaluation of potentially rare events of special interest.

For this review, the safety analysis will focus on the pre-rescue period (16 weeks in the phase 3 studies and 12 weeks in the phase 2 studies). The pre-rescue period represents the data least affected by cross-over between study arms. For certain adverse events where it was beneficial to evaluate 52 weeks and greater than 52 weeks of exposure data, the Ext BARI 2 mg/4 mg was evaluated. In general, this review focuses on the results from "method 1" described above. As anticipated, more events were captured utilizing "method 2" but there were also limitations in the assessment of these results given the design of the studies in which patients with ongoing disease activity only had the option of rescue with baricitinib 4 mg.

In addition to the presentation of safety data, during the review cycle, FDA identified numerous disagreements with Lilly in terms of the presentation of safety data. The submission minimized many of the safety concerns associated with baricitinib. For example, the submission emphasized presence or absence of statistical significance, when this is not the focus of the Agency's safety review. Rather, the review focuses on numerical imbalances and notable events, such as gastrointestinal perforation, given that such studies are typically not powered to detect effects on rare adverse events of special interest. Furthermore, absence of statistical evidence of a difference is not evidence of absence of a difference. In addition, concerns were noted regarding Lilly's minimization of safety signals. For example, there were 10 potential opportunistic infections identified in the submission, but the submission noted that none of these were confirmed opportunistic infections, and thus, this was not considered a safety concern. Further, the narratives provided by Lilly revealed other infections that do not normally occur in immunocompetent patients, such as cryptococcal pneumonia, that had not been identified as opportunistic infections. Additional concerns were raised about potential inconsistencies in the data and presentation of the data in such a manner that it obscures safety signals. An example was splitting the data into multiple groups or not providing overall incidence rates or proportions for key safety issues or utilizing definitions that are not consistent with the Code of Federal Regulations (CFR) for serious adverse events. These issues are discussed in greater detail in the following sections. Due to the numerous issues with the presentation and analyses of the safety data, multiple information requests were sent. While there were disagreements in the presentation and analysis of the safety data, after review of the additional data provided, there is adequate information to inform the risk/benefit assessment of baricitinib.

- **Adequacy of the drug exposure experience (i.e., the safety database)**

A total of 3,464 patients with RA were exposed to baricitinib. Of these patients, 2,166 patients were exposed for ≥52 weeks and 467 patients were exposed for ≥104 weeks (Table 13). In the placebo controlled studies in RA, more patients were exposed to baricitinib 4 mg (n=653) than 2 mg (n=254). The size and scope of the safety database were reasonable and consistent with the safety database of other biologic and JAK inhibitor products approved for RA.

Table 13: Exposure to Baricitinib by Dose and Duration in Placebo-Controlled Studies in RA

	BARI 4 mg RA PC		BARI 2 mg vs. 4 mg RA		Ext BARI 2 mg vs. 4 mg RA		All BARI RA	All BARI
	PBO	B4	B2	B4	B2	B4	Phases 1-3	Phases 1-3
Number of patients, n	1070	997	479	479	479	479	3464	3822
Number of patients with ≥X weeks of exposure, n								
16 weeks	722	754	333	334	--	--	--	--
24 weeks	505	653	254	281	--	--	--	--
52 weeks	--	--	--	--	172	231	2166	2230

Abbreviations: BARI or B=baricitinib; PBO=placebo; PC=placebo controlled
Source: Table 2.7.4.5, page 52, Clinical summary of safety, dated 1/15/16

Death

As of August 10, 2015, a total of 22 deaths were reported in the phase 2 and 3 RA program. Of the 22 deaths, 2 deaths occurred during the screening period, 3 occurred in placebo-treated patients, 3 occurred in methotrexate monotherapy patients, 1 occurred in adalimumab-treated patient, 2 occurred in baricitinib 2 mg, 7 occurred in baricitinib ≥4 mg, and 4 occurred in baricitinib ≥4 mg after switch or rescue. During the placebo- and active-controlled portions of the phase 2 and phase 3 studies up to rescue or switch to baricitinib, there were 7 deaths in the combined placebo, MTX monotherapy, and adalimumab arms compared to 3 deaths in the baricitinib arms.

Table 14 displays the number of patient deaths for the first 52 weeks and greater than 52 week periods. Utilizing method 1 analyses, during the first 52 weeks, 2 patients died on placebo (0.5/100 patient years), 0 patients died on baricitinib 2 mg, and 4 patients died on baricitinib 4 mg (0.4/100 patient years). Thus, mortality rates were fairly balanced on the placebo and baricitinib study arms. Utilizing method 2 analyses, additional deaths were captured, but the rates remained stable given the increased amount of exposure. After 52 weeks, the mortality rates remained fairly stable with increased baricitinib exposure. Four additional deaths in the RA clinical program were reported after the data cutoff of August 10, 2015 through November 30, 2015.

The causes of death in baricitinib-treated patients were consistent with the profile of an immunosuppressant and also with the underlying patient population, with infections, pulmonary embolus, stroke/CNS hemorrhage, MI/CAD, malignancy, and non-CNS hemorrhage occurring. See the discussion below regarding thrombosis/pulmonary embolus.

Table 14: Deaths (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY)

	Treatment as Randomized				Incidence rate difference (95% CI)	
	PBO	BARI 2/4	BARI 2	BARI 4	BARI 2/4 vs PBO	BARI 4 vs. 2
0-52 weeks						
Method 1						
Total exposure, PY	406	1318	336	904		
All deaths, n (rate)	2 (0.5)	4 (0.3)	0	4 (0.4)	-0.21 (-1.02, 0.59)	0.49 (-0.19, 1.16)
Method 2						
Total exposure, PY	405.8	2086	336	1671		
All deaths, n (rate)	2 (0.5)	8 (0.4)	0	8 (0.5)	-0.11 (-0.87, 0.65)	0.39 (-0.05, 0.83)
>52 weeks						
Method 1						
Total exposure, PY	--	1214	177	1469		
All deaths, n (rate)	--	4 (0.3)	1 (0.6)	2 (0.3)	--	-0.61 (-1.80, 0.58)

Rate per 100 PY
Abbreviations: PBO=placebo; BARI=baricitinib; PY=patient years; CI=confidence interval
0-52 weeks and >52 weeks (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY)
Source:
0-52 weeks Method 1: Table 4.17, page 78, IR response, submitted 7/21/16
0-52 weeks Method 2: Table 4.19, page 86, IR response, submitted 7/21/16
>52 weeks Method 1: Table 4.18, page 82, IR response, submitted 7/21/16

Serious adverse events

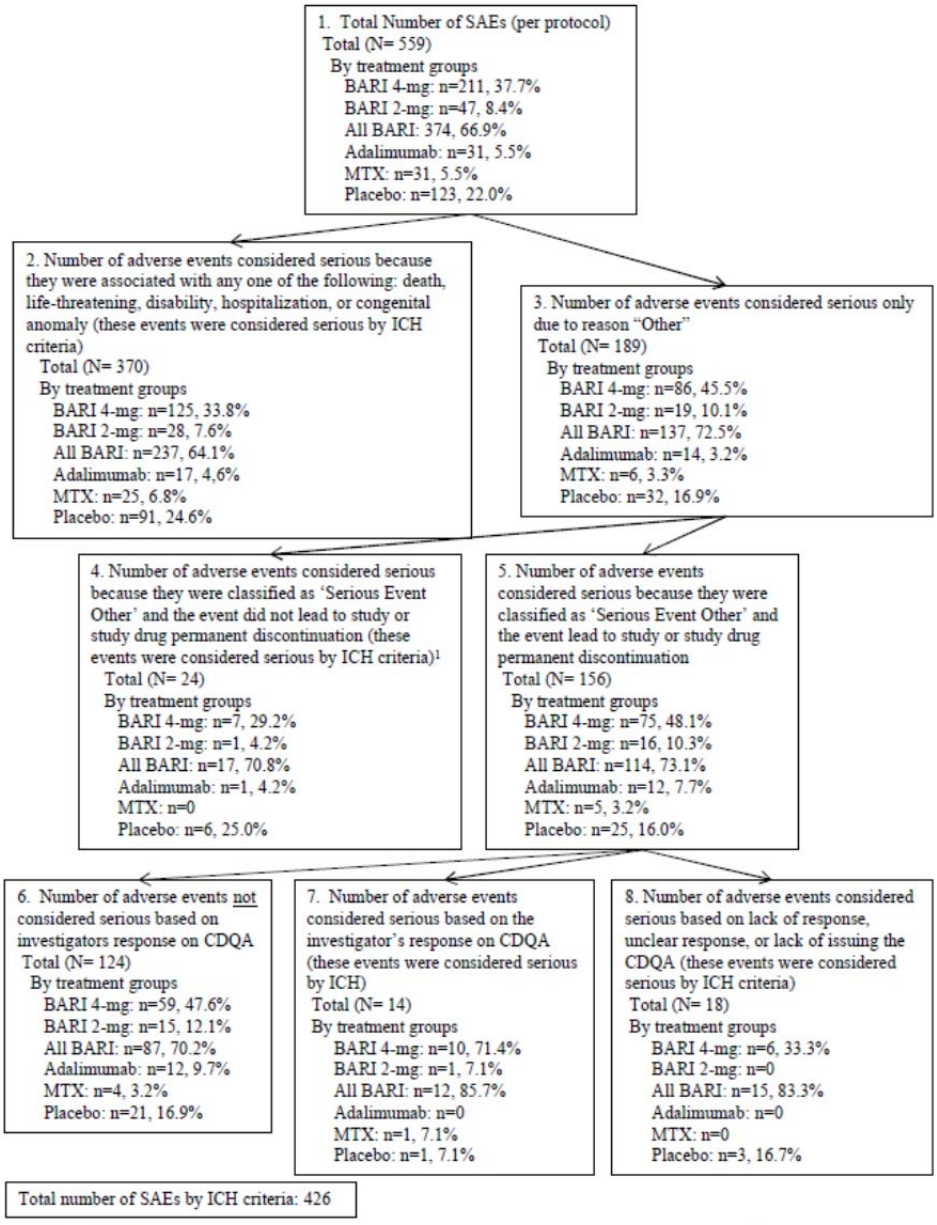
In studies JADA, JADZ, JADV, JADX, and JADW, Lilly included two definitions of serious adverse events (SAEs): 'per protocol' and 'ICH.' On the case report form for all SAEs, the investigator identified the reason for the SAE as: *Serious Event Death, Serious Event Life-threatening, Serious Event Disability, Serious Event Hospitalization, Serious Event Congenital Anomaly, and Serious Event Other.* More than one reason could be chosen. The 'per protocol' definition of SAEs included an AE that required permanent discontinuation from study drug. The 'ICH' SAEs were a subset of the 'per protocol' SAEs. If the reason for serious was 'Serious Event Other' and the event did not lead to study or study drug permanent discontinuation, the SAE was serious according to the 'ICH' definition. If the only reason for serious was 'Serious Event Other' and the event lead to study or study drug permanent discontinuation, a clinical data question and answer form (CDQA) was issued to the site with the following request for information: "In your opinion was AE#X serious by conventional GCP criteria, or designated serious only due to the protocol requirement that events leading to discontinuation be reported as SAEs? Respond 'Yes' if serious by GCP. 'No' if not serious by GCP." Events with confirmation from the study site as 'no' were designated 'protocol-defined SAEs.' Events with confirmation from the study site as 'yes', events with no response or unclear response from the study site, and events for which no CDQA was issued (applies to events in the Phase 2 Study JADA) were considered SAEs according to ICH criteria. This methodology of defining adverse events as serious is of concern because of the risk of potential misclassification of adverse events as serious or non-serious. Further, it was unclear if the employed methodology appropriately classified SAEs according to 21 CFR 312.32(a)[14]. Figure 10 provides a flow chart of the

[14] An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the

categorization of adverse events as serious according to the two definitions utilized. Lilly adjudicated all adverse events considered serious because they were classified as "Serious Event Other" and the event lead to study or study drug permanent discontinuation (boxes 6, 7, and 8 from Figure 10). Based on this adjudication, Lilly did not change the classification of any adverse events in box 6, but reclassified all adverse events in boxes 7 and 8 as not being serious due to ICH criteria (n=32). While 32 adverse events were reclassified, the conclusions from the data were similar (Table 15). Specifically, the incidence rate of serious adverse events was similar in the baricitinib groups and the placebo group.

ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Figure 10: Flow Chart of Serious Adverse Events in Studies Utilizing "Per Protocol" and "ICH" Definitions (Studies JADA, JADZ, JADV, JADX, and JADW)



Source: Figure 4.1, page 17, IR response, submitted 11/23/16

In the BARI 4mg and 2/4mg RA PC analysis sets, the most common SAEs (by SOC) were Infections and infestations, Musculoskeletal and connective tissue disorders, and Cardiac disorders. The proportion of patients with Infections and Infestations and Cardiac disorders was fairly balanced between placebo and baricitinib 4 mg. There were more patients in the placebo group (0.8%) with SAEs in the Musculoskeletal and connective tissue disorders SOC compared to baricitinib 4 mg (0.2%). During the first 16 weeks for the BARI 4mg RA PC analyses, the

most common SAEs (by preferred term) were herpes zoster, cellulitis, and coronary artery disease. The proportion of patients with herpes zoster (0.3% baricitinib 4 vs. 0.1% placebo) and coronary artery disease (0.2% baricitinib 4 vs. 0 placebo) were higher in the baricitinib 4mg group compared to placebo. The proportion of patients with cellulitis was the same in the two groups (0.2%). Infections and cardiovascular adverse events are discussed below.

When comparing the rate of SAEs in the baricitinib 2 mg and 4 mg groups between 0-52 and >52 weeks, the rate was slightly higher in baricitinib 4 mg compared to baricitinib 2 mg. The rate of SAEs remained fairly constant between 0-52 weeks and >52 weeks. In the >52 week analyses, there was a statistically significant difference in the incidence rate of SAEs for baricitinib 4 mg versus 2 mg, however there are limitations to these direct comparisons between the doses given the design of these studies.

Table 15: Analyses of SAEs (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY)

	Treatment as Randomized				Incidence rate difference (95% CI)	
# patients with ≥1	PBO	BARI 2/4	BARI 2	BARI 4	BARI 2/4 vs PBO	BARI 4 vs. 2
0-16 weeks						
N	1070	1476	479	997		
Total exposure, PY	308	438	140	298		
SAE, n (rate)	41 (13.3)	59 (13.5)	16 (11.4)	43 (14.4)	-0.02 (-5.5, 5.4)	6.1 (-2.8, 15.0)
Adjudication results						
SAE, n (rate)	40 (13.0)	53 (12.1)	16 (11.4)	37 (12.4)	-1.3 (-6.6, 4.0)	4.71 (-3.9, 13.4)
0-52 weeks					**BARI 4 vs PBO**	**BARI 4 vs. 2**
Total exposure, PY	406	1318	336	904		
SAE, n (rate)	54 (13.3)	164 (12.4)	40 (11.9)	113 (12.5)	-0.9 (-5.1, 3.4)	3.2 (-2.2, 8.6)
>52 weeks						
Total exposure, PY	--	1215	177	810		
SAE, n (rate)	--	123 (10.1)	12 (7.7)	75 (11.5)	--	6.37 (0.2, 12.6)*

Rate per 100 PY
Abbreviations: PBO=placebo; BARI=baricitinib; SAE=serious adverse events; PY=patient years; CI=confidence interval
*The 95% CI excludes 0 and is considered statistically significant
0-16 weeks: Studies JADA, JADC, JADN, JADV, JADW, and JADX
0-52 and > 52 weeks: Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY
Source: 0-16 weeks: Table 4.2, page 11, IR response dated 10/28/16; Adjudication results: Table 4.1, page 9, IR response, submitted 11/23/16
0-52 weeks: Method 1: Table 4.10, page 69, Table 4.17, page 78, IR response, submitted 7/21/16
>52 weeks Method 1: Table 4.18, page 82, IR response, submitted 7/21/16

Discontinuations due to Adverse Events

The incidence rate of patients discontinuing due to an adverse event during 0-16 weeks was higher in the baricitinib 4 mg and 2 mg treatment groups compared to the placebo group (Table 16). In the phase 2 and phase 3 RA studies up to week 16, infections and infestations were the most common reason for discontinuation (1.6% for baricitinib 4 mg versus 0.6% for placebo). The second most common reason for discontinuation was investigations, primarily related to laboratory abnormalities. Certain laboratory parameters were pre-specified to trigger discontinuation. Adverse events related to infections and laboratory abnormalities are discussed in further detail in separate sections.

In the phase 2 and phase 3 RA studies up to week 16, the incidence rate per 100 patient years of patients with adverse events leading to permanent discontinuation was slightly higher in the

baricitinib 4 mg group (14.8) versus the 2 mg group (14). Similar trends were noted in the 0-52 week and >52 week data.

Table 16: Adverse Events Leading to Permanent Discontinuation (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY)

	Treatment as Randomized				Incidence rate difference (95% CI)	
	PBO	BARI 2/4	BARI 2	BARI 4	BARI 2/4 vs PBO	BARI 4 vs. 2
0-16 weeks						
Total exposure, PY	308	438	140	298		
Discontinuations, n (rate)	35 (11.6)	61 (14.5)	19 (14.0)	42 (14.8)	2.36 (-2.9, 7.6)	5.5 (-4.4, 15.3)
0-52 weeks						
Total exposure, PY	406	1318	336	997		
Discontinuations, n (rate)	42 (10.3)	130 (9.9)	31 (9.2)	91 (10.1)	-0.76 (-4.4, 2.9)	2.10 (-2.5, 6.7)
>52 weeks						
Total exposure, PY	--	1214	177	810		
Discontinuations, n (rate)	--	43 (3.5)	4 (2.6)	26 (4)	--	2.1 (-0.7, 6.4)

Rate per 100 PY
Abbreviations: PBO=placebo; BARI=baricitinib; PY=patient years; CI=confidence interval
0-16 weeks: Studies JADA, JADC, JADN, JADV, JADW, and JADX
0-52 and > 52 weeks: Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY
Source: 0-16 weeks: Table 4.4, page 22, IR response, submitted 11/23/16
0-52 weeks Method 1: Table 4.17, page 79, IR response, submitted 7/21/16
>52 weeks Method 1: Table 4.18, page 83, IR response, submitted 7/21/16

Common AE

Adverse events in the infections and infestations SOC were the most common adverse events in the RA phase 2 and 3 studies. In the first 16 weeks of the phase 2 and 3 studies, the incidence rate per 100 patient years of patients with at least one adverse event was higher in the baricitinib groups than the placebo group, but was fairly balanced between the 2 mg and 4 mg groups (Table 17). During the first 16 weeks, approximately 30% of the baricitinib 4 mg groups experienced an infectious event, compared to 24% of the placebo group. The most common infections were upper respiratory tract infection, nasopharyngitis, and urinary tract infection. Gastrointestinal (GI) disorders were next most common, occurring in 16% of the baricitinib groups and 12% of the placebo group. The most common GI disorders were nausea, diarrhea, and vomiting. Infections remained the most common adverse events over time, with increasing exposure.

Table 17: Summary of Common Adverse Events in the RA trials

	Treatment as Randomized				Incidence rate difference (95% CI)	
	PBO	BARI 2/4	BARI 2	BARI 4	BARI 2/4 vs PBO	BARI 4 vs. 2
0-16 weeks						
Total exposure, PY	308	1476	479	997		
# TEAE, n (rate)	1405 (456)	2406 (549.3)	798 (568.3)	1608 (540.1)	68.5 (35.7, 101.3)	55.5 (-1.7, 112.7)
Patients with ≥1 TEAE, n (rate)	613 (316.6)	931 (361.1)	294 (362.9)	637 (360)	32 (-2.7, 66.7)	46.6 (-14.8, 108)
Most common SOC, n (%)						
Infections and infestations	253 (24)	436 (30)	138 (29)	298 (30)	--	--
Gastrointestinal disorders	128 (12)	230 (16)	85 (18)	145 (15)	--	--
Musculoskeletal disorders	125 (12)	151 (10)	56 (12)	95 (10)	--	--
Ext BARI 2 mg vs 4 mg						
Total exposure, PY	--	913	435	478	--	--
Patients with ≥1 TEAE, n (rate)	--	776 (85)	370 (85)	406 (85)	--	--

Rate per 100 PY
Abbreviations: PBO=placebo; BARI=baricitinib; PY=patient years; CI=confidence interval
Source: 0-16 weeks Table 4.5, page 28-75, IR response, submitted 11/23/16 (BAR 2 mg/4mg RA PC analysis set, studies JADA, JADC, JADV, JADW, and JADX)
Ext BARI 2 mg vs. 4 mg: Clin Safety Sum App 1, Table APP1.2.7.4.50, page 708, submitted 1/15/16

Laboratory Abnormalities

Hematologic abnormalities

Myelosuppression has been reported to varying degrees with other marketed JAK inhibitors, ruxolitinib and tofacitinib. Baricitinib treatment was associated with changes in certain hematologic, hepatobiliary, serum chemistry (creatinine and creatine phosphokinase), and lipid parameters.

Hematologic abnormalities

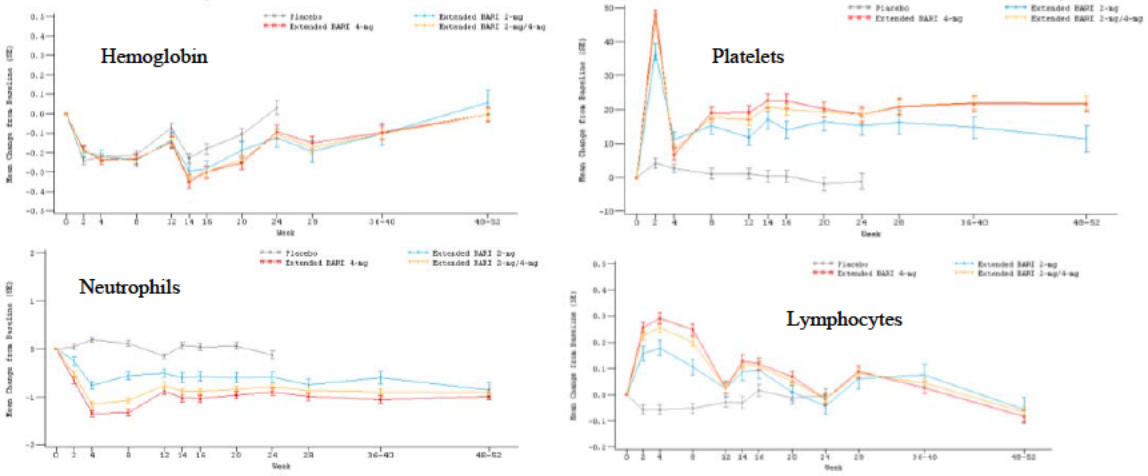
Table 18 and Figure 11 summarize the mean changes in hematologic parameters.

Table 18: Hemoglobin, Platelets, Leukocyte Count, Neutrophils, and Lymphocytes at Baseline and Change from Baseline

	PBO	BARI 2	BARI 4	BARI 2/4
Hemoglobin (g/dL)				
Baseline	12.66	12.58	12.68	12.65
Change from baseline at Week 12	-0.07	-0.14	-0.15	-0.14
Platelets (10^9/L)				
Baseline	289	285	293	290
Change from baseline at Week 12	1	12	19	17
Leukocyte count (thousand cells/uL)				
Baseline	8.18	8.25	8.40	8.35
Change from baseline at Week 12	-0.15	-0.56	-0.89	-0.79
Neutrophils (thousand cells/uL)				
Baseline	5.82	5.76	6.01	5.93
Change from baseline at Week 12	-0.15	-0.51	-0.89	-0.76
Lymphocytes (thousand cells/uL)				
Baseline	1.82	1.87	1.84	1.85
Change from baseline at Week 12	-0.03	0.02	0.03	0.03

Abbreviations: PBO=placebo; BARI=baricitinib
Ext BARI 2-mg/4-mg RA PC Dataset (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY and JADW/JADY)
Source: Table 5.16, pages 267-311, IR response, received July 21, 2016

Figure 11: Mean Change from Baseline Over 52 Weeks for hematologic parameters--Ext BARI 2-mg/4-mg RA Placebo-Controlled Dataset (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY and JADW/JADY)



Source: IR response, Figure 4.9, page 104-8, received July 21, 2016

Hemoglobin

A drop in hemoglobin is seen during the first 2 weeks of the study and at Weeks 12-16 for both placebo and baricitinib. At Week 12, baricitinib was associated with slightly greater decreases in hemoglobin than placebo. There is a gradual rise in hemoglobin to baseline or exceeding baseline after these initial drops, which could be related to control of inflammation. The proportion of patients with treatment-emergent abnormal low hemoglobin occurring at any time up to Week 16 was higher in baricitinib (27%) than placebo (25%) and slightly higher with baricitinib 4 mg (26%) than baricitinib 2 mg (25%). Treatment-emergent CTCAE ≥3 hemoglobin values or permanent discontinuations due to anemia were uncommon and occurred in patients who were anemic at baseline and/or who developed a possible or known source of

bleeding. The proposed labeling recommends interrupting baricitinib in patients that develop hemoglobin <8gm/dL.

Platelets

Administration of baricitinib was associated with an increase in platelet count which peaked about 2 weeks after starting treatment (mean increase approximately $50x10^9$/L) and then returned towards baseline and remained stable and increased from baseline (mean increase approximately $20x10^9$/L). In contrast to baricitinib, other approved JAK inhibitors (tofacitinib and ruxolitinib) are associated with decreases in platelet counts. Increases in platelet counts were greater on baricitinib 4 mg compared to baricitinib 2 mg. The proportion of patients experiencing a treatment-emergent shift from ≤600 to $>600x10^9$/L was higher for baricitinib 4-mg (2%) compared to placebo (1%), baricitinib 2 mg (1%), and adalimumab (0.9%). There were 41 patients with platelet counts $>700x10^9$ cells/L, but these were felt to be secondary or reactive thrombocytosis due to a variety of causes. In the All BARI RA analysis set, 4 patients with treatment-emergent thrombocytosis (increase platelet count from ≤600 x 10^9 cells/L to >600 x 10^9 cells/L) reported a predefined "thromboembolic event." These events included a mild DVT that was not treated, left brachial artery thrombosis that occurred 25 days after the date of last dose of baricitinib, mild peripheral vascular disorder, and cerebrovascular accident (found to have a malignancy 1 month later). Thus, there was no clear relationship between platelet elevations and thrombosis. While the exact etiology of this increase in platelet count is unknown, Lilly notes that modulation of JAK activity in the vascular endothelium due to inhibition of erythropoietin signaling may decrease the attraction of the endothelium for platelets, thus decreasing the removal of platelets from the circulation. Further, a nonclinical model involving conditional knockout of JAK2 suggests that a primary function of JAK2 in megakaryocytes and platelets could be to couple surface expression of the thrombopoietin (TPO) receptor Mpl with clearance of circulating TPO, thereby reducing the level of TPO and modulating ligand availability to promote increased platelet formation. Therefore, in the absence of JAK2 there may be an increase in levels of TPO, hence promoting an increase in platelet number. It is recommended that the labeling note the anticipated increase in platelet count with baricitinib exposure.

Leukocytes

Overall, administration of baricitinib was associated with a slight decrease in leukocyte counts, which is composed of slight increases in mean lymphocyte counts and decreases in neutrophil counts.

Lymphocytes

Administration of baricitinib was associated with an increase in mean lymphocyte counts within 1 week of starting treatment which then declined to baseline by 12-24 weeks. The mean increase was higher in the 4 mg group than the 2 mg group. Discontinuation of baricitinib due to a TEAE of lymphopenia was uncommon (6 patients in the All BARI RA analysis set, 0.2%). All patients who discontinued due to a TEAE of lymphopenia had abnormally low lymphocyte counts at baseline and counts returned to baseline in almost all patients. In the BARI 4 mg analysis set, Grade ≥1 lymphopenia was more common in placebo (32%) than baricitinib 4 mg (28%). In the BARI 4 mg PC dataset, the proportion of patients with a serious infection was higher for those with an absolute lymphocytes count (ALC) <LLN compared to those with an ALC≥LLN for

baricitinib 2mg/4mg (1.8% vs. 1.1%), but not placebo (0.7% vs. 1.4%). The proportion of patients with an infection was higher for those with ALC<LLN compared to those with an ALC ≥LLN for baricitinib 2mg/4mg (33% vs. 29%) and placebo (25% vs. 24%).

The proposed labeling does not restrict initiation of baricitinib based on baseline lymphocyte count, but does include dose interruption for ALC of $<500x10^9$/L.

Neutrophils

Administration of baricitinib was associated with a decrease in mean neutrophil counts within 1 month of starting treatment, which then remained stable. In the BARI 4mg PC analysis set, the proportion of patients with any abnormally low neutrophil count was higher with baricitinib 4 mg (8.3%) compared to placebo (2.7%). Similarly, the proportion of patients with any abnormally low neutrophil count was higher for baricitinib 4 mg (7.5%) compared to 2 mg (6.5%). CTCAE Grade ≥1 values and absolute neutrophil counts less than the lower limit of normal did not appear to be associated with a higher risk of treatment-emergent infections or serious infections. The proposed labeling includes dose interruption instructions for patients with ANC of $<1x10^9$/L. Three patients developed grade 4 neutropenia (ANC<500/mm^3). One of these patients may have had a laboratory error and one developed large granular lymphocytosis.

Hepatic enzyme abnormalities

Baricitinib was associated with small elevations in ALT, AST, and total bilirubin (Table 19). Of patients with normal ALT at baseline, a similar proportion of patients in each treatment group experienced at least one post-baseline ALT value ≥3x ULN, ≥5x ULN or ≥10x ULN. For ALT measurements in JADZ, there were fewer patients in BARI 4mg monotherapy compared to MTX monotherapy who had normal measurements at baseline and were abnormal at the last measured value.

There were 10 cases with an ALT or AST ≥10 x ULN. Five cases occurred on baricitinib and 3 cases occurred following discontinuation of baricitinib. Four of these cases were considered unlikely to be related to baricitinib while 4 were considered possibly related to baricitinib since other causes could not fully explain the elevations. Four of the patients were receiving MTX at the time of the elevation and all 8 cases had other confounders present.

No cases meeting Hy's law criteria (evidence of hepatocellular injury by any elevated aminotransferase >3xULN, evidence of liver dysfunction by increase in bilirubin ≥2xULN and without evidence of cholestasis by ALP <2xULN, and no other cause such as viral hepatitis A, B, or C; preexisting or acute liver disease, or another drug capable of causing the observed liver injury) were reported in patients receiving baricitinib.

Table 19: AST, ALT, and Total Bilirubin Levels at Baseline and Change from Baseline

	PBO	BARI 2	BARI 4	BARI 2/4
ALT (IU/L)				
Baseline	21.1	21.	20.3	20.5
Change from baseline at week 12	0.3	1.7	4.4	3.5
AST (IU/L)				
Baseline	20.7	21.8	20.4	20.8
Change from baseline at week 12	0.4	1.3	4.6	3.6
Total bilirubin (mg/dL)				
Baseline	0.326	0.283	0.304	0.298
Change from baseline at week 12	-0.004	0.017	0.041	0.034

Abbreviations: PBO=placebo; BARI=baricitinib
Ext BARI 2-mg/4-mg RA PC Dataset (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY and JADW/JADY)
Source: IR response, Table 5.16, pages 219-245, received July 21, 2016

Serum creatinine/renal function

Baricitinib was associated with small (<0.1 mg/dL) dose-dependent elevations of serum creatinine. The magnitude of the increase was slightly greater for baricitinib 4 mg compared to 2 mg. However, the mean and median creatinine values remained within the normal range throughout the treatment period. Treatment-emergent CTCAE Grade increases in creatinine from <1 to ≥ and from <3 to ≥3 were uncommon (2.4% and 0.2%, respectively). There was no increased risk of serious renal-related adverse events with longer baricitinib exposure.

Lipid abnormalities

Baricitinib was associated with dose-dependent increases in total, LDL, and HDL cholesterol within 12 weeks (the first time the lipids levels were checked post-dose) of treatment and then generally plateaued. The mean and percentage change in triglycerides, HDL, and LDL cholesterol are provided in Table 20. Internal consultation for the Division of Metabolic and Endocrine Products (DMEP) was obtained regarding the implications of these lipid parameter changes. DMEP consultants were of the opinion that it is difficult to predict the net effect of baricitinib on cardiovascular risk in patients with RA. It was noted that there is a complex interplay of inflammation with lipid levels and CV risk in patients with RA. Additional discussion of cardiovascular outcomes is provided below.

Table 20: Triglyceride, LDL, and HDL Levels at Baseline and Change from Baseline

	PBO	BARI 2	BARI 4	BARI 2/4
Triglycerides (mg/dL)				
Baseline	127	128	125	126
Change from baseline at Week 12	-1	5	17	13
% change from bassline at Week 12	3.8%	8.9%	15.7%	13.6%
LDL Cholesterol-Direct (mg/dL)				
Baseline	119	116	117	116
Change from baseline at Week 12	-1	8	14	12
% change from bassline at Week 12	0.4%	8.2%	14.4%	12.5%
HDL Cholesterol-Direct (mg/dL)				
Baseline	60.2	59.8	60.5	60.3
Change from baseline at Week 12	0.2	6.5	8.9	8.2
% change from bassline at Week 12	1.1%	11.3%	15.8%	14.4%

Abbreviations: PBO=placebo; BARI=baricitinib
Ext BARI 2-mg/4-mg RA PC Dataset (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY and JADW/JADY)
Source: IR response, Table 5.16, pages 258-264, received July 21, 2016

Serum creatinine phosphokinase (CPK)

Baricitinib was associated with dose-dependent increases in CPK. The mean change from baseline to week 12 was approximately 50 IU/L. The rapid increase in CPK occurred within 1 week of starting baricitinib treatment and plateaued after approximately 8 to 12 weeks. These changes did not appear to be associated with an increased risk of myopathic adverse events.

- **Immunogenicity**

As an orally administered small molecule, baricitinib is not expected to be associated with immunogenicity.

- **Special safety concerns**

Malignancy

There were 34 events of malignancy in the RA phase 2 and phase 3 studies. Of the 34 events, 31 occurred in patients on baricitinib (incidence rate/100 patient years 0.7). Table 21 contains a summary of malignancies during the controlled period and extension study of studies JADA/JADY, JADC, JADN, JADV/JADY, JADW/JADY, and JADX/JADY. During the controlled period, the exposure adjusted incidence rate of malignancy was low in each treatment arm. Specifically, during the first 16 weeks, the exposure adjusted incidence of malignancy was similar in the 2 mg (0.7/100 patient years) and 4 mg (0.3/100 patient years) baricitinib groups, but higher than the placebo group (0). Similar trends were noted in the 0-52 week period. Given the number of events observed, we have limited ability to rule out increases in risk based on currently available data.

Overall, the types of malignancies observed followed the pattern of malignancies that would generally be expected in the underlying patient population, with certain exceptions, such as malignant fibrous histiocytoma and chondrosarcoma. Three cases of lymphoma were reported. One case was diagnosed as MALT lymphoma. An additional case of T-cell lymphoma and diffuse large B-cell lymphoma was reported.

Table 21: Adverse Events Related to Malignancy excluding NMSC (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY)

	Treatment as Randomized				Incidence rate difference (95% CI)	
	PBO	BARI 2/4	BARI 2	BARI 4	BARI 4 vs. PBO	BARI 4 vs. 2
0-16 weeks						
N	1070	1476	479	997		
Total exposure, PY	308	438	140	298		
# pts with ≥1 malignancy, n (rate)	0	2 (0.5)	1 (0.7)	1 (0.3)	0.33 (-0.32, 0.98)	-0.73 (-2.15, 0.70)
0-52 weeks						
Method 1						
Total exposure, PY	406	1318	336	904		
# pts with ≥1 malignancy, n (rate)	2 (0.5)	8 (0.6)	2 (0.6)	6 (0.7)	0.18 (-0.70, 1.05)	0.01 (-1.12, 1.13)
Method 2						
Total exposure, PY	406	2086	336	1671		
# pts with ≥1 malignancy, n (rate)	2 (0.5)	14 (0.7)	2 (0.6)	12 (0.7)	0.21 (-0.59, 1.01)	0.11 (-0.92, 1.14)
>52 weeks						
Total exposure, PY	--	1215	155	653		
# pts with ≥1 malignancy, n (rate)	--	9 (0.7)	0	4 (0.6)	--	1.07 (-0.15, 2.3)

Abbreviations: PBO=placebo; BARI=baricitinib; PY=patient years; CI=confidence interval
0-16 weeks: Studies JADA, JADC, JADN, JADV, JADW, and JADX
0-52 and > 52 weeks: Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY
Source:
0-16 weeks, Table 4.2, page 13, IR response, submitted 10/28/16
0-52 weeks and >52 weeks: Method 1: Table 5.8, page 209 and Table 4.13, page 72, IR response submitted 7/21/16

Figure 12 displays the incidence rate of malignancies other than NMSC by 24-week time period for all baricitinib RA patients. In general, the incidence rate of malignancies remained fairly constant over time, however the confidence interval did widen over time.

Figure 12: Malignancy excluding NMSC by time period of report in RA patients

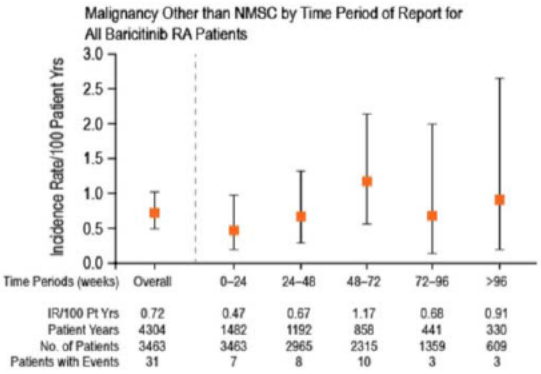


Figure 2.7.4.11. Malignancy excluding NMSC by time period of report in RA.

Source: Clinical Summary of Safety, Figure 2.4.4.11, page 178, submitted 1/15/16

Infections

There was a statistically significant larger proportion of patients with treatment-emergent infections and infections on baricitinib 4 mg compared to placebo through 24 weeks of

treatment. The higher incidence in baricitinib 4 mg was predominantly due to a higher incidence of upper respiratory tract infections, herpes zoster and herpes simplex infections. Similarly, there was a higher proportion of patients with adverse events related to infections that led to permanent discontinuation from study drug (1.6% baricitinib 4 mg vs. 0.5% placebo) and a higher proportion of patients with infections requiring antibiotic treatment with baricitinib. In JADV with treatment through 52 weeks with data up to rescue, more patients in baricitinib 4 mg compared to adalimumab experienced a TEAE of infection: 47.8% [EAIR 54.10] compared to 43.9% [EAIR 52.74], respectively.

Infections leading to death

There were 22 deaths in the phase 2/3 RA program, of which 5 were related to infections. Of the five deaths, two patients were on placebo (two cases of pneumonia), one patient was on adalimumab (infective arthritis), and two patients were on baricitinib ≥4 mg (pneumonia, abdominal infection).

Serious infections

Table 22 provides a summary of serious adverse events related to infection. See the discussion of serious adverse events regarding the adjudication results. During the first 12-16 weeks, the proportion of patients with serious infections was either balanced between the placebo and baricitinib groups (BARI 4 mg RA PC) or slightly higher in the baricitinib groups compared to placebo (BARI 2 mg vs 4 mg) depending on which data set was evaluated. In BARI 4mg RA PC dataset, the most common serious infections were herpes zoster (0.3% bari 4 mg vs 0.1% placebo), cellulitis (0.2% bari 4 mg vs. 0.1% placebo), and bacterial infection (0.1% bari 4 mg vs. 0 placebo). Table 22 shows that the proportion of patients with serious infections was slightly higher in the 2 mg than the 4 mg group between 0-52 weeks and then higher in the 4 mg than the 2 mg group after 52 weeks. One issue of note, is that the rate of infections in the placebo group is higher than other recent RA programs. While there are limitations to cross-study comparisons, this observation does stand out.

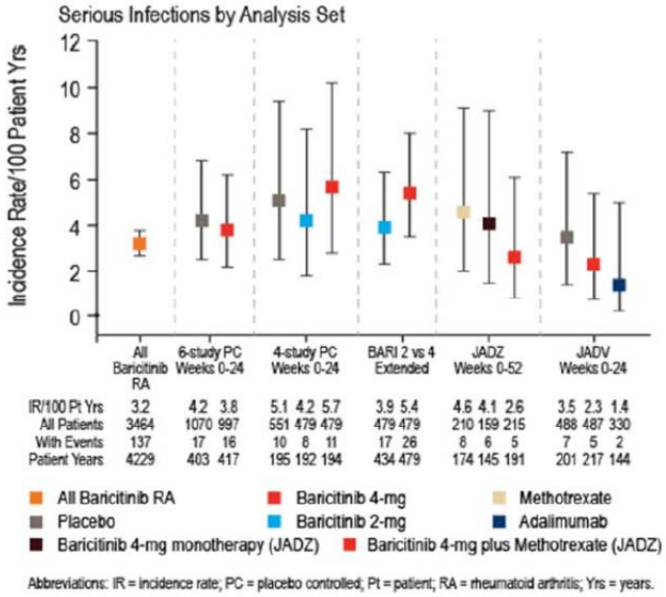
Table 22: Adverse Events Related to Serious Infections (Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY)

	Treatment as Randomized				Incidence rate difference (95% CI)	
	PBO	BARI 2/4	BARI 2	BARI 4	BARI 2/4 vs. PBO	BARI 4 vs. 2
0-16 weeks						
N	1070	1476	479	997		
Total exposure, PY	308	438	140	298		
# patients with ≥1 serious infection, n (rate)	13 (4.2)	18 (4.1)	6 (4.3)	12 (4.1)	-0.39 (-3.47, 2.70)	1.32 (-3.92, 6.57)
# serious infection, n (rate)	13 (4.2)	23 (5.3)	7 (5)	16 (5.4)	0.64 (-2.56, 3.84)	2.74 (-3.17, 8.65)
Adjudication results						
# patients with ≥1 serious infection, n (rate)	12 (3.9)	16 (3.7)	6 (4.3)	10 (3.4)	-0.47 (-3.39, 2.44)	0.62 (-4.44, 5.69)
0-52 weeks					**BARI 4 vs. PBO**	**BARI 4 vs. 2**
Total exposure, PY	405.8	1318	335.6	903.6		
# serious infections, n Rate per 100 PY	18 (4.4)	59 (4.5)	15 (4.5)	39 (4.3)	--	--
# patients with ≥1 serious infection, n (rate)	17 (4.2)	50 (3.8)	14 (4.2)	32 (3.5)	-0.69 (-3.03, 1.66)	0.65 (-2.43, 3.72)
# patients with opportunistic infection, n (rate)	0	3 (0.2)	0	3 (0.2)		
>52 weeks						
Total exposure, PY	--	1215	155	653		
# patients with ≥1 serious infection, n (rate)	--	35 (2.9)	4 (2.6)	20 (3.1)	--	1.28 (-2.20, 4.75)

Rate per 100 PY
Abbreviations: PBO=placebo; BARI=baricitinib; PY=patient years; CI=confidence interval
0-16 weeks: Studies JADA, JADC, JADN, JADV, JADW, and JADX
0-52 and > 52 weeks: Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY
Source: 0-16 weeks: Table 4.2, page 12, IR response, submitted 10/28/16; Adjudication results: Table 4.1, page 9, IR response, submitted 11/23/16
0-52 weeks and >52 weeks Method 1: Table 5.6, page 201 and Table 4.12, page 71, Table 5.14, page 217, IR response submitted 7/21/16

The incidence rate of serious infections by analysis set is displayed in Figure 13. A notable observation is that in JADV more patients in baricitinib 4 mg (n=10, 2.1%) had ≥1 serious infection compared to adalimumab (n=5, 1.5%), but that the incidence rate of infections was actually higher in the placebo group than either the baricitinib group or adalimumab group. This observation is unexpected given that adalimumab is an immunosuppressant and has a boxed warning for infections. While there is some variability in the rates of serious infection, no dramatic differences were identified in the different datasets.

Figure 13: Incidence Rate of Serious Infections by Analysis Set for All BARI RA patients



Source: Figure 2.7.4.6, page 153, Clinical Summary of Safety, submitted 1/15/16

Opportunistic Infections

In the overall RA program, 10 potential opportunistic infections were identified oesophageal candidiasis (5 events), pneumocystis pneumonia (3 events), wound infection with coccidioides species (1 event), and blood beta-D-glucan increased (1 event). Lilly provided a review of each case. For the cases of esophageal candidiasis, Lilly states that none are considered to represent an opportunistic infection with baricitinib for a variety of reasons, such as negative cultures or lack of confirmation on biopsy. However, at least 2 patients were diagnosed by endoscopy and several patients improved with antifungal therapy.

For the cases of pneumocystis pneumonia, Lilly states that none were considered to be confirmed. However, all patients received treatment with sulfamethoxazole/trimethoprim and steroids. In addition, one patient required hospitalization, had sputum that tested positive for pneumocystis by PCR, and had ground glass opacity and interstitial changes on CT scan. Another patient required hospitalization for dyspnea, had an abnormal CT scan with ground-glass findings, and an elevated beta-D-glucan local laboratory value. The sponsor concludes that "it is difficult to affirm both the diagnosis of pneumocystis pneumonia and a role of baricitinib in these cases" (page 158 Clinical Summary of Safety) given potential contributing factors, such as concomitant methotrexate treatment, the possibility of false positive beta-D-glucan assays, and the absence of confirmation of the diagnosis of pneumocystis pneumonia. However, several aspects of at least 2 cases are highly suggestive of pneumocystis pneumonia. In terms of the wound infection with coccidioides, this appeared to be a reporting error by the investigator.

During the review, FDA informed Lilly that they disagreed with discounting cases reported as opportunistic infections. Also, FDA identified additional cases of opportunistic infections that had not initially been reported as such by Lilly, including a case of histoplasmosis,

Cryptococcus, paracoccidoides, and two candida infections (lung infection and muscle abscess). Information requests were required during the review cycle to clarify and better understand these important safety issues.

There were 8 patients in the phase 1, 2, and 3 safety database who developed tuberculosis. All the events occurred in patients with RA and 7 of the 8 events occurred in patients on baricitinib (all 4 mg once daily) and 1 of the 8 events occurred in a patient on adalimumab. There were two cases of disseminated tuberculosis (1 baricitinib and 1 adalimumab). There were two cases of bone tuberculosis (both on baricitinib). All events on baricitinib occurred in patients randomized to the 4 mg dose.

The number and pattern of opportunistic infections observed with baricitinib treatment suggests significant immunosuppression that is apparent with both doses, although somewhat higher with the 4 mg dose.

Herpes Zoster

Herpes zoster events occurred more frequently in the baricitinib groups compared to the control groups. In the Bari 4mg RA PC analysis set, 1.8% of patients treated with baricitinib developed herpes zoster compared to 0.4% of patients on placebo. There were 141 cases in 3,464 patients in the All BARI RA group. Of the 141 cases, 5 were complicated or disseminated events (nerve palsy or dissemination beyond the primary or adjacent dermatomes).

Gastrointestinal perforations

Gastrointestinal perforations are included in the Warnings and Precautions Section of the tocilizumab and tofacitinib labels. Therefore, gastrointestinal perforations were an adverse event of special interest. In the All BARI RA and All BARI analysis sets 6 events of possible GI perforations were reported, of which 2 appeared to represent confirmed or probable GI perforations, while the other 4 cases were abscesses. Both patients with confirmed GI perfections were receiving concomitant glucocorticoids and NSAIDs. The occurrence of a few rare and serious events in the clinical program supports describing this safety consideration in the Warnings and Precaution section of the labeling.

Cardiovascular Adverse Events

For the phase 3 studies, an independent, external Clinical Endpoint Committee (CEC) was established to adjudicate potential cardiovascular adverse events. The CEC review remained blinded to treatment assignments and assessed each potential event individually.

Positively adjudicated cardiovascular events were categorized as either (1) MACE: cardiovascular death, MI, or stroke or (2) Other cardiovascular event: hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, or coronary revascularizations.

In general, the majority of patients were aged 30 to 74 years with no prior CVD and had a baseline score of either low risk or intermediate risk in studies JADZ, JADV, JADX, and JADW. Less than 10% of patients were considered high risk by Framingham risk score at baseline.

The few MACE events that were observed during the trials (Table 23) occurred at similar rates in baricitinib treatment groups (0.5/100 patient-years in the 4 mg and placebo groups and 0 in the 2 mg group). Importantly, the exposure-adjusted rates from the long-term safety study remained consistent with the rates observed during the controlled periods of the phase 3 studies.

Table 23: Adverse Events Related to Adjudicated MACE (Studies JADV/JADY, JADX/JADY, and JADW/JADY)

	Treatment as Randomized				Incidence rate difference (95% CI)	
	PBO	BARI 2/4	BARI 2	BARI 4	BARI 4 vs. PBO	BARI 4 vs. 2
0-16 weeks						
N	892	1294	403	891		
Total exposure, PY	267	396	123	273		
# pts with ≥1 MACE, n (rate)	2 (0.8)	2 (0.5)	0	2 (0.7)	-0.02 (-1.47, 1.42)	1.59 (-0.61, 3.79)
0-52 weeks						
Total exposure, PY	365	1189	305	825		
# patients with ≥1 MACE, n (rate)	2 (0.6)	5 (0.4)	1 (0.3)	4 (0.5)	-0.06 (-0.95, 0.82)	0.18 (-0.81, 1.16)
>52 weeks						
Total exposure, PY	--	1092	155	575		
# patients with ≥1 MACE, n (rate)	--	7 (0.6)	0	4 (0.7)	--	0.98 (-0.14, 2.09)

Rate per 100 PY
Abbreviations: PBO=placebo; BARI=baricitinib; PY=patient years; CI=confidence interval
Data are only shown for phase 3 trials that included an adjudication committee
Source: 0-16 weeks (studies JADV, JADW, JADX): Table 4.3, page 20, IR response, submitted 11/23/16
0-52 weeks and >52 weeks (studies JADV/JADY, JADX/JADY, and JADW/JADY)
Method 1: Table 5.10, page 212 and Table 4.14, page 73, IR response submitted 7/21/16

Thrombosis

During the 16 week controlled period of studies JADA, JADC, JADN, JADV, JADW, and JADX, the incidence rate per 100 patient years of thrombotic events was higher in the baricitinib groups (1.83) compared to the placebo group (0.32). This imbalance was secondary to imbalances in both venous and arterial thrombotic events (Table 24). There were more patients with thrombotic events in the 4 mg group than the 2 mg group, suggesting a dose response. Similar imbalances were seen between 0-52 weeks, and the incidence rate difference between placebo and baricitinib was statistically significantly different. During the first 52 weeks, there were 5 DVTs and 4 PEs in the Bari 2/4 mg group compared to 0 in the placebo group. After 52 weeks, there were an additional 4 DVTs and 5 PEs in the BARI 2/4 mg group. The events occurred throughout the 52 week period. On average, patients treated with baricitinib experienced increases in platelet counts and there did not appear to be a relationship between more marked platelet count elevations and thromboses. For all RA patients exposed to baricitinib, a total of 20 RA patients reported a treatment-emergent DVT/PE event while being treated with baricitinib or during post-treatment follow-up, of which 11 events were DVTs (7 SAEs) and 11 events were PEs (10 SAEs), with a total of 15 serious cases. The incidence rate of DVT/PE in the All Bari RA population was 0.46 per 100 PYE. Of note, 2 of the baricitinib-

treated patients reported both DVT and PE. There were no events in the placebo group and 1 event in the methotrexate monotherapy group.

The Division of Hematology Products (DHP) was consulted to given an impression of the increase in rate of thrombotic events. DHP noted the statistically significant increase in the rate of venous thromboembolisms in the baricitinib 4 mg group compared to placebo. Further, it was noted that the risk appears dose dependent. However, from a hematology perspective, the clinical meaningfulness of these findings was unclear as the overall rate of venous thromboembolism was low (0.6%) in the 4 mg treatment group. It was felt that the significance of this safety risk should be evaluated by DPARP. DHP did not find any evidence that the increase in venous thromboembolism was a class effect of JAK1/2 inhibitor drugs.

Given the seriousness of thrombotic events and the need to raise awareness of this safety concern, the prescribing information will include data regarding the risk of thrombosis with baricitinib. Currently, there are ongoing discussions about the labeling, however it is recommended that thrombosis be included as a Warning and Precaution.

Table 24: Adverse Events Related to Thrombosis

	Treatment as Randomized				Incidence rate difference (95% CI)	
	PBO	BARI 2/4	BARI 2	BARI 4	BARI 2/4 vs. PBO	BARI 4 vs. 2
0-16 weeks						
N	1070	1476	479	997		
Total exposure, PY	308	438	140	298		
# pts with ≥1 thrombotic event, n (rate)	1 (0.3)	8 (1.8)	2 (1.4)	6 (2.0)	1.31 (-0.10, 2.71)	1.39 (-2.02, 4.80)
# pts with ≥1 venous thrombotic event, n (rate)	0	4 (0.9)	0	4 (1.4)	0.94 (0, 1.88)	1.44 (-0.55, 3.42)
# pts with ≥1 arterial thrombotic event, n (rate)	1 (0.3)	4 (0.9)	2 (1.4)	2 (0.7)	0.37 (-0.68, 1.42)	-0.04 (-2.81, 2.72)
0-52 weeks					**BARI 4 vs. PBO**	**BARI 4 vs. 2**
Total exposure, PY	405.8	1318	335	900		
# pts with ≥1 thrombotic event, n (rate)	2 (0.5)	15 (1.1)	5 (1.5)	9 (1)	0.67 (0.13, 1.22)*	0.01 (-1.12, 1.13)
# pts with ≥1 venous thrombotic event, n (rate)	0	9 (0.7)	2 (0.6)	6 (0.7)		
# pts with ≥1 arterial thrombotic event, n (rate)	2 (0.5)	6 (0.5)	3 (0.9)	3 (0.3)		
>52 weeks						
Total exposure, PY	--	900	1206	155		
# pts with ≥1 thrombotic event, n (rate)	--	14 (1.2)	1 (0.6)	10 (1.5)	--	0.85 (-1.02, 2.73)
# pts with ≥1 venous thrombotic event, n (rate)	--	8 (0.7)	1 (0.6)	6 (0.9)		
# pts with ≥1 arterial thrombotic event, n (rate)	--	7 (0.6)	0	5 (0.8)		

Rate per 100 PY
*95% CI excludes 0
Abbreviations: PBO=placebo; BARI=baricitinib; PY=patient years; CI=confidence interval
0-16 weeks: Studies JADA, JADC, JADN, JADV, JADW, and JADX
0-52 and > 52 weeks: Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY
Source:
0-16 weeks: Table 4.2, page 14, IR response, submitted 10/28/16
0-52 weeks and >52 weeks: Method 1: Table 4.3, page 16, IR response, submitted 10/28/16; Table 4.15, page 74, IR response, submitted 7/21/16

Comparison to Adalimumab

In JADV, Lilly compared baricitinib (4 mg), placebo, and adalimumab 40 mg SC every other week. JADV was a 52-week, phase 3, multicenter, randomized, double-blind, double-dummy, placebo and active controlled, parallel-group study in 1,370 patients. The study was placebo- and active-controlled through Week 24. Patients were eligible for rescue therapy beginning at Week 16 based on nonresponse. Nonresponse was defined as lack of improvement of at least 20% in both tender joint count and swollen joint count at both Week 14 and Week 16 compared to baseline. Placebo patients eligible for rescue therapy at Week 16 received baricitinib, while patients initially randomized to baricitinib continued baricitinib. After Week 16, rescue therapy was offered to patients at the discretion of the investigator. Between Week 24 and 52, patients assigned to baricitinib and adalimumab continued to receive their randomized therapy. Patients assigned to placebo were switched to baricitinib 4 mg at Week 24. All patients were on stable background MTX treatment.

The incidence rate (per 100 patient years) of death, serious adverse events, discontinuations secondary to adverse events, treatment emergent adverse events, MACE, deep vein thrombosis, and malignancy was higher in the baricitinib arm compared to the placebo arm between baseline and week 24 (Table 25). Further, the proportion of patients with infections was higher in the baricitinib group (36%) than the adalimumab group (33%). The most commonly occurring TEAE for all treatment groups were in the SOCs of infections and infestations and GI disorders and these events were more common with baricitinib than adalimumab. These trends were consistent during the study from weeks 24 to 52. From weeks 0 through 24 there were two deaths (pneumonia after positively adjudicated MACE event and hemorrhage in the setting of a duodenal ulcer), both in patients receiving baricitinib. Between weeks 24 and 52, there were 3 deaths (MI/cardiovascular death-baricitinib, infected knee complicated by respiratory failure-adalimumab and pneumonia-placebo).

Surprisingly, the proportion of patients with SAEs was higher in the placebo group than the baricitinib and adalimumab groups. This may have been secondary to 4 SAEs in the musculoskeletal system organ class (SOC) for the placebo group. When comparing the baricitinib and adalimumab groups, there were more SAEs and more SAEs related to infection with baricitinib than adalimumab. The most common SAEs were in the infections and infestations SOC.

More patients in the baricitinib group than the adalimumab group had an event leading to study drug discontinuation. The most common SOC was infections and infestations and a higher proportion of patients in the baricitinib group (1.8%) discontinued due to infections than the adalimumab group (1.2%).

There was only one positively adjudicated MACE event during the first 24 weeks. This event occurred in a patient on baricitinib. During the entire 52 week study, there were 2 events in patients randomized to baricitinib 4 mg (0.4%) and 1 event in a patient randomized to adalimumab (0.3%). While the number of malignancies was low during the 0-24 and 0-52 week periods, it was slightly higher for the baricitinib group than the adalimumab group.

Table 25: Overview of AEs in Study JADV from Weeks 0 to 24 (with data up to rescue)

Pts with ≥1 AE	Placebo N=488 PYE=197.7 n (%) [EAIR]	BARI 4 mg N=487 PYE=215 n (%)	Adalimumab N=330 PYE=141.9 n (%)
TEAE	295 (61) [149]	347 (71) [161]	224 (68) [158]
Infections and infestations	134 (28) [68]	176 (36) [82]	110 (33) [78]
Gastrointestinal disorders	62 (13) [31]	80 (16) [37]	47 (14) [33]
Death	0	2 (0.4)	0
SAE	22 (4.5) [11.1]	23 (4.7) [10.7]	6 (1.8) [4.2]
Infections and infestations	7 (1.4) [3.5]	5 (1) [2.3]	2 (0.6) [1.4]
Pts with event leading to discontinuation	17 (3.5) [8.6]	25 (5.1) [11.6]	7 (2.1) [4.9]
MACE	0	1 (0.2)	0
Malignancy	3 (0.6) [1.52]	2 (0.4) [0.93]	0
Deep Vein Thrombosis	0	1 (0.2) [0.47]	0
Pulmonary embolus	0	1 (0.2) [0.47]	0
Gastrointestinal perforations	0	0	0

Incidence rate per 100 person-years
Source: Table JADV.12.8, page 767, Table JADV.12.11, page 776, Table JADV.12.14, pages 801-814, Table JADV.12.16, pages 824, JADV.14.136, page 3154, submitted 1/15/16

The proportion of patients with increases in ALT, AST, alkaline phosphatase, total bilirubin, creatinine, and creatine phosphokinase was higher in the baricitinib group than the adalimumab group (Table 26). Treatment emergent low hemoglobin and lymphocytes were more common with baricitinib, but treatment emergent low neutrophils were more common with adalimumab. The mean change from baseline in lipid parameters was larger for baricitinib than adalimumab (Table 27). The mean platelet count increased with baricitinib exposure, while it decreased with adalimumab exposure.

Table 26: Overview of Labs in Study JADV from Weeks 0 to 24 (with data up to rescue)

Any CTCAE increase	Placebo N=488 n (%)	BARI 4 N=487 n (%)	Adalimumab N=330 n (%)
ALT	80 (16.4)	121 (25)	77 (23.3)
AST	63 (12.9)	106 (21.9)	61 (18.5)
Alkaline phosphatase	34 (7)	34 (7)	20 (6.1)
Total bilirubin	5 (1)	6 (1.2)	3 (0.9)
Creatinine	9 (1.8)	7 (1.4)	3 (0.9)
Creatine phosphokinase	40 (8.2)	179 (37)	41 (12.4)
Treatment-emergent abnormalities occurring at any time (Weeks 0 to 24)			
Low hemoglobin	93 (29.4)	101 (32.4)	36 (16.9)
Low neutrophils	16 (3.3)	47 (9.9)	38 (11.7)
Low lymphocytes	47 (10.6)	41 (9.9)	18 (6.0)

Source: Table JADV.12.26, page 905, Table JADV.12.30, page 921, Table JADV.12.34, page 936, JADV.14.194, page 8253-4, submitted 1/15/16

Table 27: Overview of Hematologic Parameters and Lipids in Study JADV from Weeks 0 to 12

Mean change from baseline	Placebo N=488	BARI 4 N=487	Adalimumab N=330
Hemoglobin (g/dL)	-0.04	-0.02	0.5
Platelets (thousand cells/uL)	-2	12	-35
Lymphocytes (thousand cells/uL)	0	0.05	0.38
Neutrophil count (thousand cells/uL)	-0.36	-0.98	-1.21
Leukocyte count (thousand cells/uL)	-0.33	-0.99	-0.78
LDL (mg/dL)	-2	16	7
Total cholesterol (mg/dL)	-2	26	11
Triglycerides (mg/dL)	-3	16	7
HDL direct (mg/dL)	0.1	9.4	3.8

Source: Table 4.23, page 110, IR response, submitted 7/21/16

In summary, the rates of common adverse events were similar, but there was a signal of more risk on baricitinib than adalimumab for adverse events of special interest, however there is uncertainty around such comparisons given the small number of events.

- **Concerns identified through U.S. or foreign postmarket experience**

Not applicable—There is not any US or foreign postmarket experience because baricitinib has not received marketing authorization in any country to date.

- **Safety conclusions**

Dr. Nair and I are in agreement that the currently submitted safety data and analyses are adequate to inform the decision regarding the benefit-risk profile of the product. The safety data submitted for baricitinib suggest it is associated with significant immunosuppression, as manifested by increased risk of opportunistic infections. In addition, baricitinib is associated with important laboratory abnormalities, such as lipid parameter elevations, GI perforation, and thrombosis. Malignancies were seen in the clinical program.

In general, many of the safety concerns identified are consistent with other immunosuppressive agents utilized to treat rheumatoid arthritis. Many of the identified safety signals occurred at a slightly higher incidence with the 4 mg than 2 mg dose. The potential increase in risk needs to be considered in the context of data suggesting numerical trends suggesting additional benefit on some endpoints with the 4 mg dose. Thus, benefit/risk considerations are favorable for both doses, and it is reasonable for patients to initiate 4 mg, with the option to utilize the 2 mg dose.

For many adverse events of special interest, such as cardiovascular and thrombotic events, there were relatively few events observed overall and we therefore have limited ability to rule out increases in risk based on currently available data. Also, there was additional concern generated by the safety signals related to thromboses with baricitinib exposure, which has not been seen in other RA drug development programs. Thus, I recommend a long-term active-controlled safety study to be done as a postmarketing requirement.

- **Discussion of notable safety issues (resolved or outstanding)**

1) Lilly's ascertainment and classification of serious adverse events was a concern during the review cycle due to potential misclassification. Also, additional safety data and analyses were requested during the review cycle to better categorize baricitnib's safety. Data related to these issues were submitted late in the review cycle and there are ongoing discussions regarding the safety data.
2) See section 13 for the recommended postmarketing requirement.

9. Advisory Committee Meeting

No issues were identified that would warrant an advisory committee meeting. Thus, an advisory committee meeting was not held.

10. Pediatrics

- **Pediatric exclusivity board review - Proposed Pediatric Study Requests (PPSR)/Written Request (WR)—**Not applicable

- **Pediatric Review Committee (PeRC) Review Outcome-Post Marketing Commitments (PMCs), deferrals, waivers, pediatric plan, pediatric assessment**

Polyarticular juvenile idiopathic arthritis (PJIA) has been considered the juvenile equivalent of adult rheumatoid arthritis, and thus a study in PJIA patients would be required by the Pediatric Research Equity Act (PREA) if this NDA in RA patients is approved. With this NDA, Lilly submitted a partial waiver 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. A deferral was requested 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 October 5, 2016. The PeRC agreed with the requested waiver and deferral.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**

Lilly provided a list of nine clinical investigator with disclosable financial interests, including equity interests in the sponsor as defined by 21 CFR 54.2(b) and significant payments of other

sorts as defined by 21 CFR 54.2(f). Lilly certified that it did not enter into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). It is unlikely the clinical investigators with disclosable financial interests would impact the study results given that the study was large, international, and multicenter.

- **Other Good Clinical Practice (GCP) issues**

The clinical studies were conducted in accordance with Good Clinical Practices and a statement of compliance with Good Clinical Practices is located in each complete study report.

- **Office of Scientific Investigations (OSI) audits**

Four clinical sites covering study protocols JADX, JADV, and JADW were selected for inspection. These sites principally enrolled relatively large numbers of patients and were considered to have other study risk considerations. In addition, Lilly was inspected. In each case, inspection findings supported the acceptability of the clinical data submitted.

- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Prescribing Information**

The prescribing information required major revisions. The proposed prescribing information did not include information related to numerous risks associated with baricitinib and proposed an indicated patient population inconsistent with other approved products that have similar risk/benefit profiles. A summary of some changes is included below. Labeling discussions are ongoing at the time of this review.

- INDICATIONS AND USAGE section:
  - Proposed indication: treatment of adult patients with moderately to severely active rheumatoid arthritis.
  - The indication will be revised to specify inadequate response to or intolerance of methotrexate given considerations related to the overall risk/benefit of the product.
- DOSAGE AND ADMINISTRATION section:
  - Proposed dosage and administration: The recommended dose of OLUMIANT is 4 mg once daily. For some patients, a dose of 2 mg once daily may be acceptable.
  - There are ongoing discussions regarding the wording of the dosage and administration section.
- BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - Lilly did not propose a boxed warning. Lilly included Warnings for Infections, Laboratory Parameters, and Vaccinations.

- The serious risks associated with baricitinib need discussion in the label. A boxed warning regarding safety issues, such as serious infections was added. In addition, it is recommended that malignancy be included in the boxed warning. To help patients minimize the risk of serious adverse events associated with baricitinib, a Medication Guide will be added.
- The Warning and Precaution for infection needs modification and strengthening to emphasize that serious and sometimes fatal infections and opportunistic infections have been reported in patients receiving baricitinib.
- Additional Warnings and Precautions need to be added related to the risk of Malignancy and Lymphoproliferative disorders and Gastrointestinal Perforations.
- The Warning and Precaution related to Laboratory parameters needs modification to clarify the type and frequency of abnormalities and cross reference to the dosing and administration section to clarify dose changes needed in response to those abnormalities.
- A Warning and Precaution related to the risk of Thrombotic events is recommended.
- Data regarding safety events, such as tuberculosis, opportunistic infections, malignancy, lymphopenia, and serum creatinine elevations, needs to be added to the label.

- CLINICAL STUDIES section:
  - Recommend removal of information related to the SDAI given that it provides information that is already captured from other endpoints that are the core of assessment of signs and symptoms of RA, such as ACR response.
  - Information will be added to the DAS28-hsCRP results to indicate how many active joints patients have despite having DAS28-CRP<2.6.
  - Data from figures and tables that is beyond the placebo controlled period will be removed.
  - SF-36 results will be modified to include data from all of the sub-components.
  - Information related to severity of morning stiffness will be removed from labeling. There are ongoing discussions with the Clinical Outcomes Assessment Staff regarding Lilly's proposal to include results for "worst tiredness." In general, there is concern with presenting overlapping and ancillary benefits with respect to the core outcome measures currently used to support RA labeling claims. Further, it is unclear if "worst tiredness" represents benefits distinct from the benefit seen with control of disease activity in RA, which is captured by ACR response criteria.
  - For radiographic data, it is recommended that the results be displayed for analyses including data collected after escape and treatment discontinuation, rather than based on linear extrapolation.
  - There are ongoing discussions regarding whether to include data comparing baricitinib to adalimumab, which was evaluated in a single study.

- **Proprietary name**

The proposed proprietary name for baricitinib 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 found to be acceptable.

- **Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use)**

Review by the patient labeling teams is ongoing at this time.

- **Carton and container labeling**

DMEPA and CMC will review the proposed carton and container labeling. Review is ongoing.

13. Postmarketing Recommendations

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 not been finalized, but the team is in agreement that a REMS is not required.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

A controlled clinical trial to evaluate the long-term safety of baricitinib in patients with rheumatoid arthritis. The trial should include two doses of baricitinib (2 mg and 4 mg) and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular events, opportunistic infections, thrombosis, and malignancy.

See Section 10 for the PMR related to PREA studies.

14. Recommended Comments to the Applicant

None

Appendix

Table 4.5. ACR20 Response Rate Using Observed Values and NRI
Weeks 0 through 12
Modified Intent-to-Treat Population
Studies JADA, JADN, JADX, and JADW Combined

Time Point Statistics	PBO (N=551)	BARI 2-mg (N=479)	BARI 4-mg (N=480)	BARI 2-mg vs PBO	BARI 4-mg vs PBO	BARI 4-mg vs BARI 2-mg
Week 2						
N-obs	551	479	480			
ACR20 response, NRI, n (%)	104 (18.9)	149 (31.1)	192 (40.0)			
Difference in response rate				12.2	21.1	8.9
95% CI (a)				(7.0, 17.5)	(15.7, 26.6)	(2.9, 14.9)
Odds ratio				1.9	2.8	1.5
95% CI (b)				(1.4, 2.6)	(2.1, 3.8)	(1.1, 1.9)
P-value (b)				0.001	0.001	0.004
Week 4						
N-obs	551	479	480			
ACR20 response, NRI, n (%)	152 (27.6)	217 (45.3)	257 (53.5)			
Difference in response rate				17.7	26.0	8.2
95% CI (a)				(11.9, 23.5)	(20.1, 31.8)	(1.9, 14.5)
Odds ratio				2.2	3.0	1.4
95% CI (b)				(1.7, 2.8)	(2.3, 4.0)	(1.1, 1.8)
P-value (b)				0.001	0.001	0.011

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; N = number of mITT patients; n = number of patients in the specified category; N-obs = number of patients in the analysis; NRI = non-responder imputation.
(a) The 95% CI is from the Newcombe-Wilson method without continuity correction.
(b) The 95% CI and P-value are from logistic regression model: study+treatment group. When logistic regression sample size requirements are not met, P-value from Fisher's exact test is produced instead of odds ratio and 95% CI.

Program location: home/lillyce/prd/ly3009104/integrations/ra_submission/programs_nonsdd/t_acr20_wk0to12_jadanxw.sas
Data location: home/lillyce/prd/ly3009104/integrations/ra_submission/data/adam
Output location: home/lillyce/prd/ly3009104/integrations/ra_submission/programs_nonsdd/tfl_output/t_acr20_wk0to12_jadanxw.rtf

ACR20 Response Rate Using Observed Values and NRI Page 2 of 4
Weeks 0 through 12 03:21 06JUL2016
Modified Intent-to-Treat Population, Study JADA, JADN, JADX, and JADW Combined PDPM

Time Point Statistics	PBO (N=551)	BARI 2-mg (N=479)	BARI 4-mg (N=480)	BARI 2-mg vs PBO	BARI 4-mg vs PBO	BARI 4-mg vs BARI 2-mg
Week 8						
N-obs	551	479	480			
ACR20 response, NRI, n (%)	188 (34.1)	252 (52.6)	284 (59.2)			
Difference in response rate				18.5	25.0	6.6
95% CI (a)				(12.5, 24.5)	(19.1, 31.0)	(0.3, 12.8)
Odds ratio				2.2	2.8	1.3
95% CI (b)				(1.7, 2.8)	(2.2, 3.7)	(1.0, 1.7)
P-value (b)				0.001	0.001	0.039
Week 12						
N-obs	551	479	480			
ACR20 response, NRI, n (%)	192 (34.8)	284 (59.3)	294 (61.3)			
Difference in response rate				24.4	26.4	2.0
95% CI (a)				(18.5, 30.4)	(20.5, 32.3)	(-4.2, 8.2)
Odds ratio				2.8	3.1	1.1
95% CI (b)				(2.2, 3.7)	(2.4, 4.0)	(0.8, 1.4)
P-value (b)				0.001	0.001	0.518

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; N = number of mITT patients; n = number of patients in the specified category; N-obs = number of patients in the analysis; NRI = non-responder imputation.
(a) The 95% CI is from the Newcombe-Wilson method without continuity correction.
(b) The 95% CI and P-value are from logistic regression model: study+treatment group. When logistic regression sample size requirements are not met, P-value from Fisher's exact test is produced instead of odds ratio and 95% CI.

Program location: home/lillyce/prd/ly3009104/integrations/ra_submission/programs_nonsdd/t_acr20_wk0to12_jadanxw.sas
Data location: home/lillyce/prd/ly3009104/integrations/ra_submission/data/adam
Output location: home/lillyce/prd/ly3009104/integrations/ra_submission/programs_nonsdd/tfl_output/t_acr20_wk0to12_jadanxw.rtf

Division Director Summary Review for Regulatory Action

Date	February 06, 2017
From	Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 207924
Applicant	Eli Lilly and Company
Date of Submission	January 15, 2016
PDUFA Goal Date	January 15, 2017 (clock extension to April 15, 2017)
Proprietary Name / **Non-Proprietary Name**	Olumiant/Baricitinib
Dosage Form(s) / Strength(s)	4 mg and 2 mg tablets
Applicant Proposed Indication(s)/Population(s)	Adult patients with moderately to severely active rheumatoid arthritis
Action/Recommended Action for NME:	Approval, 2 mg as the recommended dose Complete response for the 4 mg proposed dose
Approved/Recommended Indication/Population(s) (if applicable)	Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**Raj Nair, MD**
Statistical Review	**Robert Abugov, PhD; Gregory Levin, PhD**
Pharmacology Toxicology Review	**Mathew Whittaker, PhD; Timothy Robison, PhD**
OPQ Review	**Sam Bain, PhD; Art Shaw, PhD, Craig Bertha, PhD**
Microbiology Review	**Ted Chang, PhD;**

Clinical Pharmacology Review	**Yunzhao Ren, MD, PhD; Yuching Yang, Phd; Anshu Marathe, PhD**
OPDP	**Adewale Adeleye**
OSI	**Anthony Orencia**
CDTL Review	**Janet Maynard, MD**
OSE/DEPI	**Efe Eworuke**
OSE/DMEPA	**Teresa McMillan**
OSE/DRISK	**Erin South**
Other	

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Patients with rheumatoid arthritis (RA) have a chronic progressive disease that is associated with morbidity and mortality. Drugs that slow down disease progression in RA, otherwise called disease-modifying anti-rheumatic drugs (DMARDs), are widely used in the treatment of RA. There are multiple small molecule drugs and large molecule biologic products, belonging to the DMARD category, are approved for the treatment of RA. Another treatment option would be a desirable addition to the treatment options available for RA. Baricitinib is a small molecule inhibitor of Janus associated kinase (JAK) for oral administration proposed for approval for use by patients with RA. Another small molecule inhibitor of JAK called tofacitinib was approved for use by patients with RA in 2012.

Efficacy of baricitinib at doses of 2 mg and 4 mg orally once-daily was demonstrated in four pivotal studies in patients with RA. These studies showed efficacy of baricitinib for reducing signs and symptoms of RA based on the proportion of patients meeting an American College of Rheumatology (ACR) response criteria and reduction in DAS28-CRP, and for improvement of physical function as measured by Health Assessment Questionnaire-Disability Index (HAQ-DI). Comparison of baricitinib 2 mg and 4 mg doses showed that the proportion of patients experiencing improvement in ACR response was numerically similar for the two doses. For HAQ-DI, the level of improvement was also similar for the two doses. Structural progression was assessed for the 4 mg dose in three studies, and for the 2 mg dose in one study. The data for structural progression showed consistent efficacy for baricitinib 4 mg dose in three studies. Radiograph response data for baricitinib 2 mg is from a single study, thus corroborative evidence from another study is not available. Nevertheless, data from the single study show statistically significant difference for baricitinib 2 mg versus placebo using linear extrapolation method, a method that been used historically in most previous RA programs.

Major safety findings were related to immunosuppression, that are consistent with other DMARDs, but a signal for a unique safety finding of thrombosis was seen with baricitinib. Thrombosis has not previously been seen with either small molecule or biologic DMARDs. Safety findings of note with baricitinib were an increased risk of malignancy, opportunistic infections, tuberculosis, herpes zoster infection, and GI perforation. Malignancy and MACE tended to occur at higher rate with baricitinib 4 mg compared to 2 mg, with the imbalance driven primarily by >52 week data. The number of patients >52 weeks was too small, particularly for baricitinib 2 mg group, for conclusive comparative assessment. There were 7 cases of tuberculosis in baricitinib 4 mg group, compared to none in the baricitinib 2 mg group and placebo group. Baricitinib treatment was associated with laboratory abnormalities including increase in platelet count, decreases in neutrophil count, increase in lipid parameters, and increase in CPK, all appeared to be dose-related.

Based on the submitted data, the benefit-risk profile of baricitinib is favorable to support the 2 mg once-daily dose. For efficacy, there was no consistent demonstrated benefit of the 4 mg dose compared to the 2 mg dose. Changes in primary efficacy variable of ACR 20 response were essentially the same for the two doses. For safety, data were suggestive of increased risk of malignancy, tuberculosis, and MACE with the baricitinib 4 mg dose compared to the 2 mg dose. Some relevant laboratory parameters also changed more with baricitinib compared to placebo with larger effect with the 4 mg dose compared to the 2 mg dose. With no convincing efficacy benefit with the baricitinib 4 mg over 2 mg, but increased safety risk with 4 mg over 2 mg, the benefit-risk assessment is favorable for the baricitinib 2 mg dose.

The recommendation made in this review supporting the 2 mg dose is different than the Cross Disciplinary Team Leader (CDTL), clinical, and statistical review recommendations supporting both 4 mg and 2 mg doses, with 4 mg as the primary dose.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• RA is an autoimmune disease that causes chronic symmetric inflammation of joints. RA impacts the live of patients due to pain and decreased physical function, and ultimately irreversible joint damage.	Most patients with RA have chronic progressive disease.
Current Treatment Options	• There are multiple drugs approved for RA. RA patients are treated with disease modifying antirheumatic drugs (DMARDs). Generally, methotrexate (MTX) is the first line of therapy for RA. The next line of therapy is a TNF-antagonist. There are multiple TNF-antagonists approved for RA. In addition, there are other drug classes approved for RA, such as IL-6R antagonist, IL-1R antagonist, JAK inhibitors, etc.	Current treatment options for this condition are effective. Additions to the treatment armamentarium would provide another choice for patients with RA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Reducing signs and symptoms of RA based on ACR response • Improvement in physical function based on HAQ-DI • Preventions of structural damage based on radiographic progression • Baricitinib 4 mg and 2 mg once daily doses showed numerically similar response for ACR and HAQ-DI. For radiographic progression, 4 mg dose showed more consistent response compared to 2 mg dose.	In clinical trials, baricitinib 4 mg and 2 mg were both effective, with effect sizes for ACR response and HAQ-DI similar for the two doses. Radiographic progression for the 4 mg dose was assessed in three trials, but for the 2 mg dose was assessed in one trial.
Risk	• Major safety concerns were: effects related to immunosuppression, such as infections including opportunistic infection, tuberculosis, and herpes zoster; thrombosis; gastrointestinal perforation; laboratory parameter change of increase in platelet count, decrease in neutrophil count, and increases in lipid parameters, and serum CPK.	The safety profile of baricitinib is well characterized. The safety finding of thrombosis is unique and not seen previously with other DMARDs.
Risk Management	• The safety findings of baricitinib are well characterized and is consistent with other DMARDs approved for the treatment of RA, except for thrombosis, which is a new and unique finding for baricitinib.	The safety risks will be communicated in labeling, with appropriate warning for infection, thrombosis, and other findings seen in the clinical program.

2. Background

Rheumatoid arthritis (RA) is a chronic, symmetric inflammatory polyarthritis that primarily involves synovial joints. In RA, synovial tissues become inflamed and proliferate, forming pannus that invades bone, cartilage, and ligament and leads to joint damage and deformities. Destruction of synovial joints can lead to severe disability and premature mortality.[1, 2] RA affects approximately 1% of the adult population in North America and Northern Europe.[3]

The classes of drugs used for treatment of RA include: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful co-therapies because of their anti-inflammatory and analgesic effects. Corticosteroids have potent anti-inflammatory effects, but their use is limited by long-term toxicity. DMARDs are a diverse group of therapeutic agents that reduce signs and symptoms of RA as well as slow disease progression or produce a disease-modifying effect on joint damage. Approved DMARDs and some of their features are listed in Table 1 and Table 2. Methotrexate is the most commonly used DMARD because of its known efficacy and well-understood long-term effects. Tumor necrosis factor (TNF)-blockers are commonly used DMARDs because of their known efficacy and safety profile and relatively long-term use experience (Table 2). Treatment of RA is typically initiated with introduction of non-biologic DMARDs early in the course of the disease to prevent joint damage and bony erosions. Methotrexate is often the initial DMARD used as a single agent in patients with low disease activity or without features of poor prognosis, and then combined with other DMARDs, commonly biologics such as TNF blockers, in patients with high disease activity or with features of poor prognosis.[4]

Table 1. Non-biologic small molecule DMARDs approved for marketing in the United States

Product Name (Trade Name) [Sponsor]	Mechanism of Action in RA	Year of First Approval for RA
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	Anti-metabolite	1953
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	Interference with antigen processing	1955
Azathioprine (IMURAN)	Cytostatic	1968

[1] Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.
[2] Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706-14.
[3] Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11(3):229.
[4] Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care and Res 2012; 64:625-39.

Product Name (Trade Name) [Sponsor]	Mechanism of Action in RA	Year of First Approval for RA
[Prometheus Labs]		
Penicillamine (CUPRIMINE) [Alton]	Unknown	1970
Auranofin (RIDAURA) [Prometheus Labs]	Unknown	1985
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]	T-cell activation inhibitor	1995, 1990
Leflunomide (ARAVA) [Sanofi-Aventis]	Anti-metabolite	1998
Tofacitinib (XELJANZ)	JAK inhibitor	2012

Table 2. Biologic large molecule DMARDs approved for marketing in the United States [does not include biosimilars]

Product Name (Trade Name) [Sponsor] {year} *	Presentation and *ROA* †	Description and *MOA* ‡	Claims for adult RA §
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF-α inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL *IV infusion*	Chimeric IgG1 k mAb *TNF-α inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 100 mg *SC injection*	Recombinant polypeptide *IL-1 receptor antagonist*	Clinical response Physical function response Radiographic response
Adalimumab (HUMIRA) [Abbott] {2002}	Prefilled syringe 40 mg/0.8 mL Prefilled syringe 20 mg/0.4 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF-α inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial *IV infusion*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor through B7-1 and B7-2*	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*	Clinical response Physical function response Radiographic response
Golimumab (SIMPONI) [Centocor] {2009}	Prefilled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF-α inhibitor*	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial Prefilled syringe 200 mg/mL *SC injection*	Humanized Fab fragment *TNF-α inhibitor*	Clinical response Major clinical response Radiographic response Physical function response
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010, 2013}	Vial 20 mg/mL *IV infusion* Prefilled syringe (162mg/0.9mL) *SC injection*	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	Clinical response Major clinical response Radiographic response Physical function response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2011}	Prefilled syringe 125 mg/mL Autoinjector 125 mg/mL *SC injection*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor through B7-1 and B7-2*	Clinical response Physical function response
Golimumab IV (SIMPONI ARIA) [Janssen] {2013}	Vial 100 mg/20 mL *IV infusion*	Humanized IgG1 k mAb *TNF-α inhibitor*	Clinical response Physical function response Radiographic response

* Year = Year of first approval for RA
† ROA = Route of administration
‡ MOA= Mechanism of action
§ Claims: Clinical response assessed by ACR 20, 50, and 70 response over at least 3-6 month; Major clinical response defined as achieving ACR 70 response continuously over 6-month period; Physical function response (or improving physical function) assessed by health assessment questionnaire (HAQ) over at least 3-6 month period; Radiographic response (or inhibiting progression of

Product Name (Trade Name) [Sponsor] {year} *	Presentation and *ROA* †	Description and *MOA* ‡	Claims for adult RA §
structural damage) assessed radiographically by standardized scoring method and sometimes its components of erosion score (ES) or joint space narrowing (JSN) score over 6 or 12 months			

Baricitinib is a small molecule inhibitor of the Janus associated kinase (JAK). If approved, baricitinib would be the second JAK inhibitor for the treatment of RA. Tofacitinib (Xeljanz, NDA 203214) was initially approved in 2012 as an oral tablet for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. Baricitinib is being proposed for oral administration in 4 mg and 2 mg dosage strengths. The proposed recommended dose is 4 mg once daily, with a notation that a dose of 2 mg once daily may also be acceptable.

All biologic DMARDs approved for the treatment for RA are injectable agents that primarily target extracellular cytokines (Table 2). Tofacitinib and baricitinib are oral, small molecule inhibitors of the intracellular tyrosine kinase called JAK. JAK is critical for cytokine receptor binding-triggered signal transduction through STAT to the nuclei of cells. The JAK family consists of four members: JAK1, JAK2, JAK3, and TyK2. Upon cytokine binding to its receptor on the cell membrane, JAKs are activated, which in turn phosphorylate cytokine receptors, creating docking sites for signaling molecules, especially for members of the STAT family. The STAT proteins form homo- or hetero-dimers and translocate to the nucleus where they induce transcription of target genes. Various JAK and STAT proteins are known to be involved in tissues affected in RA, therefore, inhibiting the JAK-STAT pathway seems a reasonable target for RA treatment. In kinase assays, tofacitinib inhibits JAK1 and JAK3 and, to a lesser extent, JAK2 and TyK2. In similar assays, baricitinib inhibits JAK1, JAK2 and TyK2, and to a lesser extent, JAK3. In the immune system, JAK1, JAK2, and TyK2 are ubiquitously expressed, whereas JAK3 expression seems to be limited to hematopoietic cells.

Regulatory interaction between the Agency and Lilly:

The Division and Lilly had typical milestone meetings regarding the development of baricitinib for RA, under IND 102204. The key interactions were as follows: End-of-Phase 2 meeting in June 2012, where discussion was held regarding studying two dose strengths and two dosing regimens (once daily and twice daily) in phase 3 studies, and the statistical analysis plans for assessment of radiographic progression; Type C written response in September 2013, where the Division accepted Lilly's rationale for studying once-daily, rather than twice-daily dosing regimen; Type C written response in January, 2015, where the Division asked Lilly to pool all four phase 3 studies, and phase 3 and phase 2 studies for safety analyses; and Pre-NDA meeting in September 2015, where the statistical methodologies to assess impact of missing data in pivotal studies were discussed, and general content and format of the NDA was discussed.

3. Product Quality

The proposed commercial drug product, Olumiant tablets, contains 4 mg and 2 mg baricitinib and standard compendial excipients. The achiral drug substance baricitinib is chemically synthesized. Lilly has submitted all data to support the quality and manufacture of the product, and expiry period of 24 months. All manufacturing and testing facilities associated with the drug product have acceptable establishment evaluation status.

4. Nonclinical Pharmacology/Toxicology

Lilly conducted a complete and adequate toxicology program that included general toxicology studies in rodent and non-rodent species (rats for 26 weeks, and dogs for 39 weeks), reproductive and embryofetal development studies, and carcinogenicity studies. In general toxicology studies, immunosuppressant effects were the major treatment-related toxicities observed in rats and dogs. Bone marrow and lymphoid organs, including the spleen, and lymph nodes were target organs of toxicity in both species. Dose limiting toxicities in the GI tract (inflammation, infiltrates) and liver (infiltrates/inflammation, bile duct hyperplasia) were observed in male and female dogs at $\geq$ 3 mg/kg/day. The dog is the more sensitive nonclinical species, with an $AUC_{0\text{-}24h}$ of 1.21 μM*hr as the limit dose. This exposure supports the clinical baricitinib exposure at the maximum recommended human dose (MRHD) of 4 mg/day. In reproductive studies, fertility (based upon achievement of pregnancy) was reduced in male and female rats that received baricitinib at oral doses of 50 and 100 mg/kg/day, respectively. Fertility was unaffected in male and female rats at oral doses of 15 and 25 mg/kg/day. However, maintenance of pregnancy was adversely affected at these doses as evidenced by increased post-implantation losses and decreased number of mean viable embryos per litter. In embryofetal development studies, baricitinib was teratogenic (skeletal malformations including bent limb bones and rib anomalies) in both rats and rabbits. In a pre- and post-natal development study, treatment of pregnant rats with baricitinib at 25 mg/kg/day from gestation day 6 to lactation day 20 resulted in multiple adverse findings in offspring in the absence of maternal toxicity. These included decreased survival from birth to postnatal day 4 (due to increased stillbirths and early neonatal deaths), decreased mean birth weight, decreased body weight gain during the pre-weaning phase, increased incidence of malrotated forelimbs, and immune suppression with decreased cytotoxic T cells. In a standard battery of genotoxicity assays baricitinib was negative. There was no evidence of tumorigenic potential in a 2-year carcinogenicity study conducted in rats or in a 26-week carcinogenicity study in Tg.rasH2 mice.

5. Clinical Pharmacology

Lilly submitted a complete and adequate clinical pharmacology program for baricitinib. The oral bioavailability of baricitinib is about 79%, with no significant effect of food. Renal elimination is the principal clearance mechanism of baricitinib. In a mass balance study, approximately 75% of baricitinib was excreted unchanged in urine, and about 20% was excreted unchanged in the feces. A minor fraction (about 5 to 6%) of orally administered baricitinib appears to be metabolized, mainly through the CYP3A4 pathway. In a renal impairment study, exposure of baricitinib was increased by 1.4 fold, 2.2 fold, and 4.1 fold, in mild, moderate, and severe renal impaired patients, for the baricitinib 4 mg dose. An appropriate dose reduction will be necessary in renal impairment. In a hepatic impairment study, exposure to baricitinib was increased by 19% compared to patient with normal liver function. Dose reduction in patients with mild to moderate hepatic impairment will thus not be necessary. In drug interaction studies, finding of note was an approximate 2-fold increase in exposure with concomitant probenecid (OAT3 inhibitor). There is no substantial impact of food, age, weight, and gender on baricitinib exposure. A thorough QT study was conducted for baricitinib and reviewed by the QT study interdisciplinary review team. No significant QTc prolongation effect of baricitinib at the doses tested was detected.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical/Statistical-Efficacy

Overview of the clinical program:

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decisions for this application are shown in Table 3. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 3. Relevant controlled clinical studies with baricitinib in RA

ID Year* *Study*	**Study Characteristics †** **- Patient age** **- Response to past treatment** **- Background treatment** **- Study design; duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
Phase 2					
JADC [05/09	- Over 18 years - Inadequate response to	Bar 4 mg QD Bar 7 mg QD	32 32	1^{O}: ACR 20 at wk 12	US, Europe (74% US)

ID Year* *Study*	**Study Characteristics †** **- Patient age** **- Response to past treatment** **- Background treatment** **- Study design; duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
to 07/10]	DMARD - DMARD background - Parallel arm, DB, no rescue; 24 weeks	Bar 10 mg QD Placebo, up to wk 12	32 31		
JADA [11/10 to 02/12 for Part B]	- Over 18 years - Inadequate response to mtx - DMARD background - Parallel arm, DB, no rescue; 12 weeks (Part A), additional 12 weeks (Part B), Open label extension to additional 52 weeks (Part C), and additional 52 weeks (Part D)	Bar 1 mg QD Bar 2 mg QD Bar 4 mg QD Bar 8 mg QD Placebo, up to wk 12 Part B explored BID dosing	49 52 52 50 98	1^{o}: ACR 20 at wk 12	US, Mexico, Europe, India (32% US)
JADN [11/11 to 12/13]	- Over 18 years - Inadequate response to mtx - DMARD background - Parallel arm, DB, 14 weeks (Part A), additional single blind for 52 weeks (Part B)	Bar 1 mg QD Bar 2 mg QD Bar 4 mg QD Bar 8 mg QD Placebo, up to wk 12	24 24 24 24 49	1^{o}: ACR 20 at wk 12	Japan (100%)
Phase 3					
JADV BEAM Study II [10/12 to 09/15]	- Over 18 years - Inadequate response to mtx; no previous biologics - Mtx with sulfalazine or hydroxychloroquine background - Parallel arm, DB, rescue at week 16; 52 weeks	Bar 4 mg QD Adalimumab Placebo, up to wk 24	488 330 487	1^{o}: ACR 20 at wk 12 2^{o}: HAQ-DI at wk 12; mTSS at wk 24	North America, Central and South America, Europe, Asia (30% North America)
JADX BUILD Study III [01/13 to 12/14]	- Over 18 years - Inadequate response to non-biologic DMARDs; no previous biologics - Non-biologic DMARD background - Parallel arm, DB, rescue at week 16; 24 weeks	Bar 2 mg QD Bar 4 mg QD Placebo, up to wk 24	229 227 228	1^{o}: ACR 20 at wk 12 2^{o}: HAQ-DI at wk 12; mTSS at wk 24	North America, Central and South America, Europe, Asia (30% North America)
JADW BEACON Study IV [01/13 to 09/14]	- Over 18 years - Inadequate response to TNF inhibitor biologics - Non-biologic DMARD background - Parallel arm, DB, rescue at week 16; 24 weeks	Bar 2 mg QD Bar 4 mg QD Placebo, up to wk 24	174 177 178	1^{o}: ACR 20 at wk 12 2^{o}: HAQ-DI at wk 12	North America, Central and South America, Europe, Asia (44% North America)
JADZ BEGIN Study I [01/13 to 08/14]	- Over 18 years - Treatment naïve early RA - None - Parallel arm, DB, rescue at week 24; 52 weeks	Mtx Bar 4 mg QD Mtx + Bar 4 mg QD	213 160 215	1^{o}: ACR 20 at wk 24 2^{o}: HAQ-DI at wk 24; mTSS at wk 24	North America, Central and South America, Europe, Asia (20% North America)
Long-term extension of other studies					
JADY BEYOND [06/13 to ongoing]	Extension of studies JADA, JADZ, JADV, JADX, JADW, and JADS [JADX and JADW (2 mg dose), and other studies (4 mg dose)]	Bar 2 mg QD Bar 4 mg QD	--	Safety	--

ID Year* *Study*	**Study Characteristics †** **- Patient age** **- Response to past treatment** **- Background treatment** **- Study design; duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
* Study ID shown (top to bottom) as Lilly's study number, other names used for the study, Product label refers to these studies as I, II, III, and IV [month/year study started-completed], † DMARD = disease modifying anti-rheumatic drugs; Mtx or mtx = methotrexate; DB = double blind ‡ Bar = Baricitinib; In studies JADV, JADX, and JADW, placebo treatment groups and active treatment groups all included background DMARDs with or without methotrexate § Intent to treat (ITT); appropriate statistical hierarchy was followed for HAQDI and mTSS ¶ ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score // Shows as regions; North America includes USA and Canada					

Design and conduct of the studies:

The primary evidence of efficacy is from studies JADV, JADX, JADW, and JADZ. Study JADV was conducted in patients with inadequate response to methotrexate, JADX in patients with inadequate response to conventional small molecule non-biologic DMARDs, JADW in patients with inadequate response to TNF inhibitors, and JADZ in patients naïve to DMARDs. All studies were randomized, double-blind, placebo-controlled and conducted in patients 18 years of age and older with moderately to severely active RA diagnosed according to the American College of Rheumatology (ACR) criteria. Patients in studies JADV, JADX, and JADW were on background non-biologic DMARDs, predominantly methotrexate, and adalimumab (study JADV) or baricitinib (studies JADV, JADX and JADW) was added on to background non-biologic DMARDs. The basic study design elements including efficacy variables are show in Table 3. The study design required patients to crossover from randomized treatment arm to baricitinib based on specified response criteria, which makes analysis of data, particularly safety data, difficult. In study JADV patients were crossed over from placebo and adalimumab to baricitinib 4 mg starting from week 16. In studies JADX and JADW patients were crossed over from placebo and baricitinib 2 mg to baricitinib 4 mg also starting from week 16. In study JADZ patients were crossed over from methotrexate and baricitinib 4 mg to baricitinib 4 mg plus methotrexate starting from week 24.

The efficacy variables relevant to this submission were ACR response criteria, Disease Activity Score 28 (DAS-28), the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the van der Heijde modified Total Sharp Score (mTSS). These are described below. An understanding of these endpoints will help the interpretation of the study results described in the subsequent section.

The American College of Rheumatology (ACR) response is a composite endpoint with seven components that are used to calculate the proportion of patients achieving a target percentage of improvement from baseline.[5,6] The ACR criteria have been used extensively in clinical

[5] DT Felson, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in Rheumatoid Arthritis. Arthritis & Rheum 1995; 38:727-735.

trials in RA as a measure of efficacy of a therapeutic agent. The ACR 20 response is calculated as at least 20% reduction in tender joint count of 68 joints, and at least 20% reduction in swollen joint count of 66 joints, and at least a 20% reduction in at least 3 of the following 5 measures: patient global assessment of arthritis on a visual analog scale, physician global assessment of arthritis on a visual analog scale, patient assessment of pain on a visual analog scale, patient assessment of physical functioning (e.g., health assessment questionnaire), and acute phase reactant (ESR or CRP). The ACR 50 and ACR 70 are similarly calculated using the higher 50% and 70% levels of improvement, respectively. The Agency has accepted the ACR 20 response as an acceptable demonstration of efficacy of a therapeutic agent supporting a "clinical response" claim, and the ACR 70 response lasting for 6 months as supportive of a claim of a "major clinical response."

Disease Activity Score 28 (DAS-28) is a composite index of RA disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and ESR.[7] An alternative equation is available for use with CRP. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. The ACR response criteria and DAS-28 are conceptually similar, but differ with number of joints counted (e.g. DAS-28 does not include the joints of the feet), and physician global assessment, patient pain, and health assessment score, which are incorporated into the ACR response criteria but not in DAS-28. Another difference is that the DAS-28 measures disease activity at a given time point, whereas the ACR response criteria are calculated as improvement in the variables over a set period of time. A DAS-28 score >5.1 is indicative of high disease activity, and <3.2 of low disease activity. A score of <2.6 has been accepted by the Agency to describe an even lower threshold of disease activity.

Health Assessment Questionnaire-Disability Index (HAQ-DI) assesses a patient's level of functional ability and includes questions regarding fine movements of the upper extremities, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning intended to represent a comprehensive set of functional activities, including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients are asked to grade their status on a scale from 0 (no difficulty) to 3 (unable to do) for each question. The 8 category scores are averaged into an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled). The HAQ-DI has been validated for use in RA, with a minimal clinically important difference (MCID) of 0.25 units (for a given patient) or 0.22 units (based on group means).[8] The Agency has accepted a "physical function response" claim based on HAQ-DI.

The van der Heijde modified Total Sharp Score (mTSS) is an accepted radiographic scoring

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[6] Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid Arthritis classification criteria. Arthritis & Rheum 2010; 62:2569-2581.

[7] J Fransen and PLCM van Riel. The Disease Activity Score and the EULAR Response Criteria. Clin Exp Rheumatol 2005; 23 (Suppl 39): S93-S99

[8] B Bruce and JF Fries. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005; 23 (Suppl 39):S14-S18

system for RA joint damage.[9] X-rays of the hands and feet are graded based on joint space narrowing (Grades 0 to 4, 15 joints per hand, 6 joints per foot) and erosions (Grades 0 to 5, 16 joints per hand, 6 joints per foot). For the hands, joint space narrowing scores and erosion scores are summed separately, and the joint space narrowing score ranges from 0 to 168 and the erosion score ranges from 0 to 280 and their sum, the total radiographic score, ranges from 0 to 448. Although the theoretical maximum score is 448, the actual scores seen in RA clinical trials are much smaller because a given patient has only a fraction of joints affected by structural damage, as assessed by radiographic criteria. The smallest detectable difference on a per-individual basis has been identified for the van der Heijde modification of the Sharp score as approximately 5 units.[10] The Agency has accepted a "radiographic response" claim based on the mTSS.

Efficacy findings and conclusions:

The submitted data show efficacy for baricitinib in RA at doses of 2 mg and 4 mg once daily. In the following sections, dose selection for baricitinib are discussed first, followed by a discussion of the efficacy data for the proposed claims of clinical response, physical function response, radiographic response, and closing with summary comments on efficacy.

Dose ranging studies and dose selection:

Lilly's selection of baricitinib dose for phase 3 studies was based on phase 2 studies JADC and JADA (JADN data is stated to be analyzed after start of phase 3 program), which assessed for probability of achieving an efficacy target on various measures, and safety assessment of adverse events and baricitinib modulating erythropoietin signaling and hemoglobin concentration. Dosing interval was selected as once daily based on popPK analysis of phase 2 studies showing approximately 15 hours half-life for baricitinib. Lilly chose 4 mg once daily as the main dose for phase 3 studies with the stated reasoning that lower doses were not predicted to perform well versus active comparators, the safety profile of the 4 mg dose was similar to lower doses and placebo, and there were no safety concerns with developing even higher doses but the higher doses were not associated with improved efficacy compared to 4 mg dose.

There are challenges with performance versus active comparator as a criterion for dose selection because such intent may drive selection of a dose that is too high. With limited phase 2 data it is often not possible to predict how a lower dose than that selected would perform in phase 3 studies, and safety assessment in phase 2 is limited to make a benefit-risk assessment. Even within phase 2 data, the efficacy trend for baricitinib was not consistent. In study JADA (study used by Lilly for dose selection) the ACR 20 response did show better

[9] S Boini and F Guillemin. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis 2001; 60:817-827

[10] K Bruynesteyn et al., Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference.Arthritis & Rheum 2002; 46:913-920

numerical response for 4 mg compared to lower doses, but in study JADN (study not used by Lilly for dose selection) the ACR response was numerically better for 2 mg dose compared to 4 mg dose, and across the two studies even 1 mg dose performed reasonably well (Table 4 and Figure 1).

Because of concerns of selecting one dose based on limited phase 2 data, at the End of Phase 2 meeting in June 2012, FDA asked that Lilly include two doses of baricitinib in the phase 3 studies. Lilly added the 2 mg dose in two phase 3 studies expecting to show minimal efficacy of the 2 mg dose in the context of the 4 mg dose.

Table 4. ACR 20 response rates (% patients with ACR response) at primary analysis time point

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

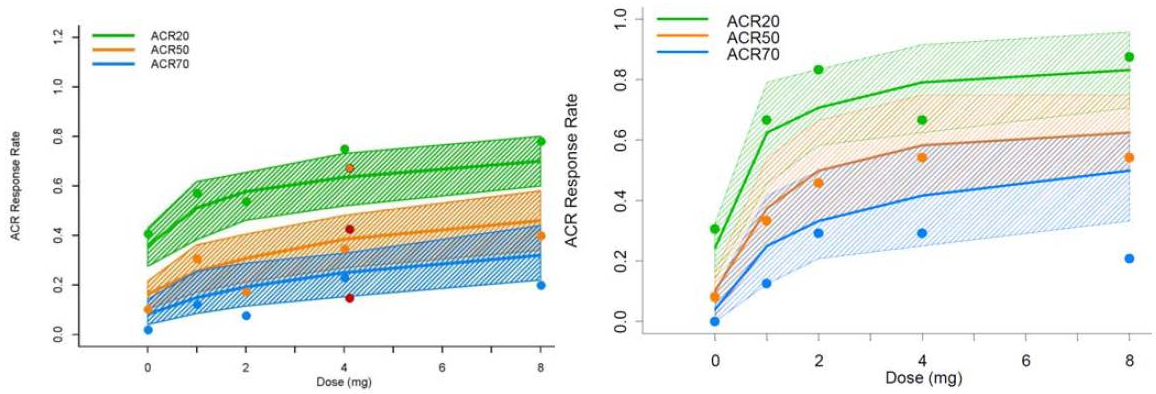

Figure 1. Dose response relationship for ACR 20, ACR 50, and ACR 70 response rates after 12 weeks of baricitinib treatment in Study JADA (left panel) and JADN (right panel)

In the phase 3 program (Table 3), among the 4 studies, 2 studies included the 2 mg dose in addition to the 4 mg dose. As discussed below, these 2 studies provide further comparative

efficacy data from larger studies. The four phase 3 studies provide safety data to better inform dose selection based on benefit-risk assessment from a much larger dataset.

Clinical response in phase 3 studies:

Baricitinib treatment was associated with a higher proportion of patients with ACR responses at both the 2 mg and 4 mg doses, and the differences between baricitinib treatment arms and placebo treatment arms were statistically significant for ACR 20 (Table 5). Results of DAS-28-CRP<2.6 results were generally similar to the results of ACR response (Table 6). The magnitude of clinical response for baricitinib across studies tended to numerically decline depending on response to previous treatment, with JADV (conducted in patients with inadequate response to methotrexate) showing the largest numerical response, JADX (conducted in patients with inadequate response to conventional small molecule non-biologic DMARDs) showing the next largest numerical response, and JADW (conducted in patients with inadequate response to TNF inhibitors) showing the least numerical response for ACR responses, and for DAS-28. In the methotrexate comparative study (JADZ), baricitinib 4 mg monotherapy was statistically superior to methotrexate monotherapy, and baricitinib 4 mg monotherapy and baricitinib 4 mg plus methotrexate was similar (Table 5, Table 6). In the adalimumab comparative study (JADV), baricitinib 4 mg was statistically superior to adalimumab (Table 5).

None of the studies were designed to assess the potential incremental benefit in clinical response when escalating from an initial dose of baricitinib 2 mg to a dose of baricitinib 4 mg.

The two studies that compared baricitinib 2 mg and 4 mg doses (JADX and JADW) did not show consistent separation between the two doses (Table 5 and Table 6), with the dose response ordering being opposite in the two studies for the ACR 20 response. For the RA patients for whom baricitinib will be indicated (inadequate response to methotrexate), study JADV (inadequate response to methotrexate) and study JADX (inadequate response to conventional small molecule non-biologic DMARDs) may be more relevant than the other two studies. Of these two studies, JADX compared baricitinib 2 mg and 4 mg doses, where the 2 mg dose showed a better numerical response than the 4 mg dose.

Table 5. ACR response rates (% patients with ACR response) at primary analysis time point

Study *	Time	Treatment †	ACR 20	ACR 50	ACR 70	OR [95%CI] (p-value) vs placebo or mtx, for ACR 20
JADV Study II	Week 12	Bar 4 mg	70	45	19	3.6 [2.7, 4.7] (<0.001) ‡
		Adalimumab	61	35	13	3.0 [1.8, 5.1] (<0.001) ‡
		Placebo	40	17	5	
JADX Study III	Week 12	Bar 2 mg	66	34	18	3.0 [2.0, 4.4] (<0.001)
		Bar 4 mg	62	33	18	2.5 [1.7, 3.7] (<0.001)
		Placebo	39	13	3	
JADW Study IV	Week 12	Bar 2 mg	49	20	13	2.7 [1.7, 4.2] (<0.001)
		Bar 4 mg	55	28	11	3.4 [2.2, 5.4] (<0.001)
		Placebo	27	8	2	
JADZ Study I	Week 24	Bar 4 mg	77	60	42	2.0 [1.3, 3.2] (0.003)
		Bar 4 mg+mtx	78	63	40	2.2 [1.4, 3,4] (0.001)
		Mtx	62	43	21	

Study *	Time	Treatment †	ACR 20	ACR 50	ACR 70	OR [95%CI] (p-value) vs placebo or mtx, for ACR 20
* Study ID shown as Lilly's study number † Bar = Baricitinib, mtx = methotrexate ‡ Bar 4 mg vs adalimumab OR (p-value) was 1.6 (0.02)						

Table 6. DAS28-CRP ≤ 2.6 change from baseline at primary analysis time point

Study *	Time	Treatment †	% responder	OR [95% CI] (p-value) vs placebo or mtx
JADV Study II	Week 12	Bar 4 mg	24	7.6 [4.7, 12.4] (<0.001)
		Adalimumab	19	
		Placebo	4	
JADX Study III	Week 12	Bar 2 mg	26	3.7 [2.1, 6.4] (<0.001)
		Bar 4 mg	26	3.7 [2.1, 6.5] (<0.001)
		Placebo	9	
JADW Study IV	Week 12	Bar 2 mg	11	3.0 [1.2, 7.4] (<0.001)
		Bar 4 mg	16	4.8 [2.0, 11.3] (<0.001)
		Placebo	4	
JADZ Study I	Week 24	Bar 4 mg	40	2.2 [1.4, 3.4] (<0.001)
		Bar 4 mg+mtx	40	2.5 [1.7, 3.7] (<0.001)
		Mtx	24	
* Study ID shown as Lilly's study number † Bar = Baricitinib, mtx = methotrexate				

During review of the application, Lilly conducted integrated analyses of some efficacy data, primarily ACR response. The reader is referred to the end of this section for comments on the integrated analyses.

Physical function response in phase 3 studies:

Baricitinib treatment was associated with an improvement in HAQ-DI scores for both the 2 mg and 4 mg doses, and the differences between baricitinib treatment arms and placebo treatment arms were statistically significant (Table 7). The comparative efficacy between the 2 mg dose and the 4 mg dose for the physical function response showed results consistent with the clinical response discussed above. In one study (JADW), the 4 mg dose compared to 2 mg dose appeared to show slightly greater improvement in HAQ-DI; in the other study (JADX), the 2 mg dose compared to 4 mg dose appeared to show slightly greater improvement in HAQ-DI.

In the methotrexate comparative study (JADZ), baricitinib 4 mg monotherapy was statistically superior to methotrexate monotherapy, and baricitinib 4 mg monotherapy and baricitinib 4 mg plus methotrexate was similar (Table 7). In the adalimumab comparative study (JADV), baricitinib 4 mg was statistically superior to adalimumab.

Table 7. HAQ-DI change from baseline at primary analysis time point

Study *	Time	Treatment †	Mean change	Difference [95%CI] (p-value) vs placebo or mtx

Study *	Time	Treatment †	Mean change	Difference [95%CI] (p-value) vs placebo or mtx
JADV Study II	Week 12	Bar 4 mg	-0.66	-0.31 [-0.38, -0.25] (<0.001)
		Adalimumab	-0.56	
		Placebo	-0.34	
JADX Study III	Week 12	Bar 2 mg	-0.57	-0.21 [-0.31, -0.11] (<0.001)
		Bar 4 mg	-0.56	-0.19 [-0.29, -0.1] (<0.001)
		Placebo	-0.36	
JADW Study IV	Week 12	Bar 2 mg	-0.37	-0.20 [-0.31, -0.1] (<0.001)
		Bar 4 mg	-0.41	-0.24 [-0.34, -0.13] (<0.001)
		Placebo	-0.17	
JADZ Study I	Week 24	Bar 4 mg	-1.04	-0.29 [-0.41, -0.16] (<0.001)
		Bar 4 mg+mtx	-1.03	-0.23 [-0.35, -0.12] (<0.001)
		Mtx	-0.74	
* Study ID shown as Lilly's study number † Bar = Baricitinib; mtx = methotrexate				

Radiographic response in phase 3 studies:

Radiographic response was assessed in studies JADV, JADX, and JADZ using mTSS as the efficacy variable. Baricitinib 4 mg was assessed in three studies (JADV, JADX, and JADZ), whereas baricitinib 2 mg was assessed in one study (JADX). A problem with data analysis was patients on placebo crossing over to the baricitinib 4 mg and baricitinib 2 mg crossing over to baricitinib 4 mg starting from week 16, necessitating some methods to account for data for patients crossing over, and to account for missing data. Lilly's preferred method was linear extrapolation to impute data after crossing over from placebo or baricitinib 2 mg to baricitinib 4 mg, and other missing data. The extrapolation has limitations, particularly as the length of the extrapolation period increases and the amount of missing data increases. Nevertheless, this imputation method has been used historically in other RA programs. The agency statistical team's preferred method was analysis using all observed data. Using all observed data also has limitations because in this analysis some patients counted under placebo actually received baricitinib 4 mg after the crossover. Between weeks 16 to 24, some patients on placebo were crossed over to baricitinib 4 mg, and 9.2% patients on baricitinib 2 mg crossed over to 4 mg in study JADX (Table 11 in Safety section). Given that some patients classified as placebo later received baricitinib 4mg, the observed data method may underestimate the disease progression in the placebo group. This is a conservative imputation method as it would make it more difficult for the baricitinib group to show a difference at later time points.

Results of both analyses are shown in Table 8. Study JADV and JADX showed statistically significant difference between baricitinib 4 mg and placebo in both analyses. Tipping point analysis supported these findings at week 24. Study JADX showed a statistically significant difference between baricitinib 2 mg and placebo in the analysis using linear extrapolation, but not in the analysis using all observed data. Between the two analyses, the mean change for baricitinib 2 mg did not differ much (0.33 vs 0.34), but the mean change for placebo differed substantially (0.70 vs 0.49), which perhaps explains the difference in concluding statistical significance when using linear extrapolation, but not when using all observed data. It is not surprising that statistical significance for baricitinib 2 mg against placebo was lost using all observed data because in this analysis patients on baricitinib 2 mg were in effect compared

against a group that included some patients on placebo who were crossed over to baricitinib 4 mg from weeks 16 to 24.

Study JADZ showed a statistically significant difference between baricitinib 4 mg with methotrexate compared to methotrexate monotherapy, but baricitinib 4 mg alone was not consistently statistically superior to methotrexate monotherapy.

These data for radiographic response show consistent efficacy for baricitinib 4 mg dose in three studies. Radiograph response data for baricitinib 2 mg is from a single study, thus corroborative evidence from another study is not available. Nevertheless, data from the single study JADX showed statistically significant difference for baricitinib 2 mg versus placebo using linear extrapolation, a method that been used historically in most previous RA programs. Also, there are multiple DMARDs with radiographic progression claim based on a single study.

Table 8. mTSS change from baseline at primary analysis time point

Study *	Time	Treatment †	LS mean change	Difference (p-value) vs placebo or mttx
Linear extrapolation				
JADV Study II	Week 24	Bar 4 mg	0.41	-0.49 [-0.73, -0.25] (<0.001)
		Adalimumab	0.33	-0.56 [-0.83, -0.29] (<0.001)
		Placebo	0.90	
JADX Study III	Week 24	Bar 2 mg	0.33	-0.38 [-0.74, -0.01] (0.04)
		Bar 4 mg	0.15	-0.55 [-0.92, -0.19] (0.003)
		Placebo	0.70	
JADZ Study I	Week 24	Bar 4 mg	0.38	-0.23 [-0.67, 0.22] (0.3)
		Bar 4 mg+mtx	0.31	-0.62 [-1.04, -0.20] (0.004)
		Mtx	0.65	
All observed data				
JADV Study II	Week 24	Bar 4 mg	0.36	-0.43 [-0.66, -0.21] (<0.001)
		Adalimumab	0.30	-0.50 [-0.75, -0.25] (<0.001)
		Placebo	0.80	
JADX Study III	Week 24	Bar 2 mg	0.34	-0.15 [-0.42, 0.13] (0.3)
		Bar 4 mg	0.19	-0.30 [-0.58, -0.03] (0.03)
		Placebo	0.49	
JADZ Study I	Week 24	Bar 4 mg	0.62	-0.47 [-0.92, -0.02] (0.04)
		Bar 4 mg+mtx	0.31	-0.78 [-1.20, -0.36] (<0.001)
		Mtx	1.09	

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

Other measures of efficacy:

Some other measure of efficacy of note included morning joint stiffness, tiredness, and SF-36 at week 12. For these measures baricitinib was generally superior to placebo (Table 9 shows results of duration of morning stiffness, Table 10 shows results of SF36), supporting the main efficacy measures described above. In study JADX (conducted in patients with inadequate response to conventional small molecule non-biologic DMARDs) the numerical response for baricitinib 2 mg seemed to be better than baricitinib 4 mg for morning stiffness and the PCS

component of SF36, which was consistent with clinical response and physical function responses discussed earlier.

Table 9. Median change from baseline in duration of morning stiffness at primary analysis time point

Study *	Time	Treatment †	Δ minutes	Difference [95% CI] (p-value) vs placebo
JADV Study II	Week 12	Bar 4 mg	-30	-28 [-45, -15] (0.001)
		Adalimumab	-13	-10 [-25, 0] (0.015)
		Placebo	-2	
JADX Study III	Week 12	Bar 2 mg	-30	-21 [-38, -7] (0.004)
		Bar 4 mg	-20	-14 [-29, -2] (0.02)
		Placebo	-9	
* Study ID shown as Lilly's study number † Bar = Baricitinib				

Table 10. Mean SF36 results at primary analysis time point

Study *	Time	Treatment †	Score	Difference [95% CI] (p-value) vs placebo
PCS				
JADV Study II	Week 12	Bar 4 mg	8.68	4.43 [3.52, 5.35] (<0.001)
		Adalimumab	7.17	2.92 [1.89, 3.94] (<0.001)
		Placebo	4.25	
JADX Study III	Week 12	Bar 2 mg	7.96	3.67 [2.27, 5.07] (<0.001)
		Bar 4 mg	7.24	2.95 [1.53, 4.37] (<0.001)
		Placebo	4.29	
JADW Study IV	Week 12	Bar 2 mg	6.03	3.38 [1.69, 5.08] (<0.001)
		Bar 4 mg	6.37	3.73 [2.04, 5.41] (<0.001)
		Placebo	2.64	
MCS				
JADV Study II	Week 12	Bar 4 mg	3.27	0.27 [-0.86, 1.41] (0.6)
		Adalimumab	3.38	0.34 [-0.93, 1.61] (0.6)
		Placebo	2.99	
JADX Study III	Week 12	Bar 2 mg	3.14	-0.09 [-1,81, 1.63] (0.9)
		Bar 4 mg	3.48	0.25 [-1.49, 1.99] (0.8)
		Placebo	3.23	
JADW Study IV	Week 12	Bar 2 mg	2.81	1.57 [-0.32, 3.46] (0.1)
		Bar 4 mg	1.84	0.6 [-1.28, 2.47] (0.5)
		Placebo	1.24	
* Study ID shown as Lilly's study number † Bar = Baricitinib				

Subgroup analyses:

Subgroup analyses based on gender, age, ethnicity, country of origin, etc., did not show any findings of concern. Efficacy was consistent across various subgroups (Figure 2).

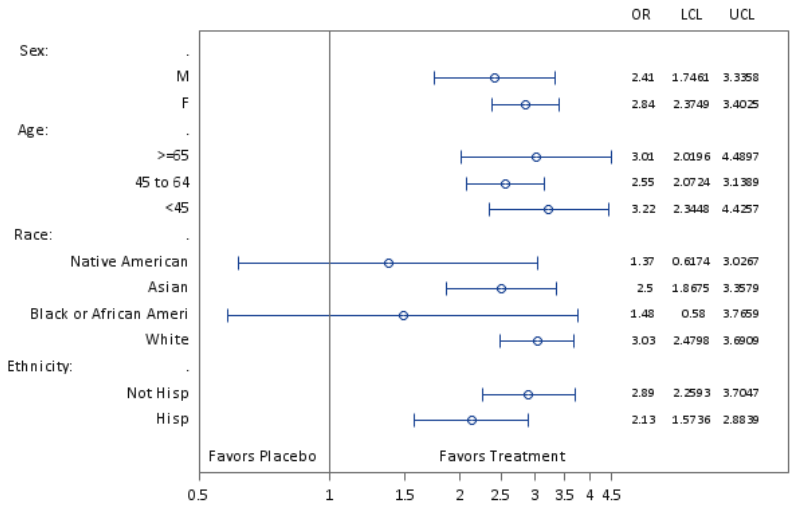

Figure 2. Meta-analysis of ACR 20 response by subgroup, Studies JADV, JADX, JADW, and JADZ.

Summary comment on efficacy:

The submitted data from four pivotal phase 3 studies showed efficacy of baricitinib at both 2 mg and 4 mg doses for signs and symptoms assessed by ACR response, as well as for physical function assessed by HAQ-DI response. Comparing the baricitinib doses showed that the proportion of patients experiencing improvement in ACR response and HAQ-DI response was numerically similar for the 2 mg and 4 mg doses. The data for structural progression assessed by radiographic response showed consistent efficacy for baricitinib 4 mg dose. Radiograph response data for baricitinib 2 mg is from a single study, thus corroborative evidence from another study is not available. Nevertheless, data from the single study show statistically significant difference for baricitinib 2 mg versus placebo using linear extrapolation method, a method that been used historically in most previous RA programs. The effect size for radiographic response for baricitinib 2 mg is not widely disparate from the effect size for baricitinib 4 mg across the three studies. Based on the efficacy data discussed above that do not show consistent benefit of 4 mg over 2 mg, along with the safety data discussed in Section 8 below that show more safety concerns for 4 mg over 2 mg, baricitinib 2 mg would appear to be the appropriate dose. This recommendation is different than the recommendation by the clinical team and statistical team who recommend both 4 mg and 2 mg dose, with 4 mg as the primary dose.

Comment on ACR response integrated analyses:

On June 24, 2016, the statistical team with concurrence of the clinical team asked Lilly to conduct an integrated analysis of 4 studies (phase 2 studies JADA and JADN, and phase 3 studies JADX and JADW). These studies were asked by the teams to be integrated because these studies included the 2 mg and 4 mg dose in each of these studies. Result of this integrated analysis showed that ACR20 response for the 4 mg dose was superior to the 2 mg

dose at week-8 with a nominal p-value of 0.04. This analysis may have partly influenced the recommended 4 mg dose as the primary dose, with the 2 mg dose as an option for some patients.

Integrated analyses of efficacy results from these studies would not be appropriate for deciding dose selection because of various differences among the studies, such as phase 2 studies being smaller in size, and shorter in duration (Table 3). Furthermore, such an integrated analysis was not specified a priori. Other integrated analyses, such as integrated analyses of the four phase 3 studies would also be problematic (note that such analysis was not conducted), because the effect sizes across the studies varied as noted above (Table 5), and only the 4 mg dose was included in the two studies (JADV and JADZ). The Division's prior precedence is to rely on individual studies for primary efficacy determination, including dose selection, and not rely on post-hoc integrated analyses. [11, 12, 13, 14] For the baricitinib RA program, phase 2 studies were conducted to explore various doses, and select doses to further assess in pivotal phase 3 studies. The individual pivotal phase 3 studies are adequately informative.

8. Safety

Safety database:

The safety assessment of baricitinib for RA is primarily based on the studies shown in Table 3. The size and scope of the safety database were reasonable and consistent with the safety database of other DMARDs approved for RA.

An important consideration in the safety analyses was crossover of patients across treatment arms (in study JADV patients crossed from placebo and adalimumab to baricitinib 4 mg starting from week 16; in studies JADX and JADW patients crossed over from placebo and baricitinib 2 mg to baricitinib 4 mg starting from week 16; in study JADZ patients crossed over from methotrexate and baricitinib 4 mg to baricitinib 4 mg plus methotrexate starting from week 24) resulting in different exposure lengths to different treatments. This resulted in different number of patients across the studies in the baricitinib 2 mg and 4 mg arms. To better characterize the safety data, the review team requested Lilly conduct additional analyses before and after crossover between treatment arms.

[11] FDA's administrative record for (b) (4) The application was not approved in April 2008. (b) (4)

Chowdhury BA, Seymour SM, Michele TM, Durmowicz AG, Liu D, Rosebraugh CJ. The risks and benefits of indacaterol – The FDA's review. N Eng J Med 2011; 365:2247-2249.

[13] Wang Y, Lee JY, Michele T, Chowdhury BA, Gobburu JV. Limitations of model based dose selection for indacaterol in patients with chronic obstructive pulmonary disease. Int J Clin Pharm Ther 2012; 50:622-630.

[14] Chin SJ, Durmowicz AG, Chowdhury BA. Tiotropium Respimat is effective for the treatment of asthma at a dose lower than that for chronic obstructive pulmonary disease. Annals Amer Thor Soc 2016; 13:173-179; Published online: 09 December 2015, as DOI: 10.1513/AnnalsATS.201510-712PS.

The safety data originally compiled and submitted in the NDA had some problems that resulted in multiple requests by the Agency review team to Lilly asking that Lilly reclassify and reanalyze the safety data. Some examples of the problems seen in the original submission included the definition of SAE Lilly used in some safety datasets, where patient withdrawal from study was classified as a SAE, which is not consistent with regulatory definition of SAE.[15] The criterion of patient withdrawal from study to define a SAE is problematic because patients could be withdrawn from the study due to lack of efficacy, which is more likely to occur in patients on placebo. It was noted that in some studies, reporting of SAEs in the placebo treatment group was more than in the active treatment groups. Another problem was that some adverse events, such as infections that were classified by study investigators as opportunistic, were not considered by Lilly as opportunistic or not an infection at all using questionable arguments. It is not typical practice that Sponsors reclassify adverse events unless there were findings of obvious errors, which was not the case for these events. Due to the submission of some new safety analyses by Lilly late in the review cycle, the PDUFA clock of the NDA review was extended by 3 months.

The primary safety data set used by Lilly and the Clinical Team of this Division for comparing baricitinib 4 mg and placebo were studies JADC, JADA, JADN, JADV, JADW, and JADX (phase 2 studies, and phase 3 studies excluding JADZ). This safety data set was also used by the Clinical Team of the Division for comparing baricitinib 2 and 4 mg doses.

Pooling of studies for safety analyses can be performed in a variety of ways. Prior to submission of the NDA (Written Response Type C meeting between Lilly and the DPARP dated January 16, 2015), the Division asked that Lilly pool the four phase 3 studies, and also pool the phase 3 and phase 2 studies for safety analyses. However, Lilly pooled studies JADC, JADA, JADN, JADV, JADW, and JADX (phase 2 studies, and phase 3 studies excluding JADZ). The rationale for excluding JADZ was lack of a placebo treatment arm as patients were naive to methotrexate and were up-titrated on methotrexate during the study. While the clinical reviews reflect this dataset, the original request by DPARP to include all four phase 3 studies in the pooled safety analysis is appropriate and preferred as these studies were conducted at around the same time (2012 to 2015 as shown in Table 3), had similar design for safety assessment, and provide the vast majority of the safety data. The rationale for excluding JADZ is questionable as the other phase 3 studies placebo treatment arms all allowed background DMARDs (e.g. methotrexate) at stable doses. In addition, exclusion of the Phase 2 studies is reasonable because of study design issues, such as higher doses of baricitinib in study JADC, twice-daily dosing in addition to once-daily dosing in JADA, and JADN conducted entirely in Japan.

[15] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

On January 6, 2017, the Division sent Lilly an information request asking for pooled analysis of all four phase 3 studies for safety events of interest (studies were JADV, JADX, JADZ, and JADW). Subsequently, further communication was held with Lilly to clarify safety analyses requests. The following safety analyses reflect this dataset. The active comparator groups in these trials (adalimumab in JADV and methotrexate in JADZ) are not included.

The crossover of patients from placebo to baricitinib 4 mg starting at week 16, and the crossover of patients from baricitinib 2 mg to 4 mg also starting from week 16 makes analysis of safety data complex. To maintain uniformity in the ascertainment of safety events, all safety events were assigned to the treatment and its dose a patient was receiving at the time of the recording, irrespective of treatment before or after crossover. To address the varying duration of exposure in different treatment groups, safety events, particularly those occurring after week 16, are presented as rates exposure-adjusted to 100 patient-years.

Due to crossover of some placebo patients to baricitinib 4 mg starting at week 16, comparison between baricitinib and placebo is not informative beyond week 16. Comparison between baricitinib 2 mg and 4 mg is difficult because the database of baricitinib 2 mg was small to begin with (403 for baricitinib 2 mg compared to 1267 for baricitinib 4 mg, Table 1), and some patients from baricitinib 2 mg also crossed over to baricitinib 4 mg starting at week 16. The number of patients crossed over from baricitinib 2 mg to 4 mg is shown in Table 11. The comparison between baricitinib 2 mg and 4 mg is less informative at later time points, particularly after week 52, because of the crossover. At the end of week 52, approximately 40% patients from baricitinib 2 mg crossed over to 4 mg.

Table 11. Patients crossed over or switched within baricitinib groups

	n	16-24 weeks Switched (%)	>24-52 weeks Switched (%)	>52 weeks Switched (%)	All weeks Switched (%)
Crossed over (rescued) from 2 mg to 4 mg, n (%)					
JADX or Study III	229	21 (9.2%)	61 (26.6%)	20 (8.7%)	102 (44.5%)
JADW or Study IV	174	38 (21.8%)	45 (25.9%)	19 (10.9%)	102 (58.6%)
JADX and JADW	403	59 (14.6%)	106 (26.3%)	39 (9.7%)	204 (50.6%)

In sections below, data integrated from the four pivotal studies (JADV, JADX, JADW, and JADZ) are shown. Data from before the safety data lock of August 10, 2015, was used in all analyses. All data and analyses in the tables and figures shown below are verified by Lilly.

Safety findings and conclusion:

The submitted safety data, along with consideration of efficacy discussed above is supportive of baricitinib 2 mg once-daily dose, but not 4 mg once-daily dose.

Safety assessment in the clinical studies included evaluation of deaths, serious adverse events (SAEs), common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. Adverse events of special interest (AESI) for baricitinib were malignancy, infections (serious infections, opportunistic infections, herpes zoster, and

tuberculosis), GI perforations, major adverse cardiovascular events (MACE), and thrombosis. Selection of these AESIs was based on the known safety profile of tofacitinib that has similar mechanism of action, other immunosuppressive DMARDs approved for RA, and laboratory findings seen in the baricitinib program.

Deaths, SAEs, and discontinuations due to AEs:

As of the data cutoff time (August 10, 2015), a total of 15 deaths were reported in the RA program. The rate of death with all available data was 0.4, 0.2, and 0.8, for baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively (Table 12). The causes of deaths were consistent with the profile of an immunosuppressant and also with other RA programs. The causes of deaths include infection, pulmonary embolus, stroke and CNS hemorrhage, MI and coronary artery disease, malignancy, etc. The overall rates of serious adverse events (SAEs) and discontinuations due to adverse events were comparable between baricitinib and placebo treatment groups (Table 12). Common causes of SAEs included malignancy, thrombosis (DVT and PE), and infection. Common causes of discontinuations due to adverse events were infections and pre-specified laboratory parameter changes.

Table 12. All cause Death, SAEs , and discontinuations due to adverse event expressed as 100 patient-years (pooled studies JADV, JADX, JADW, and JADZ; and their extension in JADY) *

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
0-16 weeks			
Number of patients	1265	403	892
Total exposure, patient years	386.7	122.6	267.2
Al case death, n (rate)	1 (0.3)	0	2 (0.7)
SAEs †, n (rate)	49 (12.7)	11 (9.0)	37 (13.8)
Discontinuations due to adverse event, n (rate)	54 (14.0)	18 (14.7)	29 (10.9)
0-52 weeks			
Total exposure, patient years	1694.9	304.8	365.0
All cause death, n (rate)	6 (0.4)	0	3 (0.8)
SAEs †, n (rate)	193 (11.4)	34 (11.2)	50 (13.7)
>52 weeks			
Total exposure, patient years	1300.6	210.2	-
All cause death, n (rate)	5 (0.4)	1 (0.5)	-
SAEs †, n (rate)	146 (11.2)	15 (7.1)	
0-any duration			
Total exposure, patient years	2995.6	515.0	365.0
All cause death, n (rate)	11 (0.4)	1 (0.2)	3 (0.8)
SAEs †, n (rate)	310 (10.3)	47 (9.1)	50 (13.7)

* Events occurring before the safety data lock of August 10, 2015
† SAEs as defined in 21 CFR 312.32

Common AEs:

Common adverse events seen were typical of studies conducted with a DMARD in rheumatoid arthritis. The three most common adverse events from pooled pivotal phase 3 studies are shown in Table 13.

Table 13. Common adverse events from 0-16 weeks of treatment expressed as 100 patient-years (pooled studies JADV, JADX, JADW, and JADZ) *

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
0-16 weeks			
Number of patients	1265	403	892
Total exposure, patient years	386.7	122.6	267.2
Nasopharyngitis, n (rate)	69 (17.8)	14 (11.4)	45 (16.8)
Upper respiratory tract infection, n (rate)	54 (14.0)	27 (22.0)	33 (12.3)
Headache, n (rate)	41 (10.6)	29 (23.7)	27 (10.1)
* Events occurring before the safety data lock of August 10, 2015			

Laboratory parameters:

Baricitinib treatment was associated with rapid and sustained decrease in neutrophil count, increase in platelet count, increase in liver enzymes and bilirubin, increase in lipid parameters, and increase in creatinine phosphokinase; all occurring in a dose-related manner with baricitinib treatment (Table 14). Increase in platelet count is unique for baricitinib, and has not been seen previously for other JAK inhibitors (such as tofacitinib approved for RA), or other DMARDs. Increase in platelet count may be related to thrombotic events seen in the baricitinib clinical program (discussed later). Increase in serum creatinine phosphokinase did not seem to be associated with muscle related adverse events in the baricitinib clinical program. Changes in neutrophil count and increase in lipid parameters are often seen with other DMARDs. Changes in neutrophil count may be associated with infection, which is a common adverse event with DMARDs. Clinical consequence in changes in lipid parameters is difficult to predict, although MACE is one concern (discussed later). Inflammation in RA is a known cardiovascular risk, DMARDs, including baricitinib, is likely to reduce the inflammation in RA, and patients with increased lipids are likely to be treated with lipid lowering drugs as part of normal clinical care.

The phase 3 studies had patient withdrawal criteria based on laboratory parameters. A total of 31 patients (1.1%) were withdrawn from the phase 3 studies due to abnormal laboratory parameters: 1.7% from baricitinib 4 mg, 1.2% from baricitinib 2 mg, and 0.3% from placebo. The most common cause was for abnormal liver function tests (3 from JADV, 2 from JADW, 4 from JADZ, and 1 from JADX; all were from baricitinib 4 mg group except one patient in JADX from baricitinib 2 mg group). Two patients were withdrawn for persistent elevation in platelet count, both from baricitinib 4 mg group.

Table 14. Laboratory parameter as mean change from baseline and threshold change as n (rate) (pooled studies JADV, JADX, JADW, and JADZ) *

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
0-16 weeks			
Number of patients	1265	403	892
Total exposure, patient years	379.9	119.6	260.8
Hemoglobin, mean change	-0.26	-0.30	-0.20
Hemoglobin, LLN threshold change, n (rate)	251 (29.2)	74 (25.8)	156 (25.2)
Neutrophil, mean change	-1.09	-0.60	0.10
Neutrophil, LLN threshold change, n (rate)	101 (8.2)	25 (6.3)	19 (2.2)
Lymphocyte, mean change	0.15	0.11	-0.01
Lymphocyte, LLN threshold change, n (rate)	70 (5.9)	24 (6.3)	79 (9.8)

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
Platelet, mean change	17	16	2
Platelet, ULN threshold change, n (rate)	260 (24.6)	60 (17.1)	71 (9.4)
ALT (IU/L), mean change	5.9	3.2	-0.1
ALT (IU/L), 3X ULN threshold change, n (rate)	20 (1.6)	5 (1.3)	10 (1.1)
AST (IU/L), mean change	4.9	1.3	0.1
AST (IU/L), 3X ULN threshold change, n (rate)	9 (0.7)	4 (1.0)	8 (0.9)
Total bilirubin (mg/dl), mean change	0.050	0.018	-0.014
Total bilirubin (mg/dl), ULN threshold change	20 (1.6)	2 (0.5)	10 (1.1)
LDL chol (mg/dL), mean change	15	8	-1
LDL chol (mg/dL), ULN threshold change	267 (31.5)	52 (19.6)	59 (11.2)
HDL chol (mg/dL), mean change	9.2	6.5	0.2
HDL chol (mg/dL), ULN threshold change	202 (18.8)	42 (12.8)	32 (4.5)
Triglyceride (mg/dL), mean change	15	5	-2
Triglyceride (mg/dL), ULN threshold change	60 (5.4)	17 (4.9)	21 (2.8)
Serum CPK (mg/dL), mean change	54	38	0
Serum CPK (mg/dL), ULN threshold change	374 (31.9)	79 (20.9)	67 (8.2)
0-52 weeks			
Total exposure, patient years	1668.8	297.9	354.4
Hemoglobin, mean change	0.00	-0.13	-0.11
Hemoglobin, LLN threshold change, n (rate)	456 (29.4)	86 (30.0)	166 (26.8)
Neutrophil, mean change	-0.96	-0.48	0.04
Neutrophil, LLN threshold change, n (rate)	199 (9.1)	34 (8.5)	25 (2.9)
Lymphocyte, mean change	0.00	0.01	-0.01
Lymphocyte, LLN threshold change, n (rate)	219 (10.3)	35 (9.3)	87 (10.7)
Platelet, mean change	21	22	2
Platelet, ULN threshold change, n (rate)	463 (24.2)	69 (19.7)	77 (10.1)
ALT (IU/L), mean change	6.2	3.5	0.4
ALT (IU/L), 3X ULN threshold change, n (rate)	48 (2.2)	6 (1.5)	13 (1.5)
AST (IU/L), mean change	5.9	2.0	1.0
AST (IU/L), 3XULN threshold change, n (rate)	27 (1.2)	4 (1.0)	12 (1.4)
Total bilirubin (mg/dl), mean change	0.043	0.016	-0.001
Total bilirubin (mg/dl), ULN threshold change	46 (2.1)	5 (1.2)	11 (1.3)
LDL chol (mg/dL), mean change	14	8	-2
LDL chol (mg/dL), ULN threshold change	604 (40.7)	87 (32.6)	77 (14.6)
HDL chol (mg/dL), mean change	8.0	5.9	0.2
HDL chol (mg/dL), ULN threshold change	446 (24.6)	62 (18.8)	44 (6.2)
Triglyceride (mg/dL), mean change	16	5	-1
Triglyceride (mg/dL), ULN threshold change	202 (10.1)	32 (9.2)	33 (4.4)
Serum CPK (mg/dL), mean change	64	35	8
Serum CPK (mg/dL), ULN threshold change	786 (37.4)	111 (29.4)	77 (9.4)

* Laboratory parameter change (mean and threshold) is calculated based on patients who had the same laboratory measures assessed at baseline and at later time point during study, noting that all patients did not have all measure at all time points; Rate represents percentage of patients

Adverse events of special interest:

In subsequent sections some adverse events of interest (AESI) for baricitinib are briefly discussed.

Malignancy:

In the baricitinib pivotal phase 3 studies for RA, as counted by Lilly, there were 29 cases of malignancies, 25 occurring in patients on baricitinib (excluding non-melanoma skin cancer), all of types typical of patients enrolled in RA studies. The malignancy cases were not adjudicated. Investigator diagnosis of malignancy was the first step in identifying a

malignancy event, with subsequent review by Lilly. Table 14 lists the cases of malignancy as reported by investigators. Some of these cases were proposed to be discounted by Lilly for the following reasons: likely symptoms of malignancy before receiving baricitinib or malignancy occurring very early, such as within 60 days; history of prior malignancy elsewhere in the body; risk factors for diagnosis of malignancy. Lilly's reasons for discounting malignancy are questionable and only two cases were ultimately discounted. Furthermore, in a randomized study the reasons raised by Lilly would apply to all treatment arms equally.

The two cases that Lilly did not agree to count as malignancy were (b) (6) and (b) (6), both in the baricitinib 4 mg group. Lilly evaluated these cases in detail and concluded that the diagnosis was not definitive of malignancy, and coded these cases with terms that do not belong to malignant tumors SMQ. (b) (6) was a 70-year-old man with worsening hematological parameters during treatment with baricitinib 4 mg that was reported by investigator as "lymphoproliferative disorder." During 9 months follow-up a number of differential diagnoses were suspected – B cell chronic lymphatic leukemia, Mantle cell lymphoma, and Non-Hodgkin's Lymphoma, but no definitive diagnosis was reached. Lilly does not consider this case as malignancy and retained the "lymphoproliferative disorder" as the diagnosis. (b) (6) was a 59-year-old female reported initially by investigator as "large granular lymphocytosis (lymphoproliferative)" and later reported as "T-cell large granular lymphocytic leukemia" based on flow cytometry. Lilly contends that "T-cell large granular lymphocytic leukemia tends to run an indolent course with a third requiring no treatment and the remaining two-thirds responding well to intermittent immunosuppressive therapy with an overall 5-year survival of about 90%" (Lilly cites the following literature reference: Dhodapkar MV et al., Blood 1994; 84:1620-7). Lilly thus categorized this patient report in the "tumors of unspecified malignancy" SMQ and not the "malignant tumors" SMQ.

In addition, there is one questionable case in baricitinib 2 mg group that Lilly counts as malignancy: (b) (6), which was diagnosed 19 days into treatment as "ovarian low malignant potential tumor," and later on surgical pathology diagnosed as "ovarian papillary neoplasm." The early diagnosis makes the association with baricitinib unlikely.

Table 16 and Figure 3 show analyses of the cases of malignancy. This analysis excludes the two patients in baricitinib 4 mg group and includes one patient in the baricitinib 2 mg group discussed above. The rate (exposure adjusted to 100 patient-years) of malignancy (excluding non-melanoma skin cancer) with all available data was 0.8, 0.4, and 0.5, for baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively. The hazards ratio comparing baricitinib 4 mg and baricitinib 2 mg was 1.8 [95% CI 0.40, 8.12] with the imbalance driven primarily by >52 weeks data. Table 17 shows alternate analyses of malignancy comparing baricitinib 4 mg and 2 mg by including the two cases that Lilly discounts, and excluding cases occurring too early with treatment with baricitinib. Interpretation of the malignancy data is challenging given the limited exposure in the placebo and baricitinib 2 mg groups due to crossover from these groups to the baricitinib 4 mg group. Therefore, the analyses may overestimate the risk of malignancies associated with the baricitinib 4 mg group. That being said, malignancy is a concern with immunosuppressant and the long-term data raise concern about malignancy with the baracitinib 4 mg dose. Overall, the baricitinib clinical program does not exclude an overall risk of malignancy with either dose of baricitinib.

Non-melanoma skin cancer listing is shown in Table 18. The trends were similar to malignancy excluding non-melanoma skin cancer discussed above. Analysis of all malignancy, including non-melanoma skin cancer, is shown in Figure 4. The hazard ratio comparing baricitinib 4 mg and baricitinib 2 mg was 1.1 [95% CI 0.41, 3.03].

During the controlled period of the phase 2 studies JADA, JADC, and JADN, there were 3 cases of malignancy (rectal cancer, chondrosarcoma, and basal cell cancer) out of 458 patients. All the malignancies were in baricitinib 4 mg or 8 mg treatment groups.

Table 15. Malignancy (excluding non-melanoma skin cancer) in pivotal studies JADV, JADX, JADW, and JADZ, (and their extension in JADY) listed in order of length of duration of treatment before diagnosis

Patient ID	Treatment Duration *	Malignancy type	Crossover
Baricitinib 4 mg (25 cases of malignancy + 2 cases not counted by Lilly)			
(b) (6)	29 days	Fibrous histiocytoma †	Adalimumab in JADV to JADY baricitinib 4mg
	49 days	Adrenocortical carcinoma †	No crossover
	92 days	Lymphoproliferative //	Adalimumab to baricitinib 4 mg on week 28
	109 days	Breast cancer ‡	No crossover
	161 days	Squamous cell lung cancer §	No crossover
	162 days	Squamous cell lung cancer ¶	Placebo to baricitinib 4 mg crossover on week 16
	204 days	Malignant melanoma ‡	No crossover
	229 days	Ovarian cancer ‡	Placebo to baricitinib 4 mg crossover on week 20
	259 days	Adenocarcinoma colon †	Placebo to baricitinib 4 mg crossover on week 20
	259 days	Laryngeal cancer ¶	Placebo in JADW to JADY baricitinib 4 mg
	283 days	Clear cell renal cancer ¶	No crossover
	316 days	Adenocarcinoma pancreas ¶	Placebo to baricitinib 4mg crossover on week 24
	334 days	Cervical carcinoma ¶	No crossover
	338 days	Lymphoproliferative //	No crossover
	341 days	MALT lymphoma †	Placebo to baricitinib 4mg crossover on week 20
	345 days	Gallbladder adeno-sq ca ¶	No crossover
	357 days	Adenocarcinoma of colon ¶	No crossover
	361 days	Renal cancer ¶	No crossover
	399 days	B cell lymphoma	Placebo to baricitinib 4 mg crossover on week 20
	401 days	Ductal breast cancer ¶	No crossover
	450 days	Prostate cancer †	Adalimumab to baricitinib 4 mg crossover on week 20
	479 days	Lung cancer ¶	Baricitinib 2 mg to baricitinib 4 mg crossover or month 9
	504 days	T cell lymphoma ‡	Placebo to baricitinib 4 mg crossover on week 20
	518 days	Gastric cancer ¶	Placebo to baricitinib 4 mg crossover on week 28
	529 days	Lung cancer §	No crossover
	575 days	Clear cell renal cancer ¶	Baricitinib 2 mg to baricitinib 4 mg crossover or month 9
	690 days	Breast cancer ¶	No crossover
Baricitinib 2 mg (2 cases of malignancy)			
(b) (6)	19 days	Ovarian low malig. pot. †	No crossover
	339 days	Ductal breast cancer §	No crossover
Placebo (2 cases of malignancy)			
(b) (6)	119 days	Breast cancer ¶	No crossover
	140 days	Ovarian cancer ¶	No crossover

* Days (closest approximate) after treatment when the malignancy was diagnosed

† ‡ § Malignancy cases proposed to be discounted by Lilly for the following reasons [pages 179-181 of Summary of Clinical Safety]; these cases were ultimately not discounted:

† likely symptoms of malignancy before receiving baricitinib, or malignancy occurring very early, such as within 60 days;

‡ history of prior malignancy elsewhere in the body;

§ risk factors (lung cancer in cigarette smoker or family history of cancer) for diagnosis of malignancy;

¶ Malignancy cases not proposed to be discounted by Lilly because of the reason that these "did not have features that would affect their underlying risk for malignancy"

Patient ID	Treatment Duration *	Malignancy type	Crossover
// Lilly does not consider these two cases as malignancy			

Table 16. Number of patients with malignancy and rates of malignancy expressed as 100 patient years (pooled studies JADV, JADX, JADW, and JADZ; and their extension in JADY) * †

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
0-16 weeks			
Number of patients	1265	403	892
Total exposure, patient years	386.7	122.6	267.2
Any malignancy, n (rate)	4 (1.0)	1 (0.8)	1 (0.4)
Any malignancy minus nmsc§, n (rate)	2 (0.5)	1 (0.8)	0
0-52 weeks			
Total exposure, patient years	1694.9	304.8	365.0
Any malignancy, n (rate)	17 (1.0)	4 (1.3)	3 (0.8)
Any malignancy minus nmsc§, n (rate)	10 (0.6)	2 (0.7)	2 (0.5)
>52 weeks			
Total exposure, patient years	1300.6	210.2	-
Any malignancy, n (rate)	21 (1.6)	1 (0.5)	-
Any malignancy minus nmsc§, n (rate)	15 (1.2)	0	
0-any duration †			
Total exposure, patient years	2995.6	515.0	365.0
Any malignancy, n (rate)	37 (1.2)	5 (1.0)	3 (0.8)
Any malignancy minus nmsc*, n (rate)	25 (0.8)	2 (0.4)	2 (0.5)

* Does not include two cases of malignancy in baricitinib 4 mg group that are discounted by Lilly
† Events occurring before the safety data lock of August 10, 2015
§ nmsc = non-melanoma skin cancer

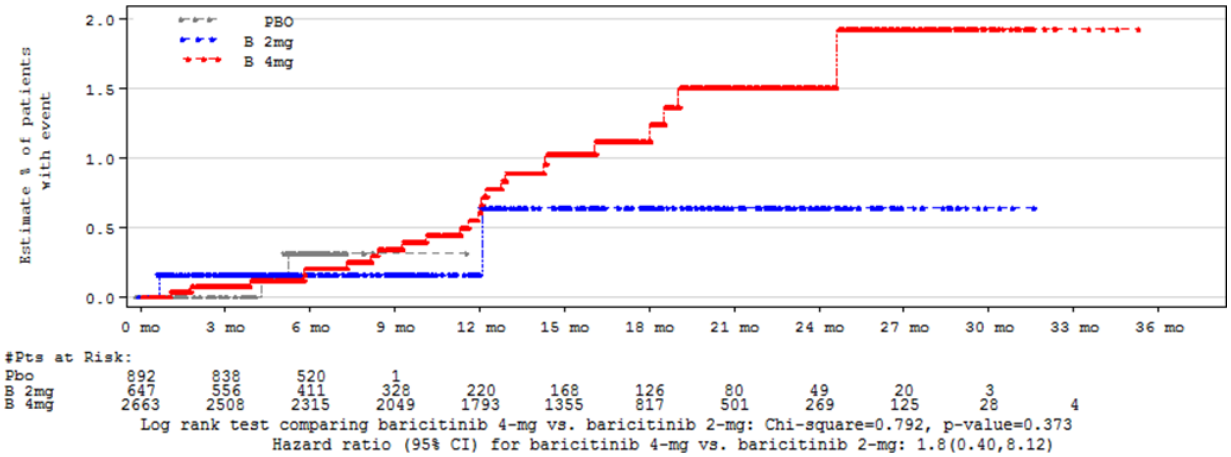

Figure 3. Kaplan-Meier plots from randomization to end of follow-up for malignancies (excluding non-melanoma skin cancers) for baricitinib 4 mg, baricitinib 2 mg, and placebo pooled across four pivotal phase 3 studies. Patients contribute time and events based on their cumulative exposure to each individual dose. Patients who crossover from placebo to baricitinib 2 mg or from baricitinib 2 mg to baricitinib 4 mg contribute time and events to assigned group before the crossover, and to the new assigned groups after the crossover. Hazard ratio [95% CI] comparing baricitinib 2 mg and baricitinib 4 mg was 1.8 [0.40, 8.12].

Table 17. Malignancy (excluding non-melanoma skin cancer) occurring in any duration in pivotal studies JADV, JADX, JADW, and JADZ (and their extension in JADY) shown as number of cases, rates expressed as 100 patient-years, and hazard ratio [95% confidence interval]; effect of different censoring methods

Censoring methods	No. of cases		Rate (100 pt-yrs)		HR [95% CI]
	4 mg	2 mg	4 mg	2 mg	4 mg vs 2 mg
Lilly's preferred:					
Exclude (b) (6) *; Include (b) (6)	25	2	0.8	0.4	1.8 [0.40, 8.12]
Alternates:					
Include (b) (6) *; Include (b) (6)	27	2	0.9	0.4	2.0 [0.45, 8.97]
Exclude (b) (6) *; exclude <30 days	24	1	0.8	0.2	3.4 [0.44, 26.11[
Exclude (b) (6) *; exclude <60 days‡	23	1	0.8	0.2	3.3 [0.43, 25.78]

* Lilly does not consider these two cases as malignancy
† Excludes cases occurring within 30 days of treatment with baricitinib (b) (6) from 4mg, (b) (6) from 2mg
‡ Excludes cases occurring within 60 days of treatment with baricitinib (b) (6) from 4mg, (b) (6) from 4mg, (b) (6) from 2mg

Table 18. Non-melanoma skin cancer (NMSC) in pivotal studies JADV, JADX, JADW, and JADZ, listed in order of length of duration of treatment before diagnosis

Patient ID	Treatment Duration *	Malignancy type	Crossover
Baricitinib 4 mg (12 cases of NMSC)			
(b) (6)	35 days	Basal cell carcinoma †	No crossover
	41 days	Squamous and basal cell ca †	No crossover
	147 days	Squamous cell carcinoma §	No crossover
	150 days	Basal cell carcinoma ¶	No crossover
	165 days	Basal cell carcinoma ¶	No crossover
	182 days	Squamous cell carcinoma ¶	No crossover
	215 days	Basal cell carcinoma †	Placebo to baricitinib 4 mg on week 24
	323 days	Basal cell carcinoma ¶	No crossover
	344 days	Squamous and basal cell ca ¶	Placebo to baricitinib 4 mg on week 24
	372 days	Bowen's disease †	No crossover
	390 days	Squamous cell carcinoma ¶	No crossover
	547 days	Squamous cell carcinoma §	Adalimumab in JADV to JADY baricitinib 4mg
Baricitinib 2 mg (3 cases of NMSC)			
(b) (6)	180 days	Squamous cell carcinoma	No crossover
	297 days	Squamous cell carcinoma §	No crossover
	690 days	Squamous cell carcinoma §	Baricitinib 4 mg to 2 mg crossover on month 15
Placebo (1 case of NMSC)			
(b) (6)	19 days	Squamous cell carcinoma ¶	No crossover

* Days (closest approximate) after treatment when the malignancy was diagnosed
† ‡ § NMSC cases proposed to be discounted by Lilly for the following reasons [pages 185-186 of Summary of Clinical Safety]; these cases were ultimately not discounted:
† likely had NMSC prior to treatment with baricitinib;
‡ history of NMSC prior to entry into the study;
§ risk factors (sun exposure, working outdoors) for NMSC;
¶ NMSC cases with no risk factors or previous history [page 186 of Summary of Clinical Safety]

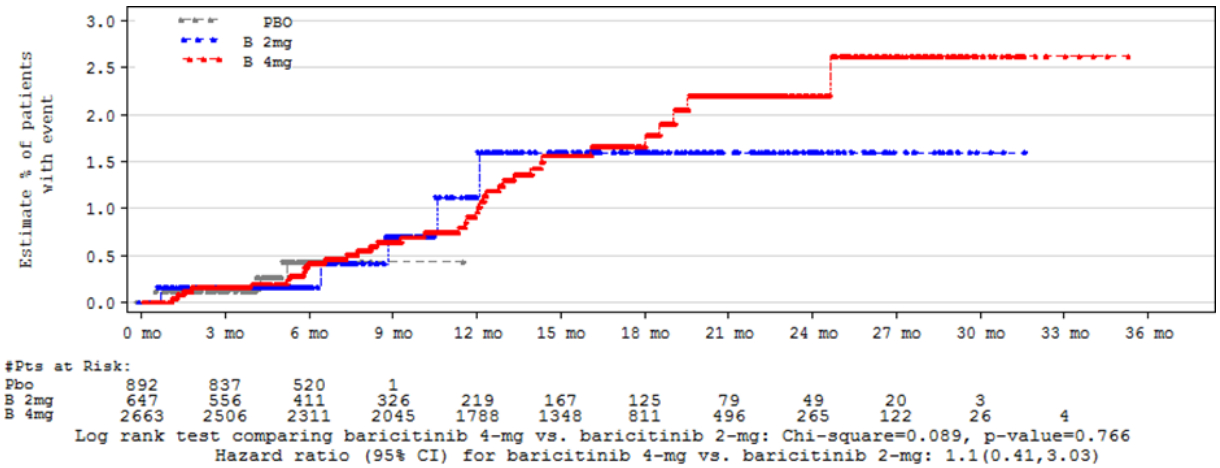

Figure 4. Kaplan-Meier plots from randomization to end of follow-up for malignancies (including non-melanoma skin cancers) for baricitinib 4 mg, baricitinib 2 mg, and placebo pooled across four pivotal phase 3 studies. Patients contribute time and events based on their cumulative exposure to each individual dose. Patients who crossover from placebo to baricitinib 2 mg or from baricitinib 2 mg to baricitinib 4 mg contribute time and events to assigned group before the crossover, and to the new assigned groups after the crossover. Hazard ratio [95% CI] comparing baricitinib 2 mg and baricitinib 4 mg was 1.1 [0.41, 3.03].

Infections:

Common infections occurred more with baricitinib treatment compared to placebo. Such injections were upper respiratory tract infections, herpes zoster, and herpes simplex. Results of analyses of infection events are shown in Table 20. The rate (exposure adjusted to 100 patient-years) of herpes zoster tended to be higher with baricitinib compared to placebo, but the rates were comparable between baricitinib 4 mg and 2 mg doses.

Table 19. Infections (SAE of infections, potential opportunistic infections, tuberculosis, and herpes zoster) as numbers and rates expressed as 100 patient years (pooled studies JADV, JADX, JADW, and JADZ, and their extension in JADY)

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
0-16 weeks			
Number of patients	1265	403	892
Total exposure, patient years	386.7	122.6	267.2
Patients with SAE of infections, n (rate)	13 (3.4)	4 (3.3)	13 (4.9)
Patients with opportunistic infections, n (rate)	4 (1.0)	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, patient years	1694.9	304.8	365.0
Patients with SAE of infections, 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, patient years	1300.6	210.2	-
Patients with SAE of infections, 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	-

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
Patients with herpes zoster, n (rate)	38 (2.9)	6 (2.9)	-
0-any duration *			
Total exposure, patient years	2995.6	515.0	365.0
Patients with SAE of infections, n (rate)	97 (3.2)	17 (3.3)	17 (4.7)
Patients with opportunistic infections, n (rate)	14 (0.5)	2 (0.4)	2 (0.5)
Patients with tuberculosis, n (rate)	7 (0.2)	0	0
Patients with herpes zoster, n (rate)	94 (3.1)	17 (3.3)	4 (1.1)
* Events occurring before the safety data lock of August 10, 2015			

There were multiple cases of opportunistic infections and tuberculosis reported in the clinical program (listed in Table 21). In the original NDA submission, Lilly discounted all opportunistic infections using arguments that were questionable. There were 7 cases of tuberculosis in baricitinib 4 mg group, compared to none in the baricitinib 2 mg and placebo groups. All pivotal phase 3 studies excluded patients from enrollment who had evidence of active tuberculosis, history or examination suggestive of tuberculosis.

Table 20. Infections (potential opportunistic, and tuberculosis) in pivotal studies JADV, JADX, JADW, and JADZ, and their extension in JADY

Patient ID	Treatment Duration *	Infection type	Crossover, [SAE or not SAE]
Baricitinib 4 mg (14 cases of opportunistic infection, 7 cases of tuberculosis)			
(b) (6)	11 days	Oesophageal candidiasis	No crossover, [not SAE]
	69 days	Zoster, multidermal	No crossover, [SAE]
	70 days	Oesophageal candidiasis	No crossover, [not SAE]
	99 days	Pneumocystis pneumonia	No crossover, [SAE, hospitalized]
	120 days	Oesophageal candidiasis	No crossover, [not SAE]
	154 days	Oesophageal candidiasis	Placebo to baricitinib crossover on week 24, [not SAE]
	171 days	Zoster, multidermal	No crossover, [SAE]
	228 days	Zoster, multidermal	Pbo to bari crossover on wk 20, [SAE, hospitalized]
	233 days	Zoster, multidermal	Pbo to bari crossover on wk 24, [not SAE]
	446 days	Zoster, multidermal	Bari 2mg to 4mg crossover on wk 24 [SAE, hospitalized]
	498 days	Candida lung infection	No crossover [not SAE]
	517 days	Zoster, multidermal	Placebo to baricitinib crossover on week 24, [not SAE]
	566 days	Parecoccidiodes infection	No crossover, [SAE, hospitalized]
	711 days	Cytomegalovirus infection	No crossover, [SAE, hospitalized]
	137 days	Tuberculosis	No crossover, [SAE, hospitalized]
	218 days	Tuberculosis	Pbo to baricitini crossover on wk 16, [SAE, hospitalized]
	396 days	Tuberculosis	No crossover, [SAE]
	474 days	Tuberculosis	No crossover, [SAE, hospitalized]
	516 days	Tuberculosis	No crossover, [SAE, hospitalized]
	566 days	Tuberculosis	No crossover, [SAE, hospitalized]
	612 days	Tuberculosis	No crossover, [not SAE]
Baricitinib 2 mg (2 cases of opportunistic infection)			
(b) (6)	264 days	Histoplasmosis	No crossover, [SAE, hospitalized]
	460 days	Cryptococcal pneumonia	No crossover, [SAE, hospitalized]
Placebo (2 cases of opportunistic infection)			
(b) (6)	2 days	Zoster, multidermal	No crossover, [SAE]
	9 days	Candida muscle abscess	No crossover, [SAE, hospitalized]
* Days (closest approximate) after treatment when the infection was diagnosed			

Gastrointestinal (GI) perforations:

There were 6 cases of possible GI perforations of which 4 cases were possibly related to abscesses. Of the 6 cases, 4 occurred in patient on baricitinib 4 mg, 2 occurred in patients on baricitinib 2 mg, and 0 occurred in patients on placebo.

Major adverse cardiovascular events (MACE) analysis:

MACE analysis to assess cardiovascular safety was of interest because of the known lipid profile alteration in patients with RA, effects of DMARDs including tofacitinib on lipid profile, and the effect of baricitinib on lipid profile (Table 13). A blinded committee external to Lilly adjudicated potential cardiovascular adverse events. The rate (exposure adjusted to 100 patient-years) of MACE with all available data was 0.5, 0.2, and 0.5, for baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively (Table 22), with the imbalance driven primarily by >52 weeks data. The hazards ratio comparing baricitinib 4 mg and baricitinib 2mg was 2.9 [95% CI 0.37, 23.26]. The ratio was estimated using Cox Proportional hazards models with treatment as a covariate, stratified by study. The pivotal phase 3 studies enrolled patients who had low-to-intermediate risk of cardiovascular disease (less than 10% of patients were considered high risk by Framingham 10-year cardiovascular risk score at baseline, and approximately 10% patients were considered moderate-to-high or high risk by Reynolds 10-year cardiovascular risk score). The studies allowed lipid lowering drugs and patients were started on such drugs due to increase in lipid levels. With treatment, lipid levels changed as expected.

Similar to the malignancy data discussed earlier, interpretation of the MACE data is challenging given the limited exposure in the placebo and baricitinib 2 mg groups due to crossover from these groups to the baricitinib 4 mg group. Therefore, the analyses may overestimate the risk of MACE associated with the baricitinib 4 mg group. That being said, MACE is a concern with changes in lipid parameter with baricitinib and the long-term data raise concern with the baricitinib 4 mg dose. Overall, the baricitinib clinical program does not exclude an overall risk of MACE with either dose of baricitinib.

Table 21. MACE events (pooled studies JADV, JADX, JADW, and JADZ, and their extension in JADY)

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
0-16 weeks			
Total exposure in patient years	386.7	122.6	267.2
Patients with MACE, n (rate)	2 (0.5)	0	2 (0.7)
0-52 weeks			
Total exposure, patient years	1694.9	304.8	365.0
Patients with MACE, n (rate)	7 (0.4)	1 (0.3)	2 (0.5)
>52 weeks			
Total exposure in patient years	1300.6	210.2	-
Patients with MACE, n (rate)	8 (0.6)	0	
0-any duration *			
Total exposure in patient years	2995.6	515.0	365.0
Patients with MACE, n (rate) †	15 (0.5)	1 (0.2)	2 (0.5)
Cardiovascular death, n (rate)	6 (0.2)	0	1 (0.3)
Myocardial infarction, n (rate)	8 (0.3)	1 (0.2)	1 (0.3)

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo
Stroke, n (rate)	4 (0.1)	0	1 (0.3)

* Events occurring before the safety data lock of August 10, 2015

† MACE defining event was the first event. Some patients had more than one event. For baricitinib 4 mg group: One patient (b) (6), placebo to baricitinib crossover) had myocardial infarction and cardiovascular death. One Patient (b) (6), no crossover) had stroke and cardiovascular death. One patient (b) (6), no crossover) had stroke and cardiovascular death. For placebo group: One patient (b) (6)) had stroke and cardiovascular death.

Thrombosis:

Thrombosis event analysis was of interest because of increase in platelet count with baricitinib (Table 13). Thrombosis events reported as DVT and PE were higher with baricitinib compared to placebo, but with no clear difference between baricitinib 4 mg and 2 mg doses (Table 23, Table 24). Platelet counts were higher in 4 mg dose group compared to the 2 mg dose group in patients with these DVT and PE events. These cases do not establish a clear relationship between platelet elevation and thrombosis, but the events do raise concerns that baricitinib induced platelet elevation may be linked to thrombosis in a dose-dependent way.

During the controlled period of the phase 2 studies JADA, JADC, and JADN, there were 2 cases of thrombosis events (thrombophlebitis in baricitinib 7 mg, and DVT in baricitinib 4 mg) out of 458 patients.

In the phase 3 studies there were some cases of arterial thrombosis as well. Arterial occlusive disease in leg was diagnosed in a patient with infected leg skin ulcer (b) (6), baricitinib 2 mg). Another case of arterial occlusive disease in the leg was diagnosed in a patient with history of diabetes and coronary artery disease (b) (6), baricitinib 4 mg). Finally, a patient with history of interstitial lung disease was diagnosed to have brachial artery thrombosis (b) (6), baricitinib 4 mg).

Table 22. 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

Table 23. Platelet counts in patients with DVT and PE events in pivotal studies JADV, JADX, JADW, and JADZ, and their extension in JADY

Patient ID	Treatment Duration *	Platelet counts			Crossover	Thrombosis events [SAE or not SAE]
		Baseline	Week 16	Last available†		
Baricitinib 4 mg (16 cases)						
(b) (6)	37 days	327	446	431	No	PE [not SAE]
	50 days	219	NA	274	No	PE [SAE, Hospitalized]
	66 days	234	301	320	No	PE [SAE, Hospitalized]
	113 days	589	652	669	No	DVT [not SAE]
	142 days	282	226	289	Pbo wk 24	DVT [not SAE]
	150 days	249	286	368	No	DVT [not SAE]
	169 days	362	324	572	Pbo wk 24	PE [SAE, Hospitalized]
	260 days	260	299	332	No	PE [SAE, Hospitalized]
	295 days	200	155	223	Pbo wk 24	DVT and PE [SAE, Hospitalized]
	330 days	278	224	354	Pbo wk 24	DVT [SAE, Hospitalized]
	395 days	264	307	326	No	DVT [SAE, Hospitalized]
	431 days	233	282	303	No	PE [SAE, Hospitalized]
	443 days	243	258	333	No	DVT [not SAE]
	466 days	174	226	255	No	PE [SAE, Hospitalized]
	479 days	275	238	385	No	DVT and PE [SAE, Hospitalized]
	523 days	219	292	308	No	PE [SAE, Hospitalized, Death]
Δ mean platelet from baseline			21.8	83.4		
Baricitinib 2 mg (2 cases)						
(b) (6)	205 days	186	230	230	No	DVT [SAE, Hospitalized]
	298 days	315	171	327	No	DVT [SAE, Hospitalized]
Δ mean platelet from baseline			-50	28		
Placebo (no cases)						
None						

* Days (closest approximate) after treatment when the thrombosis was diagnosed
† Higher of the two counts available as maximum prior to event or concurrent to event

Comparison to adalimumab:

In a single study where baricitinib 4 mg was compared to adalimumab, the adverse event profiles for some laboratory parameters and clinical measures were numerically worse with baricitinib compared to adalimumab (Table 23). Changes in lipid parameters that are often seen with DMARDs occurred with both baricitinib and adalimumab compared to placebo, but the change was higher with baricitinib 4mg compared to adalimumab. The superior efficacy seen with baricitinib 4 mg compared to adalimumab may be associated with worse safety.

Table 24. Selected relevant safety data from study JADV, week 0 to 24 (data prior to crossover)

	Placebo N=488, PYE=197.7	Baricitinib 4 mg N=487, PYE=215	Adalimumab N=330, PYE=141.9
Laboratory parameters, expressed as mean change from baseline			
Hemoglobin (g/dL)	-0.04	-0.02	0.5
Neutrophils (thousand cells/microL)	-0.36	-0.98	-1.21
Lymphocyte (thousand cells/microlL)	0	0.05	0.38
Platelets (thousand cells/micrlL)	-2	12	-35
Total cholesterol (mg/dL)	-2	26	11
LDL cholesterol (mg/dL)	-2	16	7
HDL cholesterol (mg/dL)	0.1	9.4	3.8
Triglyceride (mg/dL)	-3	16	7

	Placebo N=488, PYE=197.7	Baricitinib 4 mg N=487, PYE=215	Adalimumab N=330, PYE=141.9
Clinical adverse events, expressed as number (percentage) [rate per 100 patient year]			
Death	0	2 (0.4)	0
Infection, treatment emergent	134 (28) [68]	176 (36) [82]	110 (33) [78]
Infection, reported as SAE	7 (1.4) [3.5]	5 (1) [2.3]	2 (0.6) [1.4]
Malignancy	3 (0.6) [1.52]	2 (0.4) [0.93]	0
Deep vein thrombosis	0	1 (0.2) [0.47]	0
Pulmonary embolism	0	1 (0.2) [0.47]	0

Summary comment on safety:

Baricitinib treatment was associated with rapid and sustained decrease in neutrophil count, increase in platelet count, increase in liver enzymes and bilirubin, increase in lipid parameters, and increase in creatinine phosphokinase; all occurring at frequencies higher with baricitinib compared to placebo, and all at frequencies higher with baricitinib 4 mg compared to baricitinib 2 mg. The laboratory findings alone raises concern about higher safety risk with baricitinib 4 mg compared to baricitinib 2 mg, and given no convincing efficacy benefit of the 4 mg dose over the 2 mg dose, would tip the benefit-risk assessment in favor of the 2 mg dose over the 4 mg dose. Some clinical findings also went along with the laboratory findings, suggestive of higher safety risk with baricitinib 4 mg compared to 2 mg.

The clinical findings showed that baricitinib treatment in patients with RA is associated with possible increased risks of malignancy, opportunistic infections, tuberculosis, herpes zoster infection, MACE, and thrombosis. There was a numerical increased rate of malignancy, tuberculosis, and MACE with baricitinib 4 mg compared to 2 mg. Malignancy and infection related safety findings are consistent with the mechanism of action of baricitinib as a potent immunosuppressant. Relevant to these clinical adverse events, in laboratory tests, there was a dose dependent decrease in neutrophil count, increase in platelet count, and increase in lipid parameters with baricitinib. In addition to dose-related effect on cell numbers, it is possible that functional alterations of these cells may be dose related. The effect of baricitinib on hematopoietic cells may be related to functional suppression rather than only a lytic effect, as was seen with the related molecule tofacitinib.[16]

Thrombosis was a unique finding with baricitinib, and not seen with other JAK kinase inhibitors, such as tofacitinib, or with biologic DMARDs. The thrombosis events were not observed to be dose-related for baricitinib. However, platelet counts increased with baricitinib at a rate higher than placebo, and with dose-dependency. In the baricitinib studies, thrombotic events were not all directly related to elevated platelet counts, but the biological plausibility of elevated platelet counts resulting in thrombosis cannot be ruled out with the small number of cases in the limited database. The dose-dependent increase in platelet count with baricitinib raises a concern of possible dose-dependent increase in thrombosis with baricitinib.

[16] Maeshima K, Yamaoka K, Kubo S, et al. The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-gamma and interleukin-17 production by human CD4+ T cells. Arthr Rheum 2012; 64:1790-98.

In addition, baricitinib treatment was also associated with an increase in serum creatinine, and serum CPK, with no corresponding clinical findings. There was no case of liver injury satisfying Hy's Law seen in the program. Nevertheless, dose-related increase in liver enzymes and bilirubin with baricitinib is concerning. There were 10 patients withdrawn from the studies due to liver function test abnormalities, 9 from baricitinib 4 mg and 1 from baricitinib 2 mg treatment group. These occurred despite stringent entry criteria that did not allow patients with elevated liver enzymes and elevated bilirubin above a threshold to enroll in the studies.

A post-marketing safety study is recommended to further assess the safety finding of thrombosis. Such a study will evaluate whether there is a concerning link between baricitinib treatment and thrombosis and evaluate the relationship with platelet elevation, which will inform the safe use and risk-benefit of baricitinib in the treatment of RA. The study should include baricitinib 4 mg and 2 mg doses, as well as another DMARD as an active comparator, such as the marketed dose of tofacitinib. Such a study will also be of sufficient size to provide information on other safety events of interest, such as malignancy, infection, and MACE.

Some of the data presented above are different than those in the clinical reviews, and hence some of the conclusions are also different. The reason for the differences is mainly the different data set used in the analyses above compared to the data set used in the clinical reviews.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application because the safety and efficacy of DMARDs for RA are well understood. Another JAK inhibitor tofacitinib for RA was previously discussed at an AC meeting. There were no unique findings in the baricitinib program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatrics

Polyarticular juvenile idiopathic arthritis (PJIA) has been considered the juvenile equivalent of adult RA, and thus a study in PJIA patients would be required under the Pediatric Research Equity Act (PREA) upon approval of this NDA. The agreed Pediatric Study Plan (PSP) for baricitinib is waiver for studies in PJIA for patients below 2 years of age because studies in this age group will be impractical due to rarity of PJIA in children under 2 years of age, and a deferral for studies for patients 2 to less than 18 years of age. The deferred studies include a PK study comparing a baricitinib suspension formulation to tablet formulation, and a randomized withdrawal design study in patient 2 to less than 18 years of age with PJIA. The baricitinib pediatric program was discussed with the Pediatric Review Committee (PeRC) on October 5, 2016. The PeRC agreed with the requested waiver and deferral.

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP):

Review of the application did not raise concerns of any wrongful acts that raise significant questions regarding data reliability.

Exclusivity and patent issues of concern:

There are no exclusivity and patient issues of concerns with this application.

Office of Scientific Inspections (OSI) Audits:

OSI audited four clinical sites selected based on relatively large number of patient enrollment in these sites. In addition, an audit at the Sponsor level was also conducted. No irregularities were identified during the OSI audit that would impact data integrity.

Financial Disclosure:

The applicant submitted acceptable financial disclosure statements. Nine investigators had significant financial interest in Lilly. The number of subjects enrolled in the investigator sites was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

Other Good Clinical Practice (GCP) issues:

There are no GCP issues with this application. All studies were conducted in accordance with accepted ethical standards.

Other regulatory issues – Regulatory Action:

The proposed regulatory action for this NDA is approval. The submitted data are adequate to support use of baricitinib at a dose of 2 mg once daily for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.

12. Labeling

Prescribing Information: The product label was reviewed by various disciplines of this Division, and by other Divisions and Offices of the Center. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. High-level summary of significant labeling elements are as follows:

- Indication and Usage: The product will be indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. The language is supported by the submitted data and is consistent with tofacitinib.
- Dosage and administration: The recommended dose of baricitinib will be 2 mg once daily.
- Efficacy information: The main efficacy information that will be conveyed in the labeling will be the ACR data, and physical function data as assessed by HAQ-DI.
- Safety information: There will be a boxed warning for the safety fining of serious infection. Warning and Precaution section of the label will contain information on thrombosis events, serious infections including opportunistic infections, GI perforation, and some laboratory parameters that will require dose changes.
- Proprietary name: The proprietary name Olumiant was reviewed by DMEPA and found to be acceptable.

Patient labeling and Medication Guide: Baricitinib will have patient counseling information. There will be a Medication Guide for this product.

Carton and container labeling: These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

13. Postmarketing

Postmarketing Risk Evaluation and Mitigation Strategies:

REMS will not be required for this application. The information necessary to use baricitinib safely and effectively will be provided through prescribing information and patient labeling.

Other Postmarketing Requirements and Commitments:

A post-marketing required (PMR) safety study is recommended to further assess the safety finding of thrombosis. Such a study will evaluate whether there is a concerning link between baricitinib treatment and thrombosis and evaluate the relationship with platelet elevation, which will inform the safe use and risk-benefit of baricitinib in the treatment of RA. The study should include baricitinib 4 mg and 2 mg doses, as well as another DMARD as an active comparator, such as the marketed dose of tofacitinib. Such a study will also be of sufficient size to provide information on other safety events of interest, such as infection, malignancy, and MACE events.

The PREA studies will also be PMR studies.

Date: March 16, 2017

To: NDA 207924, Baricitinib

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA

Subject: Addendum to the Division Director Review

This document comments on Lilly submission, sequence number 0039, dated March 3, 2017, during labeling discussion of baricitinib NDA. Lilly in this submission asserts that baricitinib 4 mg should be the recommended dose for rheumatoid arthritis as opposed to the Division's labeling revision that recommends the baricitinib 2 mg dose.

Lilly acknowledges that the FDA's current view is that the baricitinib 2 mg dose for rheumatoid arthritis is based on benefit-risk assessment, and that there is no evidence of benefit with the 4 mg dose over the 2 mg dose to offset the difference of possible increased risk with the 4 mg dose over the 2 mg. The reader is referred to Lilly's submission that details Lilly's position and rationale to support the 4 mg dose. The high level summary of Lilly's position is as follows.

1. Baricitinib 4 mg has more rapid onset of effect than the 2 mg dose. Lilly submitted data for time course of response measures from study JADW (study IV) (study in patients who are bDMARDs inadequate responders or bDMARD-IR) at weekly intervals as the main data to support this position. Lilly also submitted data for time course of response measures from study JADX (study III) at daily intervals to show quicker onset for the 4 mg over comparators.
2. Withdrawal study shows greater efficacy of the 4 mg dose compared to the 2 mg dose. Lilly submitted data from study JADY (long-term extension of studies JADZ or I, JADV or II, JADX or III, or JADW or IV) where patients with low disease activity on 4 mg were re-randomized to continue on 4 mg or tapered to 2 mg, and new data from withdrawal.
3. Baricitinib 4 mg addresses the need of patients with refractory disease. Lilly submitted data from study JADW (study I) in bDMARD-IR patients showing numerically better response for 4 mg compared to 2 mg for low-disease activity and remission. Similar analysis was also submitted from study JADY (long-term extension study).
4. Baricitinib 4 mg showed larger and consistent improvement in efficacy across studies and comparators. Lilly noted that in study JADX (study III), radiographic progression data were more robust for baricitinib 4 mg compared to 2 mg, and noted comparative superior efficacy of baricitinib 4 mg to adalimumab.
5. Safety of baricitinib 4 mg is consistent with approved DMARD class, and manageable through labeling including Medication Guide and pharmacovigilance plans. Difference in safety between 2 mg and 4 mg are not in important measures

of safety. Lilly acknowledges dose-related changes in some laboratory parameters (called as pharmacodynamics effects of baricitinib), but does not see any meaningful measures between the 2 mg and 4 mg dose for important measures of safety. Lilly notes that safety findings seen with baricitinib 4 mg is consistent with other bDMARDs and in addition states that baricitinib would be easy to initiate and easy to interrupt if needed, compared to bDMARDs.

6. Lilly submitted minutes of interaction with FDA noting that they are not required to show statistical benefit of 4 mg over 2 mg. Lilly also submitted statements from some academic experts that basically re-states Lilly's position.

My comments on Lilly's position are below. Rather than point-by-point rebuttal of Lilly's position, some broad comments are made on efficacy and safety. The reader is referred to the Division Director's review for further details. On further review of the baricitinib data prompted by Lilly's arguments, I am now questioning if the submitted data are adequate to recommend approval of the baricitinib 2 mg dose. This position is different than my original Review where I recommended approval of the 2 mg dose.

Efficacy of baricitinib 2 mg versus 4 mg:

1. Lilly's argument of numerically better efficacy of baricitinib 4 mg over 2 mg mainly pivots around study JADW (study IV) conducted in patients who are bDMARD-IR (biologic DMARD inadequate responder). This is a study where the efficacy of 4 mg was numerically superior to 2 mg (ACR20 response of 2.7 for 2 mg compared to 3.4 for 4 mg). Therefore, some analyses of the individual components of the composite or earlier time point analysis of the primary analysis time point would be expected to be numerically superior for the 4 mg compared to 2 mg. The other study that included baricitinib 4 mg and 2 mg was study JADX (study III) conducted in patients who are conventional DMARD inadequate response or cDMARD-IR (primarily methotrexate inadequate responders) showed efficacy of 2 mg was numerically superior to 4 mg (ACR 20 response of 3.0 for 2 mg compared to 2.5 for 4 mg). It is likely that in this study analyses of the individual components of the composite or earlier time point analysis would show the opposite, for some measures 2 mg would be numerically superior to 4 mg. Lilly's program essentially shows similar efficacy of 2 mg compared to 4 mg based on the data submitted, and both the doses are highly effective. Both doses also have positive benefit for radiographic progression, although in the single study where the 2 mg and 4 mg were compared (study JADX or II), the 4 mg dose had superior numerical response than the 2 mg dose. In the two other studies (Study JADV or II and JADZ or I) where radiographic progression effect was assessed for the 4 mg dose only, the numerical responses for the 4 mg dose were similar to the numerical response with the 2 mg dose. The submitted data are not adequate to conclude that the 4 mg dose is superior to the 2 mg dose for radiographic progression effect.

2. Lilly also asserts that baricitinib 4 mg would address the need for patients with refractory disease, which may not be addressed by the 2 mg dose. This assertion is primarily based on study JADW (study IV) conducted in bDMARD-IR patients. Even in this study in bDMARD-IR patients, baricitinib 2 mg was highly effective, and the numerical superior response of 4 mg over 2 mg is small, and not replicated in another study. A limited or restricted indication for barictinib is not proposed by Lilly and would not be practical because there is no reason to do so and the actual use of baricitinib would be similar to that of tofacitinib, irrespective of any restricted labeling. The labeled indication of baricitinib is proposed to be: " … … patients with moderately to severely active rheumatoid arthritis who have an inadequate response or intolerance to methotrexate." The indication language is similar to that of tofacitinib, and would be more consistent with patients who are cDMARD-IR, patients who were in study JADX (study III) where baricitinib 2 mg was numerically superior to 4 mg.

3. Lilly brings up other DMARDs in their discussion. The other relevant DMARD would be tofacitinib, which is also a small molecule JAK-inhibitor, similar as a class to baricitinib. Pfizer studied 5 mg and 10 mg doses of tofacitinib in the phase 3 program. Unlike baricitinib, tofacitinib 10 mg compared to 5 mg showed consistent numerically superior response. At month 3, the proportion of patients with ACR20 response for 10 mg vs 5 mg was 65% vs 59% in study I (DMARD-IR patients), 67% vs 55% in study IV (methotrexate-IR patients), and 48% vs 41% in study V (TNF inhibitor-IR patients). As opposed to baricitinib 4 mg versus 2 mg, efficacy of tofacitinib 10 mg was numerically superior to 5 mg across spectrum of RA patients, including cDMARD-IR and bDMARD-IR. Even with this efficacy data, the approved dose for tofacitinib is 5 mg, a decision that was made by taking into consideration the benefit and risk. The tofacitinib program also had robust phase 2 dose-ranging data showing numerical decrease in efficacy response with tofacitinib 3 mg and 1 mg compared to higher doses. In two dose-ranging studies with tofacitinib, the 1 mg dose was not statistically significantly superior to placebo, but doses starting at 3 mg and above was statistically significantly superior to placebo. The tofacitinib dose-ranging data show that 5 mg dose was at a reasonable place in the dose-response efficacy curve.

4. The phase 2 dose-ranging data for baricitinib showed that any dose starting from 1 mg (the lowest dose studied) was effective, and the 1 mg dose was numerically comparable to the 2 mg and 4 mg dose. In the two dose-ranging studies that included the 1 mg dose, all doses including the 1 mg dose were statistically significantly superior to placebo. Lilly's reasoning for selection of the 4 mg dose as the main dose for phase 3 program was that the lower doses are expected to perform worse than comparators, the safety profile of the 4 mg dose was similar to lower dose and placebo, and there are no safety concerns with developing even higher doses but the higher doses were not associated with improved efficacy compared to 4 mg dose. Lilly made this conclusion based on small phase 2 data. Based on the baricitinib program, it is not possible to conclude where the

baricitinib 2 mg dose would reside in the dose-response efficacy curve. It is a guess at best that the 2 mg dose is at a reasonable place in the dose-response efficacy curve. It is possible that 1 mg dose or even lower doses of baricitinib can provide reasonable and comparable efficacy to the 2 mg and 4 mg doses.

5. Lilly cites the comparative superior efficacy of baricitinib 4 mg to adalimumab as another support for the 4 mg dose. Comparison between baricitinib to adalimumab was done in only one study (study JADV or II) and not replicated in the program. Superior efficacy of baricitinib 4 mg to adalimumab seen in one study was accompanied by numerically worse safety findings in the same study. Platelet count, lipid levels, infections reported as SAE and treatment emergent, malignancy, thrombosis events, and death were numerically worse for baricitinib 4 mg compared to adalimumab in the study. Comparative assessment to adalimumab was not unique for the baricitinib program. Adalimumab as an active comparator was also included in two studies in the tofacitinib program - in a phase 2 dose-ranging study and in a phase 3 study. In both the studies, tofacitinib 3 mg and higher doses (phase 2 study), and 5 mg and 10 mg doses (phase 3 study) showed numerically higher efficacy response assessed by ACR criteria compared to adalimumab, with some safety finding differences; a situation similar to that of baricitinib.

Safety of baricitinib 2 mg versus 4 mg:

1. Lilly acknowledges the dose-related changes in some laboratory parameters (called pharmacodynamics effects of baricitinib), but does not seem to consider these as relevant. The laboratory parameter changes for some measures (liver enzymes and bilirubin, platelet count, lipid parameters, etc) raises concerns about higher safety risk with baricitinib 4 mg compared to 2 mg, and with no convincing efficacy benefit of 4 mg over 2 mg, would tip benefit-risk assessment in favor of the 2 mg dose.

2. The liver enzyme and bilirubin parameter changes are worth further discussion. The phase 3 studies had enrollment criteria to exclude patient with liver function abnormality (AST or ALT >1.5 times ULN, total bilirubin ≥1.5 times ULN). The studies also had criteria to remove patients from the study with liver function abnormality (temporary removal for AST or ALT >5 times ULN; permanent removal for AST or ALT >8 times ULN, or, AST or ALT >5 times ULN persisting for more than 2 weeks after temporary interruption of investigational product, or, AST or ALT >3 times ULN and total bilirubin >2 times of normal, or, AST or ALT >3 times ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or >5% eosinophilia). In the phase 3 studies (during the first 6-months), 15 patients were permanently removed for meeting the liver function test criteria, 10 from the baricitinib 4 mg group (8 within the first 3-months), 2 from the baricitinib 2 mg group (1 within the first 3-months), 2 from the adalimumab group (1 within the first 3-months), and 1 from

the placebo group (within the first 3-months). Details of these patients are in the appendix to this document. With about 1265 patients originally enrolled in the baricitinib 4 mg group, the frequency of patients removed for liver function abnormality approaches about 1% for baricitinib 4 mg, which is rather a high number considering this drug class. The permanent removal for laboratory criteria only for baricitinib 4 mg were 8 patients, of which one appeared to be related to other medical events (see Appendix for details). The removal of patients for liver safety criteria occurred despite excluding patients at risk for entering the study. There was one case in the baricitinib 4 mg group with a preferred term of drug induced liver injury (Appendix, Patient # (b) (6)). The number of drug induced liver injury reported in the baricitinib program need to be taken in the context of patients being actively excluded and removed from study for liver function test abnormality.

For comparison, tofacitinib program also had liver function exclusion criteria (AST or ALT >1.5 times ULN or any uncontrolled clinically significant laboratory abnormality that would affect interpretation of the study data or patient's participation in the study) and permanent discontinuation criteria (two sequential AST or ALT >3 time ULN with at least one total bilirubin >2 times ULN or increase INR, or, two sequential AST or ALT >3 times ULN accompanied by symptoms consistent with hepatic injury, or, two sequential AST or ALT elevations >5 ULN regardless of total bilirubin or accompanying symptoms). In the tofacitinib program, there was one case of liver injury with the 10 mg dose in the entire program. In the tofacitinib program, discontinuations due to meeting the liver enzyme criteria were rare (less than 1 patients per 1000 patient) and were comparable between the two tofacitinib doses and placebo. Discontinuations within the first 3-months for all phase 3 studies for tofacitinib 5 mg, tofacitinib 10 mg, and placebo were 1 out 1220 patients, 0 out of 1217 patients, and 2 out of 681 patients, respectively. Liver enzymes elevations were noted in the tofacitinib program. In the tofacitinib monotherapy trials during controlled treatment period (0-3 months) there were no differences in the incidence of ALT and ALT elevations for tofacitinib 5 mg or 10 mg or placebo. In the tofacitinib trials with background DMARDs, during controlled treatment period (0-3months) ALT elevations >3 times ULN were observed in 1.0%, 1.3%, and 1.2% of patients receiving placebo, 5 mg, and 10 mg tofacitinib, respectively. In these trials, AST elevations >3 times ULN were observed in 0.6%, 0.5%, and 0.4% of patients receiving placebo, 5 mg, and 10 mg tofacitinib, respectively.

3. Thrombosis is a unique risk for baricitinib, not seen with biologics DMARDs or with tofacitinib. Deep vein thrombosis and pulmonary embolism occurred with both baricitinib 2 mg and 4 mg at comparable rates and at rates higher than placebo. There were also few cases of arm and leg artery thrombosis with baricitinib. The thrombosis findings are of particular concern because these events are not predictable, and some were associated with death. As for laboratory parameters, it is worth noting that 2 patients were withdrawn from the studies for meeting platelet threshold criteria for withdrawal, both were from

baricitinib 4 mg dose. Lilly argues against the thrombosis risk by comparing to population data. Comparison to population data is not relevant because the risk with baricitinib was seen in controlled clinical studies.

4. Immunosuppressive DMARDs have the risk of malignancy and infection. Both of these safety findings were seen with baricitinib. Comparison between baricitinib 2 mg and 4 mg was difficult for these events because the 2 mg database was smaller than the 4 mg database (403 for 2 mg versus 1265 for 4 mg at randomization), and became smaller over time with patients switching from baricitinib 2 mg to 4 mg. Recognizing these limitations, it is worth noting the malignancy data. The rate of malignancy for baricitinib 2 mg and 4 mg was 0.4 and 0.8 per 100-patient years, respectively, with hazard ratio comparing 4 mg to 2 mg of 1.8 [95% CI 0.4, 8.1]. Most of the malignancy differences were from time points beyond 52-weeks where the number of patients in the 2 mg group was small. For comparison, for tofacitinib, the rate of malignancy (available data were up to 52 weeks) for tofacitinib 5 mg and 10 mg was 0.4 and 0.6 per 100-patient years, respectively. It is worth noting that for tofacitinib, this difference of malignancy rate was a consideration in recommending the 5 mg dose and not the 10 mg dose, even with the numerical efficacy benefit of the 10 mg dose over the 5 mg dose discussed above.

Benefit-risk assessment of baricitinib:

As noted above, I now question if the submitted data are adequate to recommend approval of even the baricitinib 2 mg dose. This position is different than my original review where I recommended approval of the 2 mg dose. On further review and consideration, I now question if the baricitinib 4 mg dose is not safe, why the lack of safety of the 4 mg dose would not be applicable to the 2 mg dose. The safety database of the 2 mg dose is not large enough to independently assess safety of the 2 mg dose and compare that to the 4 mg dose. Furthermore, of the various safety findings for baricitinib mentioned above and in my original review, the safety finding that is of particular concern is the thrombosis event. The bDMARDs and tofacitinib do not have this safety risk. There will need to be further safety data generated to understand the thrombosis risk for baricitinib, and it would be reasonable to obtain the data and address this safety risk pre-approval.

One of the aims of benefit-risk assessment is to project what was seen in the controlled clinical trials to real world experience where a broader range of patients will be exposed to baricitinib post-approval with disease severity and safety risk that was not assessed in the clinical program. From the efficacy side for baricitinib, it is possible that for some patients under some circumstances the 4 mg dose may provide some benefit over the 2 mg dose. But keeping to the labeling indication of " … … patients with moderately to severely active rheumatoid arthritis who have an inadequate response or intolerance to methotrexate" it is not possible to define who these patients would be, noting that in cDMARD-IR patients the numerical trend was better for the 2 mg dose compared to 4 mg

dose. From the safety side for baricitinib, based on laboratory measures alone, it is likely that 4 mg dose would carry a higher risk of harm compared to the 2 mg dose. In short-term measure, the finding that about 1% patients were permanently removed from the studies based on liver function test and clinical adverse events related to liver to protect from liver injury raises the possibility that in real life use of baricitinib without stringent adherence to monitoring, liver injury cases will occur with higher frequency with the higher baricitinib dose. In long-term measure, the concern is increased effect of immunosuppression, such as increased infection and malignancy with the 4 mg dose compared to the 2 mg dose based on the limited short-term data available from clinical trials. The thrombosis safety finding applies equally to the baricitinib 2 mg and 4 mg doses. Of the two doses of baricitinib studied in the phase 3 program, the emphasis was clearly on the 4 mg dose. Even with limited efficacy and safety data available for the 2mg dose, the 2 mg dose would appear more reasonable for rheumatoid arthritis between the two dose options. However, it is an open question if even a lower dose would be more appropriate.

The limited exposure data for the baricitinib 2 mg dose presents a challenge. The Division has historically expected that for an immunosuppressive product for rheumatoid arthritis, the safety database would need to be approximately one thousand patients exposed for one year. For the baricitinib 4 mg dose, we have that number. For baricitinib 2 mg, the number of patients at randomization was approximately 400, and at one-year was approximately 200. To support the safety of the 2 mg dose, we are essentially applying the 4 mg dose safety finding to the 2 mg dose, and making an assumption that the 2 mg dose would be safer than the 4 mg dose. Lilly's assertion that the 4 mg dose is safe and should be approved, open up the question whether my initial thought of applying the safety finding from the 4 mg dose to the 2 mg dose and assuming that 2 mg dose would be safer that the 4 mg dose is reasonable. It is possible that in real life post-approval use by a wide range of patients with rheumatoid arthritis, the 2 mg dose may turn out to carry the same safety risk that is worrisome for the 4 mg dose. Also, as discussed above, it is possible that a dose lower than the 2 mg dose may be effective as well and have a better safety profile. Given that baricitinib is another member of the DMARD class that has many choices, and baricitinib is not serving an unmet medical need that is above and beyond bDMARDs and tofacitinib, it would be reasonable to not approve any of the doses of baricitinib at this time and have Lilly assess efficacy of a dose or doses lower than 2 mg and assess safety of these doses with a larger exposure database. It is possible that the 2 mg dose may ultimately be the appropriate dose, but that needs to be supported by a dose-ranging study exploring doses lower than 1 mg.

Appendix: Case summaries of permanents withdrawn because of liver criteria

Overview of cases of permanent discontinuations secondary to liver related abnormalities

	bari 2 mg	bari 4 mg	Adalimumab 40 mg	Placebo
Appears drug related		(b) (6) (DILI) N=4	(b) (6) N=1	
Unclear if drug related given underlying factors, such as hepatic steatosis		(b) (6) N=1	(b) (6) N=1	
Confounded by isoniazid	(b) (6) N=1	(b) (6) N=2		(b) (6) N=1
Does not appear drug related given other medical events, such as cholecystitis		(b) (6) N=1		
Did not actually meet criteria for discontinuation secondary to LFTs	(b) (6) (mild elevations) N=1	(b) (6) (alk phos) (b) (6) (mild elevations) N=2		
Total	2	10	2	1

All of the patients were on background methotrexate in each of the groups, except patient (b) (6) who receive baricitinib 4 mg and hydroxychloroquine.

Baricitinib 4 mg dose:

There were 10 patients on 4 mg baricitinib permanently discontinued, which includes 2 patients with moderate renal impairment but on 2 mg dose. There were also one patient with positive HBV DNA result and one patient with cholecystitis who did not show any LFT abnormality, which are not included in this listing.

1. Patient # (b) (6) was a 24-year-old Asian female who received 4 mg treatment. The patient had moderately to severely active RA and was on 10 mg oral MTX QW treatment in the study. The patient reported no history of liver disease. The baseline ALT and AST level of this patient was within the normal range. Increase of ALT and AST level (< 3x ULN) was first observed on Day 30 and gradually increased to >5x ULN on Day 73. The patient was suspended on baricitinib on Day 78. Baricitinib was resumed on Day 114 when patient's ALT dropped within normal range whereas AST was marginally high. After the resumption, patients' ALT and AST gradually increased again and reached > 5x ULN and ≥3x ULN on Day 172. The patient was permanently discontinued on Day 175. In the opinion of the investigator, the events of ALT increased and AST increased were possibly related to the study drug.

2. Patient # (b) (6) was a 53-year-old American Indian or Alaska Native male received 4 mg treatment. The patient had moderately to severely active RA and was on MTX and indomethacin treatment. The patient reported no history of liver disease. The baseline ALT and AST level of this patient was within the normal range. On Day 29, blood test results showed >8 ULN for ALT and AST, which met

permanent drug discontinuation criteria. The patient was asymptomatic with his alkaline phosphatase, total bilirubin, and albumin were all within the normal range. The patient permanently discontinued on Day 31. In the opinion of the investigator, the SAEs of ALT increased and AST increased were possibly related to the study drug.

3. Patient # (b) (6) was a 30-year-old Asian male who received 4 mg treatment. The patient had moderately to severely active RA and was on 16 mg oral MTX QW treatment in the study. The patient reported a history of 3-year mild hepatic steatosis before the screening visit. The ALT and AST level of this patient at the screening visit was within the normal range. On the first dosing day, ALT increased to > 1.5x ULN. The ALT remained at that level and AST was within the normal range till Day 85, when ALT increased to > 3x ULN and AST increased to > 1.5x ULN. The patient took the last dose of baricitinib on Day 88 and permanently discontinued on Day 92. On day 113, patient's ALT level was still >2 ULN and AST > 1x ULN. During the study, the patient initiated new medications, including alprazolam, brotizolam, and chlorpromazine. This adverse event of hepatic function abnormal was deemed by the investigator as not related to study drug.

4. Patient # (b) (6) was a 57-year-old white female who received 4 mg treatment. The patient had moderately to severely active RA and was on 200 mg oral hydroxychloroquine BID treatment in the study. The patient had a medical condition of 8-month mild increase of blood alkaline phosphatase (ALP) before the screening visit. The ALP level of this patient at screening visit was > 2x ULN. Baseline AST and ALT were within the normal range. The ALP level increased to > 2.5x ULN on Day 59, and > 3x ULN on Days 86. The ALP level remained at that level till the permanent discontinuation day (Day 113). During the follow-up visit (Day 147), the ALP increase had not resolved. The adverse event of blood alkaline phosphatase increase was deemed by the investigator to be possibly related to study drug. **(Did not actually met LFT discontinuation criteria)**

5. Patient # (b) (6) was a 42-year-old black female with eGFR<60 mL/min/BSA and who received 2 mg treatment (assigned in 4 mg treatment group). The patient had moderately to severely active RA and was on 25 mg oral MTX QW treatment in the study. The patient reported no history of liver disease. The baseline ALT and AST level of this patient was within the normal range. On Day 56, the patient's ALT elevated to ≥ 3 ULN whereas other hepatic parameters were normal. MTX was reduced to 12.5 mg QW from that visit. On Day 100, ALT increased to > 8x ULN and AST increased to > 5 ULN. The ALP and total bilirubin were normal. 2 Days later MTX was stopped and baricitinib was suspended. The patient's last baricitinib dose was taken on Day 102. On Day 104, the patient was hospitalized for severe acute cholecystitis and sepsis. The adverse events of elevated ALT (alanine aminotransferase increased), elevated AST (aspartate aminotransferase increased), acute cholecystitis, and sepsis were deemed by the investigator as not possibly related to study drug.

6. Patient # (b) (6) was a 71-year-old Asian male with eGFR<60 mL/min/BSA and received 2 mg + MTX treatment [assigned in 4 mg + 7.5 mg (initial) MTX treatment group]. The patient had moderately to severely active RA and was on isoniazid treatment for 40 days before the first treatment. The patient reported no history of liver disease. The ALT and AST level of this patient at screening visit (same day started isoniazid treatment) was within the normal range. 2 days after the first dose, both ALT and AST levels reached > 8x ULN. The patient was permanently discontinued on baricitinib and MTX treatment. Meanwhile isoniazid was also stopped. During follow-up visit on Day 29, both ALT and AST levels returned to normal range. In the opinion of the investigator, the SAE of severe hepatic function abnormal was not related to the study drug, but was possibly related to study procedures (initiation of isoniazid prophylaxis).

7. Patient # (b) (6) was a 53-year-old Asian female received 4 mg + 7.5 mg (initial) MTX treatment. The patient had moderately to severely active RA and was on isoniazid treatment for 40 days before the first treatment. The patient reported no history of liver disease. The ALT and AST level of this patient at screening visit (same day started isoniazid treatment) was within the normal range. 2 days after the first dose of baricitinib, both ALT and AST levels reached > 8 ULN. It did not appear that labs had been checked after initiation of isoniazid, but before initiation of baricitinib. The patient was permanently discontinued on baricitinib and MTX treatment. Meanwhile isoniazid was also stopped. During follow-up visit on Day 30, both ALT and AST levels returned to normal range. In the opinion of the investigator, the event of severe hepatic function abnormal was not related to the study drug, but was possibly related to study procedures (varicella zoster vaccination and initiation of isoniazid prophylaxis at baseline).

8. Patient # (b) (6) was a 26-year-old Asian female who received 4 mg + 7.5 mg (initial) MTX treatment. The patient had moderately to severely active RA. The patient reported no history of liver disease. The baseline ALT and AST level of this patient was within the normal range. The QW MTX started at 7.5 mg in Week 0 and increased to 10 mg starting at Week 4. The MTX dose increased to 12.5 mg starting Week 8 and stayed for the remainder of the study. The patient's ALT started to increase > 1 ULN on Day 28 and reached >8 ULN on Day 83. On the same day AST reached > 3 ULN. The study drug (baricitinib + MTX) and concomitant medications (celecoxib and esomeprazole) were discontinued 2 days later. The hepatic function abnormality was resolved about 7 weeks later. In the opinion of the investigator, the SAE of mild hepatic function abnormal was possibly related to the study drug and study procedures.

9. Patient # (b) (6) was a 39-year-old white male who received 4 mg + 10 mg (initial) MTX treatment. The patient had moderately to severely active RA. The patient had historical hepatic steatosis but recovered before trial enrollment. The baseline ALT and AST level of this patient was within the normal range. The patient's ALT started to increase > 1 ULN on Day 15 and stayed at that level for 3 weeks. The highest ALT reading during this period was just >1.5 ULN. The patient was permanently discontinued from the study and the study drug (baricitinib + MTX) on Day 36. The patient's ALT level remained > 1 ULN at the follow-up visit one month later. In the opinion of the

investigator, the SAE of moderate severity ALT increased was possibly related to the study drug. **(Did not actually met LFT discontinuation criteria)**

10. Patient # (b) (6) was a 56-year-old white male who received 4 mg treatment. The patient had moderately to severely active RA and was on 15 mg oral MTX QW treatment in the study. 2 days after starting baricitinib, the patient experienced dyspepsia, abdominal pain, fever, dark urine, acolia, jaundice and choluria, was hospitalized, and on the same day, baricitinib was permanently discontinued. The abnormal laboratory test results on Day 5 were: GPT > 3x ULN, ALP >1x ULN, GGT > 9x ULN, total bilirubin 2.1 mg/dL (0.2-1.3 mg/dL), The treponema test (VDRL), anti HIV antibody 1 and 2, hepatitis B surface antigen, hepatitis A IgM antibody, hepatitis B Anti IgG, Anti hepatitis C antibody were all non-reactive, and hepatitis A IgG antibody was reactive. The ALT and AST results were not available. An endoscopy on Day 11 supported diagnosis of moderate severity esophageal candidiasis and portal hypertensive gastropathy (congestive gastropathy). The diagnosis of severe hepatitis induced by drugs (preferred term: drug-induced liver injury) was made. The patient recovered from the event of drug-induced liver injury on Day 12 and was discharged from hospital. In the opinion of the investigator, the SAE severe drug-induced liver injury and the event of esophageal candidiasis were not related to the study drug.

<u>Baricitinib 2 mg dose:</u>

There were 2 patients on 2 mg baricitinib treatment permanently discontinued.

1. Patient # (b) (6) was a 52-year-old Asian male with normal renal function who received 2 mg treatment. The patient had moderately to severely active RA. The patient had a history of hepatic steatosis. The baseline ALT and AST levels of this patient were within the normal range. Elevation in ALT and AST (< 1.5x ULN) first appeared on Day 53. The ALT increased to >2x ULN and AST increased to > 2.5x ULN on Day 84. On the same day, baricitinib, MTX, and sulfasalazine were suspended. On Day 97, an abdominal ultrasound was performed and results were consistent with hepatic steatosis. The patient was discontinued from the study on Day 117. On Day 208 during follow-up, ALT and AST levels remained at > 3x ULN. The adverse events of hepatic steatosis and hepatic function abnormal were deemed by the investigator as not possibly related to study drug. **(Did not actually met LFT discontinuation criteria)**

2. Patient # (b) (6) was a 44-year-old white female with normal renal function who received 2 mg treatment. She was diagnosed with latent tuberculosis (positive local PPD) and started on isoniazid treatment approximately one month before baricitinib 2 mg QD treatment. The patient was suspended on baricitinib treatment on Day 25 due to metrorrhagia (though patient also qualified ALT >5 times ULN criterion). The suspension lasted for 32 days after the metrorrhagia was resolved on Day 52 by a 9-day treatment with norethisterone. Blood was drawn on Day 57, the same day that 2 mg QD treatment was resumed. The results showed ALT 655 U/L (>8X ULN), AST 125 U/L (> 3X ULN), and platelet count 650 x10^9 cells/L. The patient was permanently discontinued on Day 59. The ALT readings (normal range 6-37) are listed following: 51

(screening), 47 (Week 0), 43 (Week 1), 185 (Week 4, suspension started), 655 (Week 8, suspension ended), 70 (Week 12). The adverse events of alanine aminotransferase increased and metrorrhagia were deemed by the investigator to be possibly related to study drug.

Adalimumab:

There were 2 patients on adalimumab treatment permanently.

1. Patient # (b) (6) was a 48-year-old white female who received 40 mg adalimumab Q2W treatment. The patient had moderately to severely active RA. The patient had no history of liver disease. The baseline ALT and AST levels of this patient were within the normal range. Elevation in ALT and AST (< 1.5x ULN) first appeared on Day 29. The AST level increased to > 3x ULN and ALT increased to > 2.5x ULN on Day 57. On Day 169, the patient's ALT and AST were high at >5x ULN meeting temporary drug interruption criteria. The patient was permanently discontinued and the last dose of adalimumab was on Day 169. The patient's ALT and AST levels remained at an abnormal level during 4 months after the discontinuation. ALT and AST levels returned to the normal range 7 months after the drug discontinuation. In the opinion of the investigator, the SAE of moderate severity transaminases increased was not related to the study drug.

2. Patient # (b) (6) was a 62-year-old white female who received 40 mg adalimumab Q2W treatment. The patient had moderately to severely active RA. The patient had no history of liver disease. The baseline ALT and AST levels of this patient were within the normal range. The baseline ALP was at 2x ULN. On Day 15, the patient's ALT and AST were high at >8x ULN whereas ALP was at 1.5x ULN. The patient was permanently discontinued from the study drug on Day 17. The patient only received 2 doses of 40 mg adalimumab. On Day 22, an ultrasound of the liver was performed and showed mild hepatic steatosis grade 1. In the opinion of the investigator, the SAEs of AST increased and ALT increased were possibly related to the study drug.

Placebo:

There was one patient on placebo treatment permanently discontinued.

1. Patient # (b) (6) was a 56-year-old female (miscellaneous race) who received placebo/MTX (initial 25 mg QW dose)/hydroxychloroquine treatment in Study JADV. The patient had moderately to severely active RA. The patient had no history of liver disease. The patient was on isoniazid and pyridoxine treatment starting in the screening period. The baseline ALT and AST levels of this patient were within the normal range. The ALT and AST levels marginally increased (<1.5x ULN) on Day 7 and reached > 3x ULN on Day 30. The MTX dose was reduced to 22.5 mg from Day 30. The ALT and AST levels increased to > 8 ULN on Day 77 and patient was permanently discontinued on MTX/isoniazid/pyridoxine therapy. The ALT and AST levels returned to normal

range on Day 107. In the opinion of the investigator, the SAE of liver function test abnormal was possibly related to the study drug.

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.

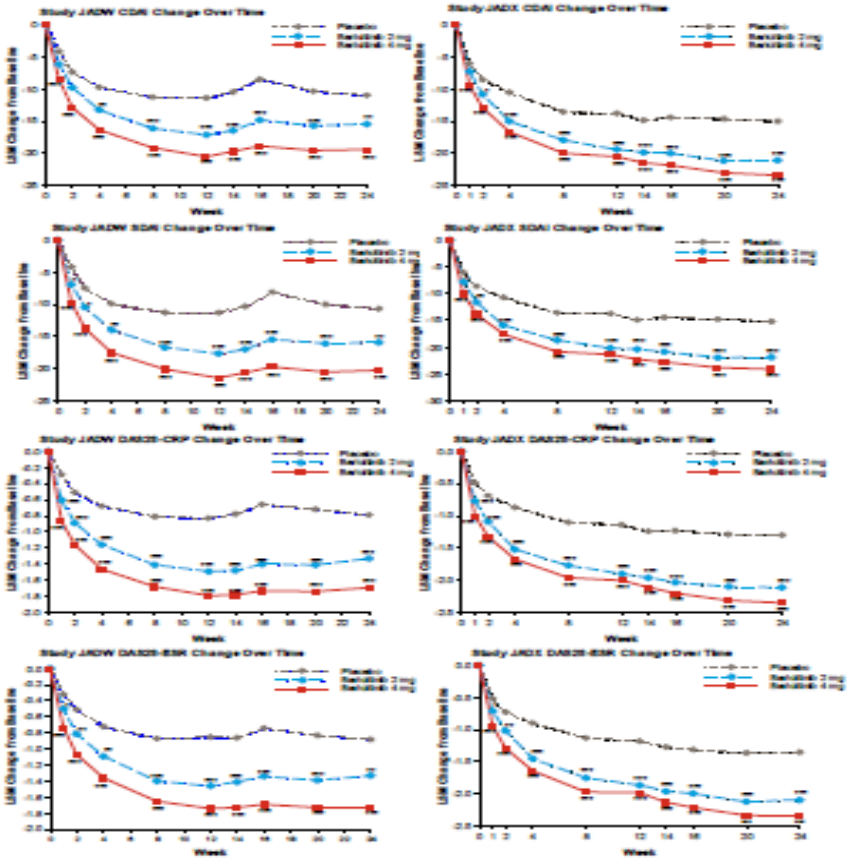


Figure 4.2. CDAI, SDAI, DAS28-hsCRP, and DAS28-ESR through Week 24 in Studies JADW and JADX.

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.

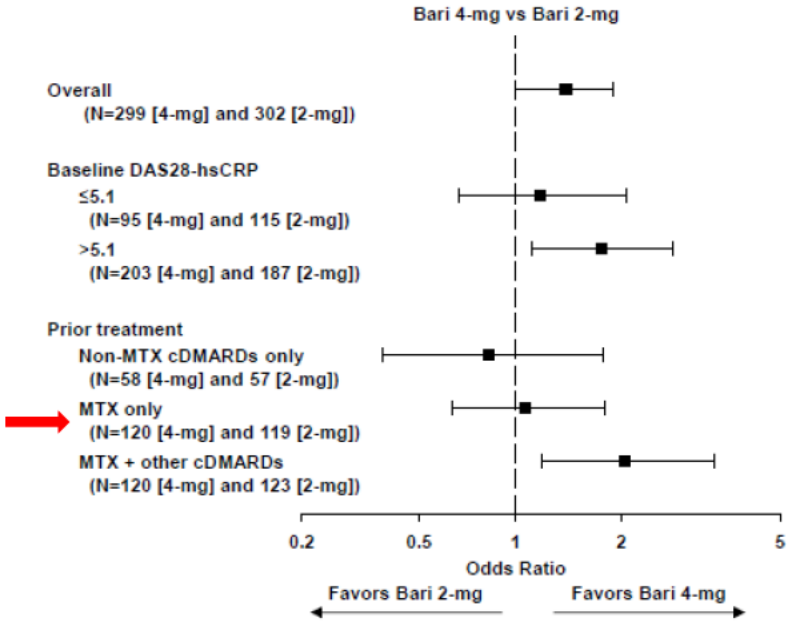
Sources: t_cdai_resp_jadvxwy_stepdown.rtf, t_cdai_resp_jadvxy_stepdown.rtf, t_cdai_resp_jadzy_stepdown.rtf, and t_cdai_resp_jadwy_stepdown.rtf.

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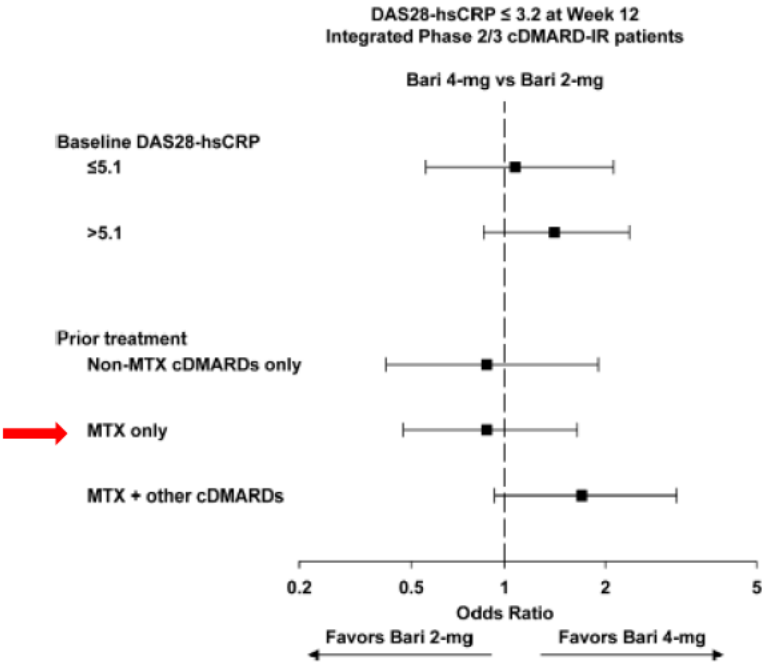
Figure 4.7 Study JADX – 4 vs 2 mg achieving LDA by Baseline Disease Severity and Prior RA Treatment



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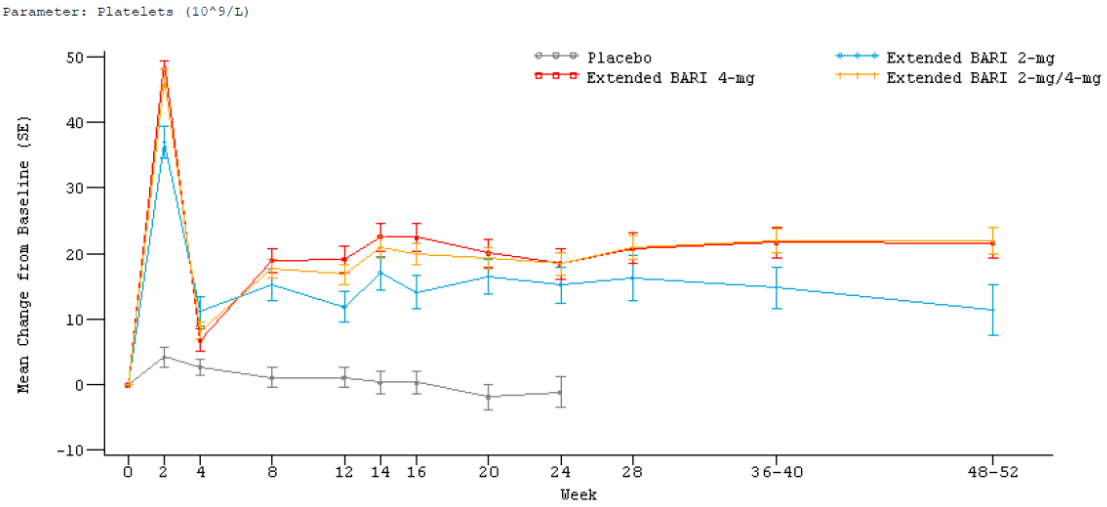
Figure 1. Mean Change in Platelets in Pooled Datasets for Placebo-controlled studies



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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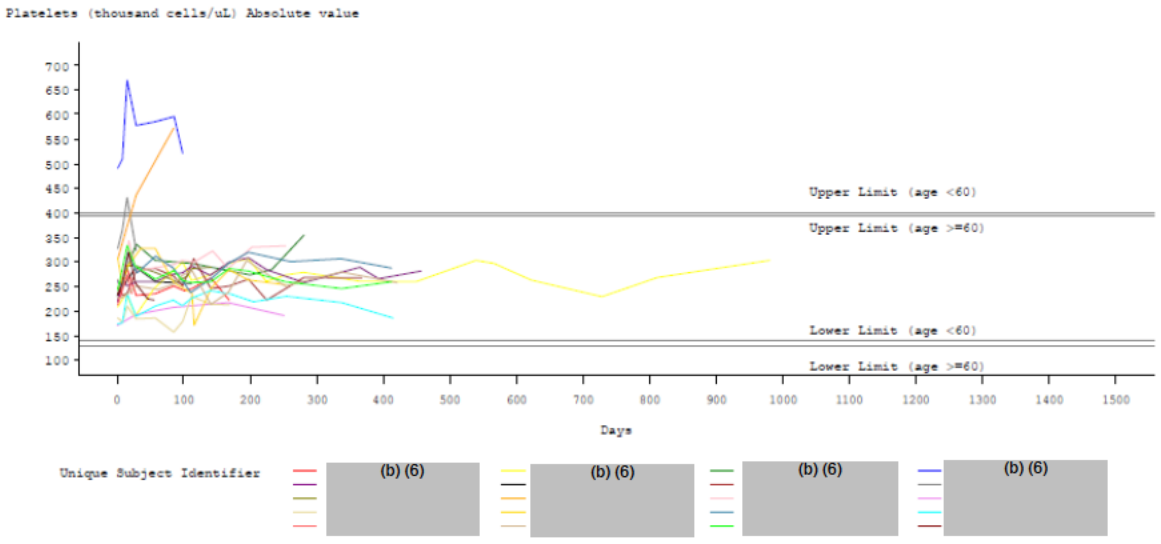

Thrombotic event is defined by treatment emergent deep vein thrombosis and/or pulmonary embolism.
The event day are: 37, 50, 66, 113, 142, 150, 169, 205, 225, 260, 295, 298, 330, 395, 431, 443, 466, 479, 523, 1063.

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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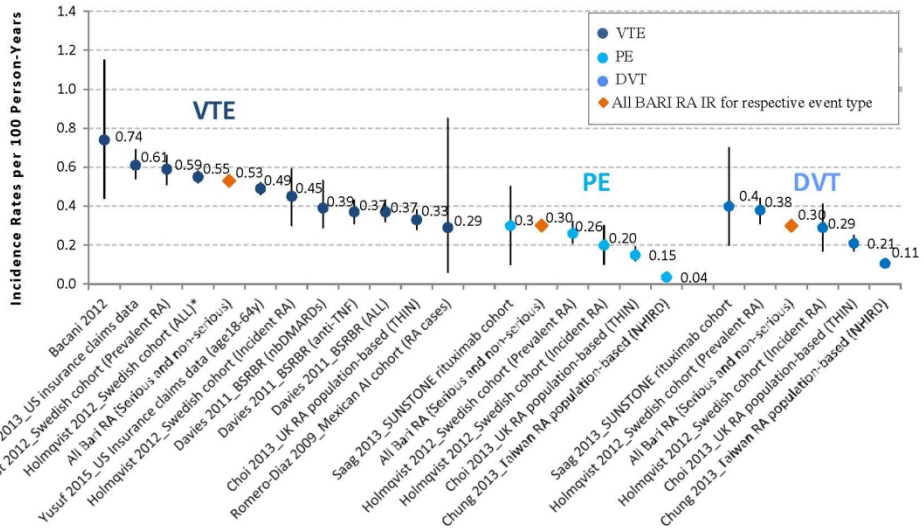

Abbreviations: BARI = baricitinib; DVT = deep vein thrombosis; IR = incidence rate; nbDMARDs = non-biologic disease-modifying anti-rheumatic drugs; PE = pulmonary embolism; RA = rheumatoid arthritis; TNF = tumor necrosis factor; UK = United Kingdom; US = United States; VTE = venous thromboembolic event; 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 July 2012 of two to three hours duration and one car trip of three to four hours duration. On May 10, 2012 the patient received his first dose of study drug (baricitinib 8 mg which was increased to 10 mg on August 9, 2012). 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.

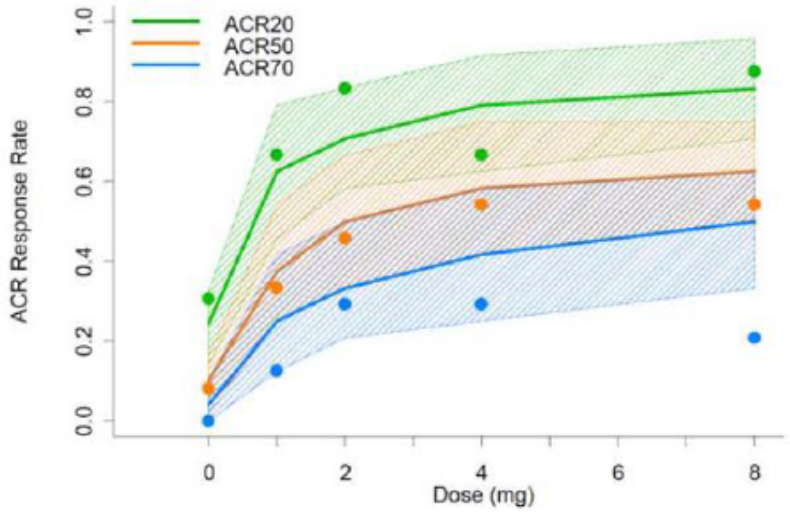
This application was discussed at a CDER Regulatory Briefing on March 17, 2017.

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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SUMMARY 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 years	2996	515	NA
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)ǂ	0.77 (0.70, 0.84)ǂ
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

ǂ 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.[1,2] 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."*

[1] 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.
[2] Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circ Res. 2016;118(9):1340-1347.

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.

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,[3] 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 (

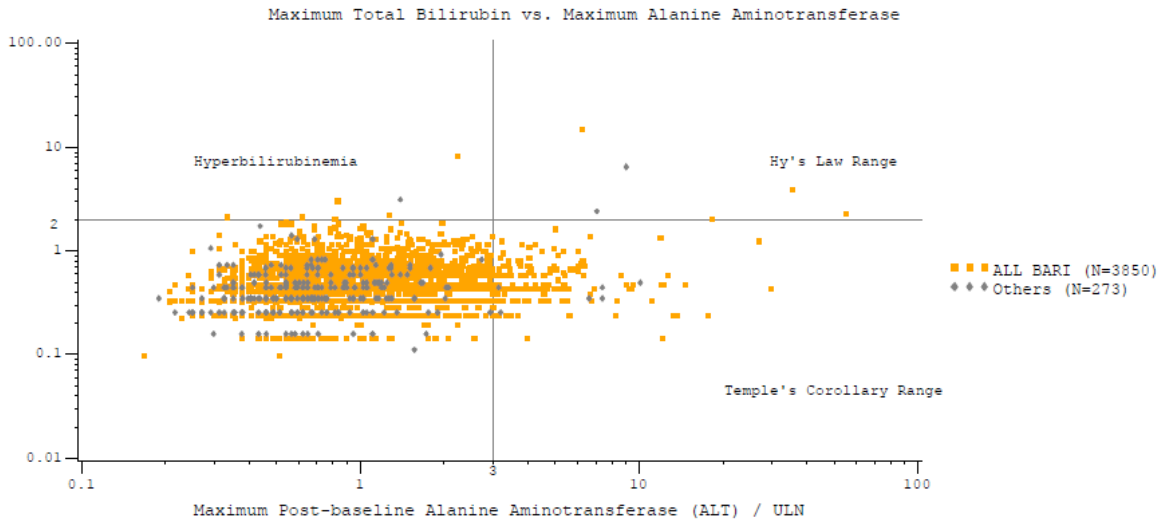
Figure ***2***) for patients in the 'All Bari' analysis set. Importantly, all acute liver injury cases of interest in the Hy's law range, the right upper quadrant (RUQ) of the graphic displays, were individually analyzed by the Applicant's internal hepatologist and a hepatic and gastrointestinal safety 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

[3] 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.

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.

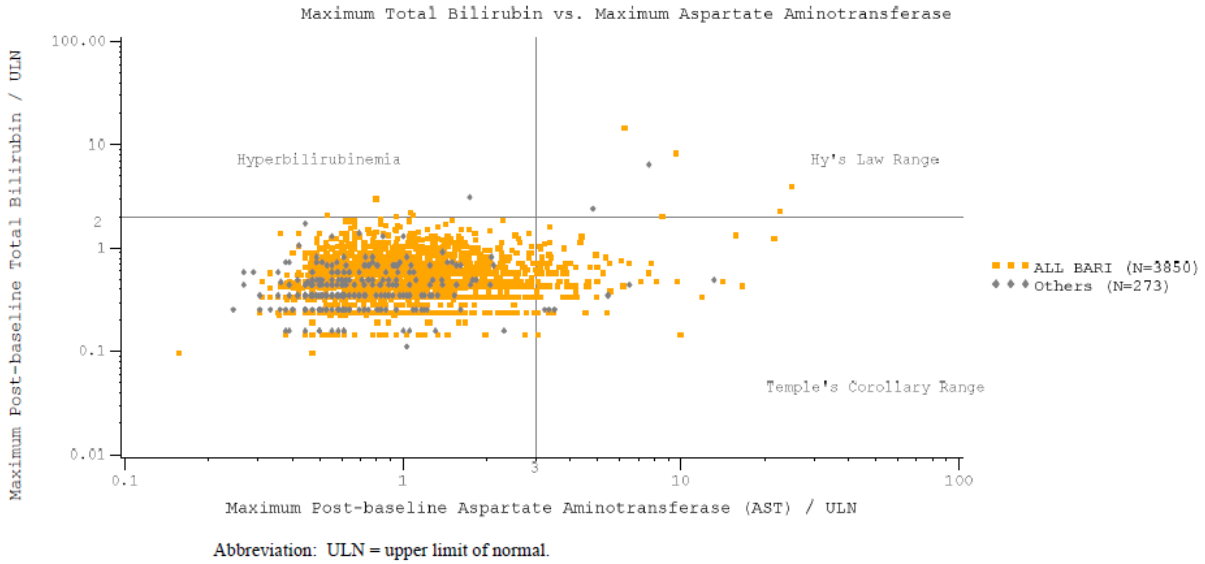
Figure 1. eDISH plots of ALT vs total bilirubin



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

Thrombocytosis

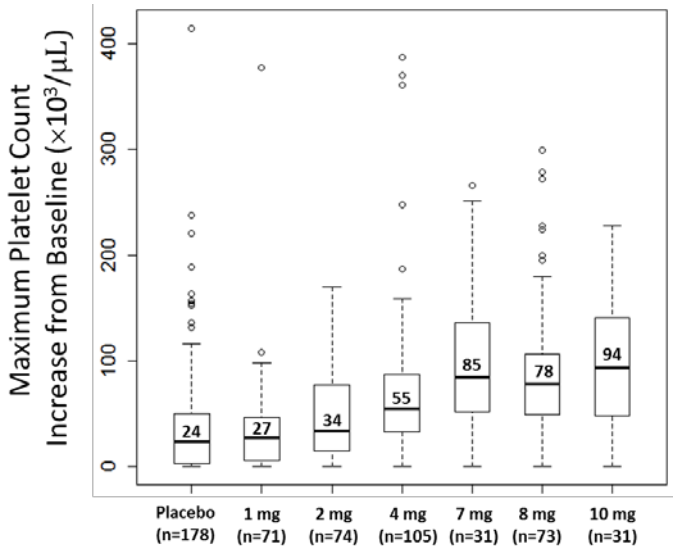
As noted in the original reviews, baricitinib use was also associated with dose-dependent platelet elevations, which appear unique to this product and deserves further consideration. To further explore these observations, the FDA review team considered potential underlying pathogenic mechanisms based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

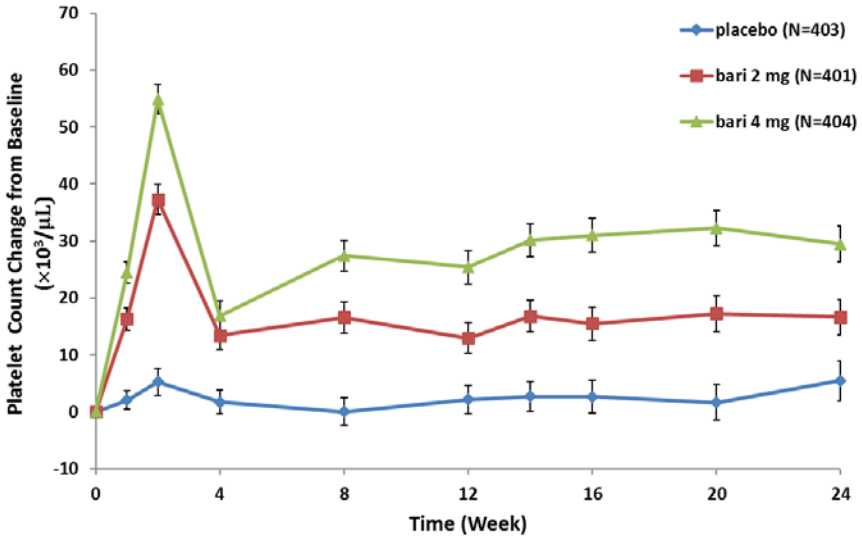


Source: platelet.xpt dated on 2/15/2018

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

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.[4] 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

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

baricitinib preferentially inhibited JAK1 and JAK2 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[5]. Platelets circulate with a lifespan of approximately 7 - 10 days in humans[6].

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)[7]. 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[8].

[5] Grozovsky et al. (2015) Regulating billions of blood platelets: glycans and beyond. *Blood*. 126: 1877-1884.
[6] Li, R. et al (2016) Glycans and the Platelet Life Cycle. *Platelets*. 27, 505 – 511.
[7] Geddis A. (2010) Megakaryopoiesis. *Seminars in Hematology*. 47: 212-219.
[8] 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.

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.

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[9]. 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[10]. In contrast, thrombocytosis was observed in mice in which *Jak2* was selectively deleted in megakaryocytes and mature platelets[11]. Ng et al. showed that selective deletion of *Mpl* in megakaryocytes and mature platelets in mice also led to thrombocytosis[12].

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

[9] Kile, B. (2015) Aging platelets stimulate TPO production. *Nature Medicine*. 21: 11 – 12.
[10] Grisouard et al. (2014). Selective deletion of Jak2 in adult mouse hematopoietic cells leads to lethal anemia and thrombocytopenia. *Haematologica*. 99: e52 – e54.
[11] Meyer S. et al. (2014) Genetic studies reveal an unexpected negative regulatory role for Jak2 in thrombopoiesis. *Blood*. 124: 2280 – 2284.
[12] 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 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.[11] and Ng et al.[12] 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 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

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 19 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 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 dailty 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 20 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 21 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 22 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 23 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 24. 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.

Resubmission Conclusions

Overall, the additional data provided in the resubmission did not substantially alter the efficacy and safety data in the original submission. Thus, questions remain regarding the benefit/risk assessment of baricitinib for RA patients.

Both the 2 and 4 mg doses of baricitinib demonstrated efficacy compared to placebo in RA patients. Given the safety issues identified with baricitinib, whether there is additional benefit of the 4 mg dose over the 2 mg dose is an issue we would like you to discuss at the AC meeting.

Baricitinib has several safety signals consistent with a potent immunosuppressive. Thrombosis is a notable safety issue and we ask for you to discuss this safety issue and how that impacts the benefit/risk profile of baricitinib. Since most of the safety data are with the 4 mg dose of baricitinib and there are limited placebo control data, interpretation of the safety data is challenging, particularly when events continue to accrue in patients treated with open-label baricitinib. This raises the question of whether the 2 mg dose has a favorable benefit/risk profile; however, an important issue is whether there is sufficient safety data to inform the benefit/risk assessment of the baricitinib 2 mg dose. We ask for your input on all of these issues and look forward to the discussion.