

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

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**MEDICAL REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION  
DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS**

**Medical Officer Consult Reply and Responses to Questions**

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<b>NDA</b>	207-924
<b>Sponsor</b>	Eli Lilly and Company
<b>Drug</b>	Baricitinib
<b>Proposed Indication</b>	Treatment of adults with rheumatoid arthritis (RA)
<b>Consulting Division</b>	Division of Neurology Products (DNP) Raj Nair, MD
<b>Date review Completed</b>	April 7th, 2017
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### ***1 Introduction***

The Division of Neurology Products has requested a consult concerning a potential signal of hepatotoxicity in a drug currently under NDA review, baricitinib for treatment of rheumatoid arthritis (RA).

### ***2 Disease Background***

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, that are approved for the treatment of RA. Another treatment option would be a desirable addition to the non-curative treatment options available for RA. Baricitinib is a small molecule inhibitor of janus associated kinase (JAK) for oral administration proposed for approval for use in patients with RA. Another oral small molecule inhibitor of JAK called tofacitinib was approved for use in patients with RA in 2012.

### **3 Drug Mechanism**

Tofacitinib and baricitinib are oral, small molecule inhibitors of the intracellular tyrosine kinase called janus associated kinase (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 tyrosine kinase 2 (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. JAK kinases, especially JAK1, also play a pivotal role in transmitting proliferative growth signals in hepatocytes caused by Il-6, one of the key growth factors that drive liver cell regeneration after organ injury. The impact that blockade of this signaling by JAK kinase inhibitors has on liver cell adaptation during combined treatment with hepatotoxic agents such as MTX has not been fully defined.

### **4 Preclinical Findings Related to Hepatotoxicity**

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 were performed. 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<sub>0-24h</sub> of 1.21  $\mu\text{M}\cdot\text{hr}$  at the limit dose. In the 9 month dog study, the additional finding of liver toxicity was seen in the higher dose animals (3 mg/kg and 9/6 mg/kg).

### **5 Clinical Pharmacology**

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 dedicated hepatic impairment study, the geometric mean AUC<sub>0-inf</sub> and C<sub>max</sub> 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, its use is not recommended in this setting.

In drug interaction studies, a notable finding 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 Other JAK Inhibitors and Hepatotoxicity**

### **A. Tofacitinib**

Another JAK inhibitor that is approved is tofacitinib (Xeljanz XR) (NDA 208-246) approved in February of 2016 and tofacitinib (Xeljanz) (NDA 203-214) approved in November of 2012, both are oral formulations for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.

The LiverTox<sup>1</sup> website noted the following information about tofacitinib:

“In the large registration clinical trials, serum aminotransferase elevations occurred in 28% to 34% of tofacitinib treated subjects compared to 25% in comparator arms and 10% in placebo recipients. These elevations were typically mild and transient, but values above 3 times the upper limit of normal (ULN) occurred in 1% to 2% of patients on tofacitinib compared to <1% on placebo. The elevations occasionally led to early discontinuations, but more often resolved even without dose adjustment. In prelicensure studies, there were no instances of clinically apparent liver injury attributed to tofacitinib. Since approval and more wide scale availability of tofacitinib, there have been no published reports of hepatotoxicity associated with its use.

Likelihood score: E\* (unproven but suspected cause of clinically apparent liver injury and drug with limited general availability that was associated with ALT elevations in prelicensure clinical trials).

The causes of serum enzyme elevations during tofacitinib therapy are not known. Tofacitinib is metabolized in the liver largely through the CYP 3A4

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<sup>1</sup> <https://livertox.nih.gov/Tofacitinib.htm>

pathway and liver injury may be related to production of a toxic or immunogenic intermediate. Because it is a substrate for CYP 3A4, tofacitinib is susceptible to drug-drug interactions with agents that inhibit or induce this specific hepatic microsomal activity.”

*Comment:*

*In addition, whether these liver enzyme changes induced by tofacitinib reflect a disturbance of normal adaptation of hepatocytes when injured by other drugs or diseases because of the inhibition of JAK kinases has not been defined.*

The labeling of tofacitinib has a warning for liver enzyme elevations:

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy.

Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

## **B. Ruxolitinib**

Ruxolitinib (Jakafi) (NDA 202192) is another JAK inhibitor approved for myelofibrosis and polycythemia vera; there were no significant signals of liver enzyme elevations noted in the reviews or the literature for ruxolitinib.

## **7 NDA - Summary of Efficacy and Safety Results**

### Efficacy

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<sup>2</sup> and reduction in Disease Activity Score-28,<sup>3</sup> and for improvement of physical function as measured by Health Assessment

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<sup>2</sup> 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).

<sup>3</sup> 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

Questionnaire-Disability Index (HAQ-DI)<sup>4</sup>. 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.

### Safety

The safety assessment of baricitinib for RA is primarily based on the studies shown in Table 1. The size and scope of the safety database were reasonable and consistent with the safety database of other DMARDs approved for RA. The primary safety data set used by the Applicant and the Clinical Team of the Division of Neurology Products 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).

**Table 1: Relevant Controlled Clinical Studies with Baricitinib in RA**

ID Year* Study	Study Characteristics <sup>†</sup>	Treatment groups <sup>†</sup>	N <sup>§</sup>	Efficacy Variables <sup>§</sup>	Regions and Countries <sup>  </sup>
<b>Phase 2</b>					
JADC [05/09 to 07/10]	- Over 18 years - Inadequate response to DMARD - DMARD background - Parallel arm, DB, no rescue; 24 weeks	Bar 4 mg QD Bar 7 mg QD Bar 10 mg QD Placebo, up to wk 12	32 32 32 31	1 : ACR 20 at wk 12	US, Europe (74% US)
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 : ACR 20 at wk 12	US, Mexico, Europe, India (32% US)

<sup>4</sup> 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.

ID Year* Study	Study Characteristics†	Treatment groups‡	N§	Efficacy Variables¶	Regions and Countries//
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°:ACR 20 at wk 12	Japan (100%)
<b>Phase 3</b>					
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°:ACR 20 at wk 12 2°: 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°: ACR 20 at wk 12 2°: 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°: ACR 20 at wk 12 2°: HAQ-DI at wk 24	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°: ACR 20 at wk 24 2°: HAQ-DI at wk 24; mTSS at wk 24	North America, Central and South America, Europe, Asia 20% North America)
<b>Long-term extension of other studies</b>					
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	-

\*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

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. 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), and some patients from baricitinib 2 mg also crossed over to baricitinib 4 mg starting at week 16. 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. To better characterize the safety data, the DNP review team requested that the Applicant conduct additional analyses before and after crossover between treatment arms.

Major safety findings were related to immunosuppression that is 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. Multiple incidences of pulmonary embolism, deep venous thrombosis and 3 SAEs of arterial thrombosis were noted in the treatment group. 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.

Other 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. More patients discontinued secondary to liver function test abnormalities with baricitinib than placebo and with 4 mg compared to 2 mg (See Section 7 below).

## 8 Review of Hepatotoxicity Data from NDA

There was no case of liver injury satisfying Hy's Law (ALT or AST >3x upper limit of normal **AND** TBL > 2xULN; not primarily cholestatic; not caused by disease but by drug) seen in the program. Nevertheless, dose-related increase in liver enzymes and bilirubin with baricitinib were seen. There were 14 patients withdrawn from the studies due to liver function test abnormalities, 10 from baricitinib 4 mg and 1 from baricitinib 2 mg treatment group and one from placebo. These occurred despite entry criteria that did not allow patients with elevated liver enzymes above a threshold of 1.5 x ULN for transaminases and total bilirubin to enroll in the studies. All patients (approximately 13 of 14) who consented to follow up appeared to resolve elevations in transaminases and bilirubin. See Table 2 and 3 and Figures 1-3 below.

**Table 2: Laboratory parameter as mean change from baseline and threshold change as n (rate) (pooled studies JADV, JADX, JADW, and JADZ)**

	4mg	2mg	placebo
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)

Source: Applicant's NDA Submission

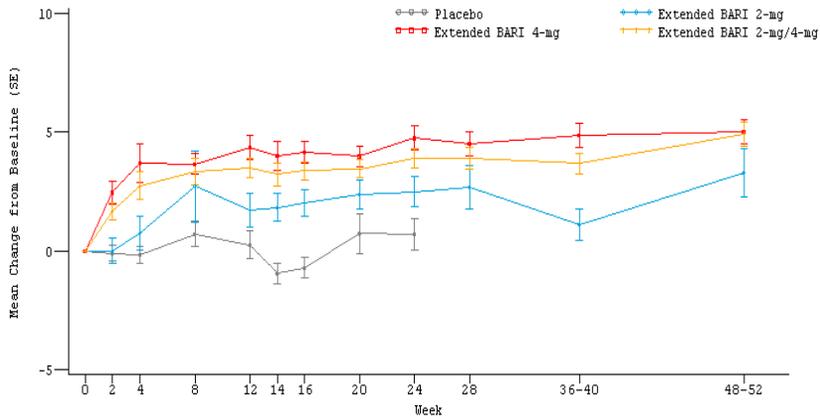
**Table 3: Overview of Cases of Permanent Discontinuations Secondary to Liver related abnormalities in Baricitinib Drug Development Program**

	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		JADX 61250 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		
<b>Total</b>	2	10	2	1

Source: Applicant's NDA Submission

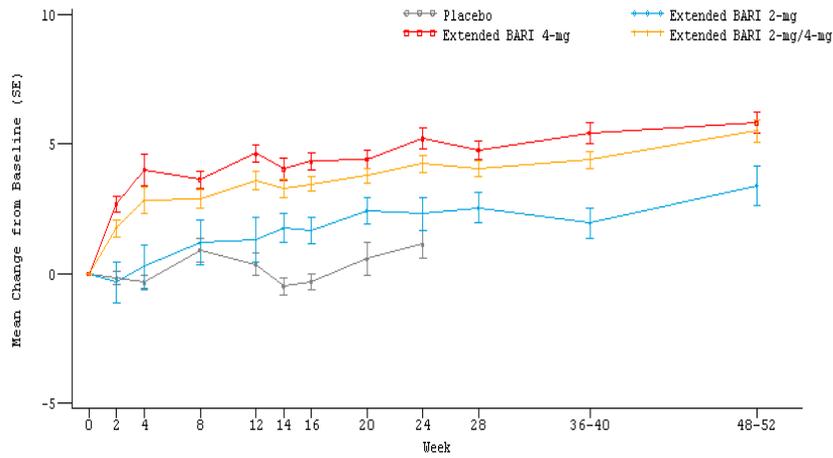
All of the patients in Table 3 were on background methotrexate in each of the groups, except patient (b) (6) who receive baricitinib 4 mg and hydroxychloroquine.

**Figure 1: Mean Change from Baseline Over 52 Week for ALT/SGPT (IU/L)**



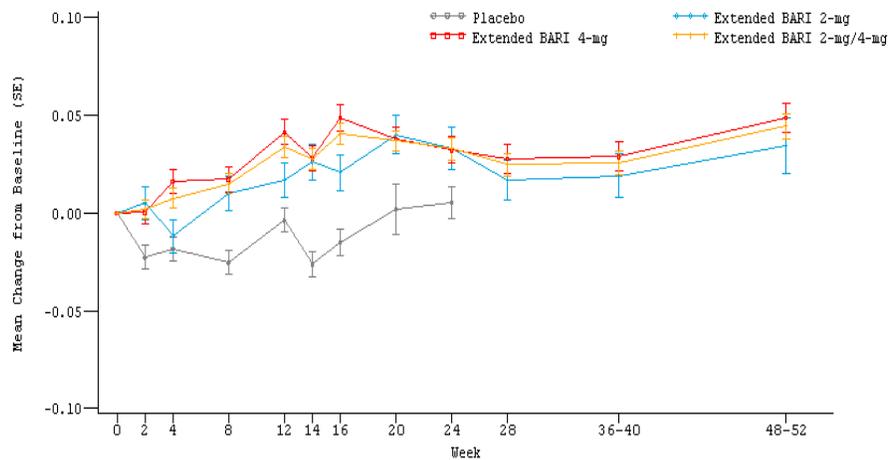
Source: Applicant's Response to IR dated July 21<sup>st</sup>, 2016

**Figure 2: Mean Change from Baseline Over 52 Week for AST/SGOT (IU/L)**



Source: Applicant's Response to IR dated July 21<sup>st</sup>, 2016

**Figure 3: Mean Change from Baseline Over 52 Week for Total Bilirubin (mg/dL)**



Source: Applicant's Response to IR dated July 21<sup>st</sup>, 2016

## Narratives

### *MO Comment:*

*The narratives are poorly written and organized making interpretation of causality difficult if not impossible in some cases.*

### Baricitinib 4mg dose:

1. Patient # [REDACTED]<sup>(b) (6)</sup> is 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. At baseline there were negative results for Hepatitis B and C (she was not tested for cytomegalovirus, Epstein Barr Virus, Hepatitis A or E virus). The baseline ALT and AST levels were 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. Phosphatidyl choline, glycyrrhizic acid, and glucuronic acid were started on day 73 for ALT increased. Baricitinib was discontinued on Day 78. Baricitinib was resumed on Day 114 when patient's ALT dropped within normal range whereas AST was marginally high and glucuronic acid was discontinued. After the resumption, patients' ALT and AST gradually increased again. Phosphatidyl choline and glycyrrhizic acid were stopped on day 147. ALT and AST and reached >5x ULN and ≥3x ULN on Day 172. The patient was permanently discontinued on Day 175. The patient never received any testing of antinuclear antibody levels, anti-smooth muscle antibody or anti-actin antibodies. The patient had no abnormal symptoms Transaminases gradually returned toward normal but were still mildly elevated at last follow-up. In the opinion of the investigator, the events of ALT increased and AST increased were possibly related to the study drug.

### *MO Comment:*

*This case is consistent with a chronic DILI secondary to baricitinib which is supported by the recovery with discontinuation of drug and the recurrence of transaminase elevations with rechallenge.*

2. Patient # [REDACTED]<sup>(b) (6)</sup> is 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, the patient was apparently asymptomatic, however blood test results showed >8x ULN for ALT and AST, which met permanent drug discontinuation criteria. The patient was asymptomatic and his alkaline phosphatase, total bilirubin, and albumin were all within the normal range. The patient permanently discontinued drug on Day 31. In the opinion of the investigator, the SAEs of ALT increased and AST increased were possibly related to the study drug. During study participation, the patient took

methotrexate 15 mg PO weekly, prednisone 7.5 PO QD, indometacin 50 mg PO QD and folic acid 5 mg PO weekly for RA.

*MO Comment:*

*The sponsor attributes this to blinded subcutaneous (sq) study drug<sup>5</sup>. It is not clear how long the patient was on methotrexate and indomethacin prior to introduction of study drug.*

3. Patient # [REDACTED]<sup>(b) (6)</sup> is 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 drug on Day 92. On day 113, patient's ALT level was still >2x ULN and AST mildly improved to >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 # [REDACTED]<sup>(b) (6)</sup> is 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 until permanent discontinuation of the drug (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. (The patient did not actually meet discontinuation criteria for elevated liver biochemical tests.)

*MO Comment:*

*It is not clear from the narrative why the patient had elevated ALP prior to enrollment or if any evaluation for this elevation in ALP was performed.*

5. Patient # [REDACTED]<sup>(b) (6)</sup> is 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 ≥3x ULN whereas other hepatic

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<sup>5</sup> Trial JADV compared baricitinib (oral) to adalimumab (sq) in a double dummy design.

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 >5x 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.

*MO Comment*

*This may not be DILI and appears to be related to acute cholecystitis, however the narrative is very poorly written and it appears the transaminase elevations occurred before the cholecystitis so DILI cannot be ruled out in light of similar signals.*

Patient # (b) (6) is 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. Two days after the first dose, both ALT and AST levels reached > 8x ULN. The patient was permanently discontinued from 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 abnormality was not related to the study drug, but was possibly related to study procedures (initiation of isoniazid prophylaxis).

7. Patient # (b) (6) is 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. Two days after the first dose of baricitinib, both ALT and AST levels reached >8x ULN. It did not appear that labs had been checked after initiation of isoniazid, but before initiation of baricitinib. The patient was permanently discontinued from 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) is 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 were 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 >1x ULN on Day 28 and reached >8x ULN on Day 83. On the same day AST reached >3x ULN. The study drug (baricitinib + MTX) and concomitant medications (celecoxib and esomeprazole) were discontinued 2 days later (Day 85). 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 # [REDACTED]<sup>(b) (6)</sup> is 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 were within the normal range. The patient's ALT started to increase >1x ULN on Day 15 and stayed at that level for 3 weeks. The highest ALT reading during this period was just >1.5x ULN. The patient was permanently discontinued from the study and the study drug (baricitinib + MTX) on Day 36. The patient's ALT level remained >1x 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. (The patient did not actually meet discontinuation criteria for elevated liver biochemical tests).

10. Patient # [REDACTED]<sup>(b) (6)</sup> is 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. The patient had normal baseline liver biochemistries and denied taking any liver toxins or alcohol. His baseline medications included methotrexate 15 mg PO weekly, prednisone 10 mg PO QD, meloxicam 15 mg PO QD and folic acid 5 mg PO weekly for RA. These medications were apparently started approximately two months prior to trial entry.

Two 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 2 were: glutamic pyruvic transaminase 258 U/L (21-72 U/L), alkaline phosphatase 163 U/L (38-126 U/L), G glutamyl transpeptidase 695 U/L (15-73 U/L) and 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. Ultrasound of the liver and computerized tomography of the abdomen were normal. An endoscopy 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 but refused further follow-up. In the opinion of the investigator, the SAE of severe drug-induced liver injury and the event of esophageal candidiasis were not related to the study drug.

*MO Comment:*

*While the patient was apparently not tested for hepatitis E or autoimmune hepatitis, no other cause of DILI was noted and the case is potentially consistent with baricitinib induced DILI. From my assessment of the narratives, I do not agree with the Applicant that since the drug was discontinued at day 2 and the laboratory was not available until day 5, that therefore it could have been caused by something else. It appears to me that the first labs reported were from day 2 or 3 (around drug discontinuation (day 2) depending on how the observer counted the days. Also, the patient had symptoms consistent with DILI 2 days after starting baricitinib.*

Baricitinib 2 mg dose:

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

1. Patient # [REDACTED] <sup>(b) (6)</sup> is 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 meet discontinuation criteria for elevated liver biochemical tests)
2. Patient # [REDACTED] <sup>(b) (6)</sup> is 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 for discontinuation by meeting ALT >5x times ULN criterion). Treatment suspension lasted for 32 days after the metrorrhagia was resolved on Day 52 with a 9-day treatment of 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<sup>9</sup> cells/L. The patient was permanently discontinued on Day 59. The ALT readings (normal range 6-37)

are listed as follows: 51(screening), 47 (Week 0), 43 (Week 1), 185 (Week 4, drug suspended), 655 (Week 8, drug restarted Day 57 and permanently discontinued Day 59), 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 (humira) Arm:

Adalimumab is an approved tumor necrosis factor (TNF) blocker and was a comparator in some of the baricitinib trials discussed above. There is no warning for liver injury in the labeling. There were 2 patients on adalimumab discontinued for liver test abnormalities in the studies that compared baricitinib to adalimumab.

1. Patient # [REDACTED] <sup>(b) (6)</sup> is 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 adalimumab discontinuation. In the opinion of the investigator, the SAE of moderate severity transaminases increased was not related to the study drug.
2. Patient # [REDACTED] <sup>(b) (6)</sup> is 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 adalimumab 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 Arm:

There was one patient on placebo who had treatment permanently discontinued.

1. Patient # [REDACTED] <sup>(b) (6)</sup> is 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 >8x ULN on Day 77 and patient was permanently discontinued from 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.

*MO Comment:*

*There appears to be an increase in cases of hepatotoxicity in the baricitinib 4mg group, but interpretation is confounded by the higher patient years of exposure in the 4 mg group vs. the 2mg group or the placebo groups. Interpretation is also confounded by the fact that almost all patients were on methotrexate and the cumulative dose of methotrexate is not given.*

## **8 Summary and Conclusions**

There is a signal of liver enzyme elevations and potential DILI. Based on information that has been provided by the sponsor, so far, there were no cases that met the criteria for Hy's law. Nonetheless, several patients had symptoms and significant elevations consistent with DILI. However the data is not presented in such a way that a definitive analysis of DILI risk linked to baricitinib can be performed. Most of the patients with a signal for liver injury were on concomitant methotrexate which can cause chronic liver injury over time and with increasing total exposure. We are concerned that the combination of methotrexate with the JAK inhibitor may be synergistic. Although not yet characterized, if baricitinib exposure blunts normal cytoprotective responses to known hepatotoxic agents such as MTX the risk for liver injury (acute or chronic) may be increased. In addition, some patients were on concomitant INH which may also cause liver injury though patients generally will adapt (liver adaptation refers to resolution of increased serum aminotransferase levels attributed to a drug while continuing its use at the same dose) to INH. We have the following recommendations:

- 1 Please submit all the data for the study subjects in the phase 2 and 3 trials in an e-DISH format, with narratives compiled by someone with expertise in the diagnosis of DILI. See attached document with the requirements for submission of the e-DISH data. See instructions in Appendix A, below.
- 2 The cases of interest should be reviewed by a panel of expert hepatologists, and drug causality and narratives and summary of conclusions provided. Within this expert assessment, distinguish individuals with background/concomitant medications esp. methotrexate. The review of cases should also assess the impact of different doses compared to placebo.

- 3 Discuss whether there is potential for drug/drug interaction increasing baricitinib's risk of DILI, especially with concurrent exposure to methotrexate. The cumulative exposure to methotrexate should be taken into account.
- 4 You will also need to identify risks of long-term exposure in RA patients and discuss if there is a potential for adaptation to occur vs. the risk for baricitinib to cause chronic liver injury (e.g., chronic hepatitis, fibrosis etc.).
- 5 Discuss what monitoring should occur to detect cases of liver injury, and propose an algorithm for response to occurrences of liver enzyme elevations with use of baricitinib.
- 6 Request a consult from the Divisions of Pharmacovigilance in OPE to interrogate the FAERS database for serious post-marketing adverse events marked by either acute or chronic hepatotoxicity, associated with tofacitinib or ruxolitinib.

## Appendix A

### Format of Standard Narrative Data

Requirement	Standard variable	The variable means...	Variable-type
1. <b>Required</b>	STUDYID	Unique identifier for a study within the submission	Char
2. <b>Required</b>	USUBJID	Unique subject identifier within the submission	Char
3. <b>Required</b>	NARRAT1* (Required): Clinical Narrative, first part (Char, length<=200) NARRAT2* (Required): Clinical Narrative, continued (Char, length<=200) NARRAT3* (Required): Clinical Narrative, continued (Char, length<=200) ... NARRATn* (Required): Clinical Narrative, last part (Char, length<=200)	Clinical Narrative*	Char

**\* Requirements for Variables NARRAT11-NARRATIn - To the medical writer:**

Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hys Law" cases of elevated ALT or AST > 3xULN and TBL > 2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are: 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then 2) evaluating the narrative data gathered to adjudicate the probable

cause of the abnormal findings. This may require additional questions, tests, examinations to search for the cause, and only after ruling out other causes can a presumptive diagnosis of probable drug-related liver injury (DILI) be made. Liver biopsy is not definitive, and there is no single test or finding that proves DILI. For the adjudication to be successful, your investigators must search actively for the cause of all cases of elevated ALT or AST >3xULN and TBL > 2xULN. Finding a probable, very likely, or definite cause of the liver injury other than the drug is very important. The eDISH system, as used by medical reviewers at CDER, includes the capability to create time-course graphs for each subject, and to read the narrative summaries, helping them in drawing their own conclusions as to whether the drug may have caused the abnormal findings. We will want to review the data independently. Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently difficult and requires information to rule out or rule in other possible causes.

Therefore, we recommend that the narratives should be written by physicians or other medical personnel skilled in medical differential diagnosis. Pertinent negative findings should be included in any narrative. The data that needs to be gathered by the investigator are those that can establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune hepatitis.

It is not necessary to include all subjects in this patient narrative data set. However, make sure to include narratives for subjects with ALT or AST >3xULN and TBL > 2xULN.

The narratives should include information described in the following points:

1. Indication
2. Subject's medical history and concomitant medications
3. Dates and laboratory values of diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy
4. Time course of any signs or symptoms of liver disease, including jaundice
5. Differential diagnosis and final diagnosis of liver disease
6. The study site investigator and the sponsor's assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events
7. Clinical course of liver-related adverse events including treatment and outcome
8. Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation.
9. It is also helpful to include in the narrative:
  - Dose and duration of study therapy in weeks
  - Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements

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/s/  
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STEPHANIE O OMOKARO on behalf of LARA DIMICK-SANTOS  
04/10/2017

STEPHANIE O OMOKARO  
04/10/2017

DRAGOS G ROMAN  
04/10/2017

MARK I AVIGAN  
04/10/2017

NDA: 207924  
Product: Baricitinib  
Date: March 24, 2017

Subject: Addendum to CDTL review  
Addendum to Division Director review

This document provides an addendum to the Division Director Review dated February 6, 2017 and the CDTL review dated January 5, 2017. Please see the Division Director and CDTL reviews for additional details regarding the development program. Following finalization of these reviews, additional safety analyses and discussion have occurred for this application. This document summarizes internal discussions at a Safety Outcomes Trial Subcommittee Meeting and a Regulatory Briefing.

### **Medical Policy Council Safety Outcomes Trial (SOT) Subcommittee Meeting**

On March 10, 2017, the Division presented data from the baricitinib application to the SOT subcommittee to obtain input on whether a cardiovascular outcome trial (CVOT) should be a post-marketing requirement (PMR) for baricitinib recognizing that similar trials have been requested for other rheumatoid arthritis products that cause elevations in lipid parameters.

The main focus of the meeting was the dose-dependent elevation in lipid parameters noted in the baricitinib program and the small number of MACE events during the controlled trials. In addition, the dose-dependent increases in platelet counts and the imbalance in thrombotic events seen during the trials were discussed. The Division did not recommend a post-marketing CVOT, but did recommend a PMR safety study to further evaluate thrombotic events that occurred during the phase 3 studies. Such a study would also provide information about other safety events of interest, such as malignancy, infection, and MACE. In general, the SOT subcommittee agreed with the Division's recommendation not to require a post-marketing CVOT; however, concerns were raised regarding the safety signal related to thrombosis. Committee members questioned whether additional data are needed pre-marketing to assess this risk. To help address these questions, the overall risk/benefit of baricitinib was discussed at a Regulatory Briefing.

### **Regulatory Briefing Summary**

On March 17, 2017, the risk/benefit assessment for baricitinib for rheumatoid arthritis was discussed at a Regulatory Briefing. This document summarizes key points from the Regulatory Briefing.

At the Regulatory Briefing, concerns were raised regarding several aspects of Lilly's development program, including the adequacy of Lilly's dose ranging, inconsistent efficacy separation between the 2 mg and 4 mg doses, and safety concerns.

First, given the safety concerns, the adequacy of Lilly's dose ranging was questioned. In the phase 2 dose-ranging studies, all of the doses studied, including the lowest dose (1 mg), were effective compared to placebo. In study JADA, the ACR20 response was numerically better for 4 mg compared to lower doses, but in study JADN the ACR20 response for 1 mg was similar to 4 mg. Further, in the two studies with 1 mg, 1 mg was statistically superior to placebo. Lilly's rationale for selection of the 4 mg was based on the hypothesis that lower doses were expected to

perform worse than active comparators, similar safety findings for the 4 mg dose and lower doses, and lack of safety concerns with developing doses even higher than 4 mg (without added efficacy above 4 mg). Dose selection based on limited phase 2 data was a concern, especially given the safety findings discussed below. Further, it was noted that it is unclear where the 2 and 4 mg doses reside on the dose-response curve for efficacy or safety.

Second, the committee agreed that both 2 mg and 4 mg are effective, but did not feel that there was strong evidence of a benefit of 4 mg compared to 2 mg in the phase 3 studies. It was acknowledged that there was separation for some endpoints in some studies, but not consistently throughout the program. Specifically, in study JADW, the ACR20 response and the mean change in the components of the ACR20 were higher for 4 mg compared to 2 mg, but similar trends were not seen in study JADX.

Third, concerns were raised regarding the safety profile of baricitinib. Baricitinib is an immunosuppressant associated with an increased risk of certain types of infection, such as herpes zoster and malignancy. Further, there were dose-dependent changes in laboratory parameters, including increases in liver function tests, lipids, and platelets, and decreases in neutrophils and hemoglobin. In general, these risks are consistent with the known risks of other disease modifying anti-rheumatic drugs used in the treatment of rheumatoid arthritis (RA). However, significant concerns were raised regarding the thrombosis safety risk, which has not been seen in other RA development programs. It was acknowledged that the numerical imbalances were small, but the consistent imbalance, with more events in the baricitinib treatment arms than the comparator arms, was of concern. In addition, many of these events were serious, with some being fatal. Safety concerns related to pulmonary embolism and thrombosis have not been seen in previous RA development programs. The applicant tried to minimize the imbalance noting risk factors that were present in the cases, such as use of methotrexate or obesity, but it was emphasized that these risk factors were also present in the placebo arm. Further, there were cases in patients who had no significant underlying risk factors and cases were seen throughout the development program, including in psoriasis. While the majority of cases were venous, additional notable arterial thrombotic events on the baricitinib arms were highlighted.

Additional discussion focused on whether baricitinib-associated increases in platelet counts could contribute to thrombosis risk. Baricitinib was associated with dose-dependent increases in platelet counts, but there was no clear association between platelet elevations and thrombotic events since all patients, with or without thrombotic events had platelet elevations and the majority of patients still had platelet counts within the normal range despite these elevations. However, the baricitinib associated platelet elevation raised concern for a possible underlying mechanism of increased thrombotic risk. While the magnitude of elevation itself might not account for the risk, other platelet-related changes could increase the risk.

Given the safety concerns with baricitinib, the discussion turned to whether baricitinib offers any unique efficacy advantages over currently available drugs approved for rheumatoid arthritis. While one study of baricitinib 4 mg showed superior efficacy to adalimumab, this study was not replicated and was accompanied by numerically worse safety findings compared to adalimumab in the same study. Further other DMARD programs, such as tofacitinib, also have shown numerically higher efficacy response assessed by ACR criteria compared to adalimumab. It was

noted that baricitinib is an oral therapy, as compared to many approved RA therapies, which are given by infusion or injection. However, it was noted that other oral therapies, such as tofacitinib and methotrexate, are available for RA. Thus, the committee did not feel that the available data supported a unique clinical advantage over available therapies.

The committee discussed whether the risk/benefit of baricitinib is favorable for approval for the treatment of RA. Some committee members felt the available data supported approval, with adequate labeling and a post marketing safety trial, citing the need for additional therapies for patients noting that there was only one other JAK inhibitor approved. However, the majority of the committee members did not feel that the overall risk/benefit of baricitinib is favorable to support approval for RA. Key concerns were the safety signal related to thrombosis and need for better dose ranging given the safety concerns at the studied doses. In general, it was felt that additional data and analyses are needed pre-approval.

### **Summary**

While the two proposed doses of baricitinib (2 mg and 4 mg) are clearly effective for the treatment of rheumatoid arthritis, there are significant concerns that the overall risk/benefit is not favorable given the unique safety risk of thrombosis and the other safety risks, such as herpes zoster and malignancy. The safety finding of thrombosis has not been seen with other development programs for rheumatoid arthritis. While the number of cases is limited, there were serious and fatal cases. The safety findings occurred at both 2 mg and 4 mg and the size of the 2 mg safety database is limited to draw definitive conclusions on differential risk between the doses. Additional safety data needs to be generated to understand the thrombosis risk for baricitinib, and it would be reasonable to obtain the data and assess this safety risk. Given that several safety findings, such as changes in laboratory parameters, are dose-dependent, the safety events seen at the studied doses, and the concerns with inadequate dose-ranging, it would be reasonable to assess the efficacy and safety of lower doses and generate a larger safety database for dose or doses lower than 2 mg preapproval.

### **Draft CR language if a final decision is taken to not approve this application:**

1. The submitted data do not provide substantial evidence of safety to support the use of baricitinib at the proposed doses of 2 mg and 4 mg once daily in patients with rheumatoid arthritis. At the proposed doses, there were unacceptable higher frequencies of safety events, such as thrombotic events, compared to placebo in patients with rheumatoid arthritis.
2. The submitted data are not adequate to support dose selection of either the 2 mg or 4 mg dose. Dose ranging studies suggest that a 1 mg dose of baricitinib may be effective. The submitted studies do not show a clinically meaningful efficacy difference between the 1 mg once daily dose compared to the 2 mg or 4 mg once daily doses or the 2 mg dose compared to the 4 mg dose.
3. The submitted data do not provide substantial evidence to support use of 4 mg in patients with rheumatoid arthritis. The data submitted do not show a clinically meaningful advantage of the 4 mg dose over the 2 mg dose, especially in regards to potential safety disadvantages associated with the administration of a higher dose.

To support approval of baricitinib in rheumatoid arthritis, provide data to support the dose selection, efficacy, and balancing safety of baricitinib. Given the safety signal of thrombotic events and the dose related increase in laboratory parameters, for the proposed dose(s) of baricitinib, provide data to support dose selection of a dose of baricitinib that will provide efficacy with a balancing safety profile in patients with rheumatoid arthritis. Exploration of 1 mg of baricitinib or lower may be necessary to adequately evaluate the dose response curve for baricitinib. Your program should include sufficient safety data to evaluate the risk of thrombotic adverse events. If you propose two doses of baricitinib, you will need to provide data to support the benefit of the higher dose as well as the balancing safety data.

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/s/  
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JANET W MAYNARD  
03/28/2017

BADRUL A CHOWDHURY  
03/28/2017

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 baricitinib 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  $\geq$ 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 than 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		
<b>Total</b>	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 # [REDACTED] <sup>(b) (6)</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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.

#### Baricitinib 2 mg dose:

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

1. Patient # [REDACTED] <sup>(b) (6)</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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<sup>9</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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 # [REDACTED] <sup>(b) (6)</sup> 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.

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BADRUL A CHOWDHURY  
03/17/2017

## Division Director Summary Review for Regulatory Action

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

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

Clinical Pharmacology Review	<b>Yunzhao Ren, MD, PhD; Yuching Yang, Phd; Anshu Marathe, PhD</b>
OPDP	<b>Adewale Adeleye</b>
OSI	<b>Anthony Orenca</b>
CDTL Review	<b>Janet Maynard, MD</b>
OSE/DEPI	<b>Efe Eworuke</b>
OSE/DMEPA	<b>Teresa McMillan</b>
OSE/DRISK	<b>Erin South</b>
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
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>• 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.</li> </ul>	Most patients with RA have chronic progressive disease.
<b>Current Treatment Options</b>	<ul style="list-style-type: none"> <li>• 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.</li> </ul>	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
<b>Benefit</b>	<ul style="list-style-type: none"> <li>• Reducing signs and symptoms of RA based on ACR response</li> <li>• Improvement in physical function based on HAQ-DI</li> <li>• Preventions of structural damage based on radiographic progression</li> <li>• 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.</li> </ul>	<p>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.</p>
<b>Risk</b>	<ul style="list-style-type: none"> <li>• 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.</li> </ul>	<p>The safety profile of baricitinib is well characterized. The safety finding of thrombosis is unique and not seen previously with other DMARDs.</p>
<b>Risk Management</b>	<ul style="list-style-type: none"> <li>• 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.</li> </ul>	<p>The safety risks will be communicated in labeling, with appropriate warning for infection, thrombosis, and other findings seen in the clinical program.</p>

## 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.<sup>1, 2</sup> RA affects approximately 1% of the adult population in North America and Northern Europe.<sup>3</sup>

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.<sup>4</sup>

**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

<sup>1</sup> Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.

<sup>2</sup> Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706-14.

<sup>3</sup> Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11(3):229.

<sup>4</sup> 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 <i>SC injection</i>	Fusion protein consisting of TNF-R and human IgG1 Fc <i>TNF-α inhibitor</i>	Clinical response Major clinical response Physical function response Radiographic response
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL <i>IV infusion</i>	Chimeric IgG1 k mAb <i>TNF-α inhibitor</i>	Clinical response Major clinical response Physical function response Radiographic response
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 100 mg <i>SC injection</i>	Recombinant polypeptide <i>IL-1 receptor antagonist</i>	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 <i>SC injection</i>	Human IgG1 k mAb <i>TNF-α inhibitor</i>	Clinical response Major clinical response Physical function response Radiographic response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial <i>IV infusion</i>	Fusion protein consisting of CTLA-4 and human IGg1 Fc <i>T cell activation inhibitor through B7-1 and B7-2</i>	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL <i>IV infusion</i>	Chimeric murine/human IgG1 k mAb <i>Anti CD20, B cell depletor</i>	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 <i>SC injection</i>	Humanized IgG1 k mAb <i>TNF-α inhibitor</i>	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial Prefilled syringe 200 mg/mL <i>SC injection</i>	Humanized Fab fragment <i>TNF-α inhibitor</i>	Clinical response Major clinical response Radiographic response Physical function response
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010, 2013}	Vial 20 mg/mL <i>IV infusion</i> Prefilled syringe (162mg/0.9mL) <i>SC injection</i>	Humanized IgG1 k mAb <i>IL-6 receptor inhibitor</i>	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 <i>SC injection</i>	Fusion protein consisting of CTLA-4 and human IGg1 Fc <i>T cell activation inhibitor through B7-1 and B7-2</i>	Clinical response Physical function response
Golimumab IV (SIMPONI ARIA) [Janssen] {2013}	Vial 100 mg/20 mL <i>IV infusion</i>	Humanized IgG1 k mAb <i>TNF-α inhibitor</i>	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<sub>0-24h</sub> of 1.21  $\mu\text{M}\cdot\text{hr}$  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**

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

<b>ID</b> Year* Study	<b>Study Characteristics †</b> - Patient age - Response to past treatment - Background treatment - Study design; duration	<b>Treatment groups ‡</b>	<b>N §</b>	<b>Efficacy Variables ¶</b>	<b>Regions and Countries //</b>
to 07/10]	DMARD - DMARD background - Parallel arm, DB, no rescue; 24 weeks	Bar 10 mg QD Placebo, up to wk 12	32 31		
<b>JADA</b> [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 <sup>o</sup> : ACR 20 at wk 12	US, Mexico, Europe, India (32% US)
<b>JADN</b> [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 <sup>o</sup> : ACR 20 at wk 12	Japan (100%)
<b>Phase 3</b>					
<b>JADV</b> 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 <sup>o</sup> : ACR 20 at wk 12 2 <sup>o</sup> : HAQ-DI at wk 12; mTSS at wk 24	North America, Central and South America, Europe, Asia (30% North America)
<b>JADX</b> 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 <sup>o</sup> : ACR 20 at wk 12 2 <sup>o</sup> : HAQ-DI at wk 12; mTSS at wk 24	North America, Central and South America, Europe, Asia (30% North America)
<b>JADW</b> 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 <sup>o</sup> : ACR 20 at wk 12 2 <sup>o</sup> : HAQ-DI at wk 12	North America, Central and South America, Europe, Asia (44% North America)
<b>JADZ</b> 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 <sup>o</sup> : ACR 20 at wk 24 2 <sup>o</sup> : HAQ-DI at wk 24; mTSS at wk 24	North America, Central and South America, Europe, Asia (20% North America)
<b>Long-term extension of other studies</b>					
<b>JADY</b> 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 //
<p>* 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],</p> <p>† DMARD = disease modifying anti-rheumatic drugs; Mtx or mtx = methotrexate; DB = double blind</p> <p>‡ Bar = Baricitinib; In studies JADV, JADX, and JADW, placebo treatment groups and active treatment groups all included background DMARDs with or without methotrexate</p> <p>§ Intent to treat (ITT); appropriate statistical hierarchy was followed for HAQDI and mTSS</p> <p>¶ ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score</p> <p>// Shows as regions; North America includes USA and Canada</p>					

### **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.<sup>5,6</sup> The ACR criteria have been used extensively in clinical

<sup>5</sup> 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.<sup>7</sup> 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).<sup>8</sup> 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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<sup>6</sup> Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid Arthritis classification criteria. *Arthritis & Rheum* 2010; 62:2569-2581.

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

<sup>8</sup> B Bruce and JF Fries. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005; 23 (Suppl 39):S14-S18

system for RA joint damage.<sup>9</sup> 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.<sup>10</sup> 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

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

<sup>10</sup> 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

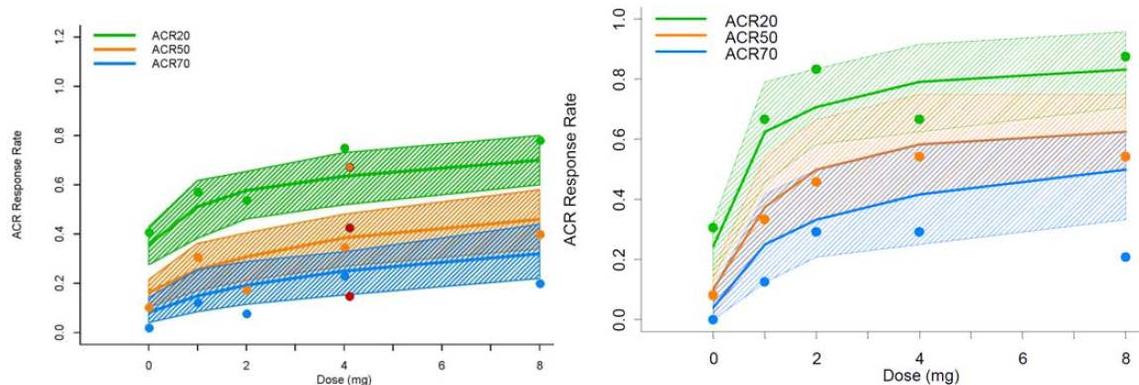
numerical response for 4 mg compared to lower doses, but in study JADN (study not used by Lilly for dose selection) the ACR response was numerically better for 2 mg dose compared to 4 mg dose, and across the two studies even 1 mg dose performed reasonably well (Table 4 and Figure 1).

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  $\leq$  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
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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	
		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	
		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	
		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 mtx
<b>Linear extrapolation</b>				
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	
<b>All observed data</b>				
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**

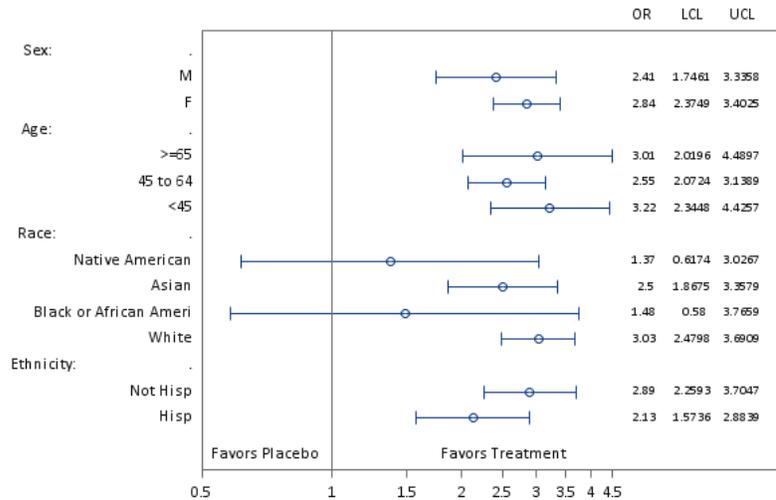
Study *	Time	Treatment †	Δ minutes	Difference [95% CI] (p-value) vs placebo
JADV Study II	Week 12	Bar 4 mg	-30	-28 [-45, -15] (0.001)
		Adalimumab	-13	-10 [-25, 0] (0.015)
		Placebo	-2	
JADX Study III	Week 12	Bar 2 mg	-30	-21 [-38, -7] (0.004)
		Bar 4 mg	-20	-14 [-29, -2] (0.02)
		Placebo	-9	
* Study 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
<b>PCS</b>				
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	
<b>MCS</b>				
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.<sup>11, 12, 13, 14</sup> 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.

<sup>11</sup> FDA's administrative record for [REDACTED]

(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.

<sup>13</sup> 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.

<sup>14</sup> Chin SJ, Durmowicz AG, Chowdhury BA. Tiotropium Respiat 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.<sup>15</sup> 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.

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<sup>15</sup> 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
<b>0-16 weeks</b>			
Number of patients	1265	403	892
Total exposure, patient years	386.7	122.6	267.2
All cause 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)
<b>0-52 weeks</b>			
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)
<b>&gt;52 weeks</b>			
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)	-
<b>0-any duration</b>			
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
<b>0-16 weeks</b>			
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
<b>0-16 weeks</b>			
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)
<b>0-52 weeks</b>			
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 baricitinib 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**

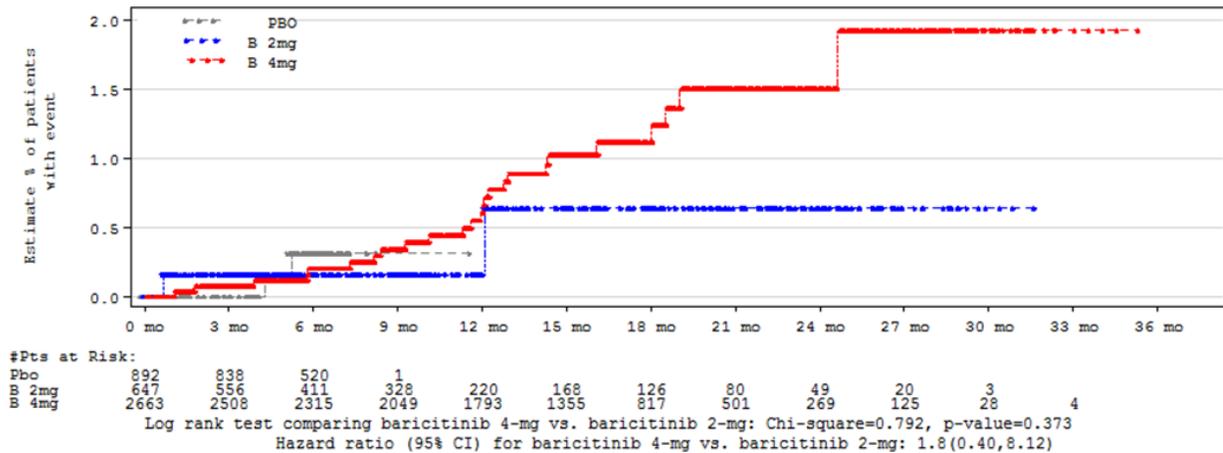
Patient ID	Treatment Duration *	Malignancy type	Crossover
<b>Baricitinib 4 mg (25 cases of malignancy + 2 cases not counted by Lilly)</b>			
(b) (6)	29 days	Fibrous histiocytoma †	Adalimumab in JADV to JADY baricitinib 4mg
	49 days	Adrenocortical carcinoma †	No crossover
	92 days	Lymphoproliferative //	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
<b>Baricitinib 2 mg (2 cases of malignancy)</b>			
(b) (6)	19 days	Ovarian low malig. pot. †	No crossover
	339 days	Ductal breast cancer §	No crossover
<b>Placebo (2 cases of malignancy)</b>			
(b) (6)	119 days	Breast cancer ¶	No crossover
	140 days	Ovarian cancer ¶	No crossover
<p>* 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”</p>			

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
<b>0-16 weeks</b>			
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 nm <sup>§</sup> , n (rate)	2 (0.5)	1 (0.8)	0
<b>0-52 weeks</b>			
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 nm <sup>§</sup> , n (rate)	10 (0.6)	2 (0.7)	2 (0.5)
<b>&gt;52 weeks</b>			
Total exposure, patient years	1300.6	210.2	-
Any malignancy, n (rate)	21 (1.6)	1 (0.5)	-
Any malignancy minus nm <sup>§</sup> , n (rate)	15 (1.2)	0	-
<b>0-any duration †</b>			
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 nm <sup>§</sup> , 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  
§ nm<sup>§</sup> = non-melanoma skin cancer



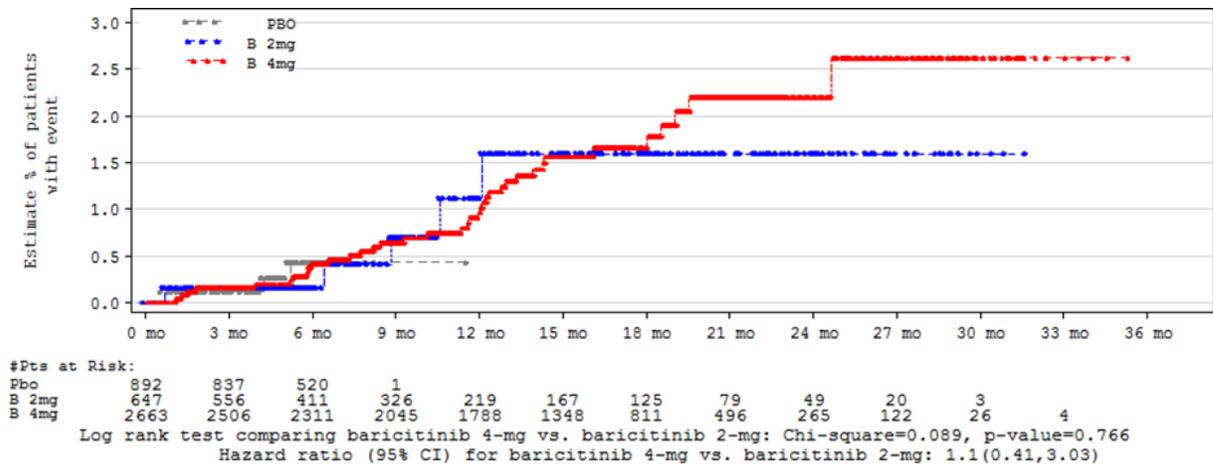
**Figure 3. Kaplan-Meier plots from randomization to end of follow-up for malignancies (excluding non-melanoma skin cancers) for baricitinib 4 mg, baricitinib 2 mg, and placebo pooled across four pivotal phase 3 studies. Patients contribute time and events based on their cumulative exposure to each individual 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 vs 2 mg
	4 mg	2 mg	4 mg	2 mg	
<b>Lilly's preferred:</b>					
Exclude (b) (6)*; Include (b) (6)	25	2	0.8	0.4	1.8 [0.40, 8.12]
<b>Alternates:</b>					
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 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
<b>Baricitinib 4 mg (12 cases of NMSC)</b>			
(b) (6)	35 days	Basal cell carcinoma †	No crossover
(b) (6)	41 days	Squamous and basal cell ca †	No crossover
(b) (6)	147 days	Squamous cell carcinoma §	No crossover
(b) (6)	150 days	Basal cell carcinoma ¶	No crossover
(b) (6)	165 days	Basal cell carcinoma ¶	No crossover
(b) (6)	182 days	Squamous cell carcinoma ¶	No crossover
(b) (6)	215 days	Basal cell carcinoma †	Placebo to baricitinib 4 mg on week 24
(b) (6)	323 days	Basal cell carcinoma ¶	No crossover
(b) (6)	344 days	Squamous and basal cell ca ¶	Placebo to baricitinib 4 mg on week 24
(b) (6)	372 days	Bowen's disease †	No crossover
(b) (6)	390 days	Squamous cell carcinoma ¶	No crossover
(b) (6)	547 days	Squamous cell carcinoma §	Adalimumab in JADV to JADY baricitinib 4mg
<b>Baricitinib 2 mg (3 cases of NMSC)</b>			
(b) (6)	180 days	Squamous cell carcinoma	No crossover
(b) (6)	297 days	Squamous cell carcinoma §	No crossover
(b) (6)	690 days	Squamous cell carcinoma §	Baricitinib 4 mg to 2 mg crossover on month 15
<b>Placebo (1 case of NMSC)</b>			
(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
<b>0-16 weeks</b>			
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)
<b>0-52 weeks</b>			
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)
<b>&gt;52 weeks</b>			
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)	-
<b>0-any duration *</b>			
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]
<b>Baricitinib 4 mg (14 cases of opportunistic infection, 7 cases of tuberculosis)</b>			
(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	Pareococcidiodes 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]
<b>Baricitinib 2 mg (2 cases of opportunistic infection)</b>			
(b) (6)	264 days	Histoplasmosis	No crossover, [SAE, hospitalized]
	460 days	Cryptococcal pneumonia	No crossover, [SAE, hospitalized]
<b>Placebo (2 cases of opportunistic infection)</b>			
(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
<b>0-16 weeks</b>			
Total exposure in patient years	386.7	122.6	267.2
Patients with MACE, n (rate)	2 (0.5)	0	2 (0.7)
<b>0-52 weeks</b>			
Total exposure, patient years	1694.9	304.8	365.0
Patients with MACE, n (rate)	7 (0.4)	1 (0.3)	2 (0.5)
<b>&gt;52 weeks</b>			
Total exposure in patient years	1300.6	210.2	-
Patients with MACE, n (rate)	8 (0.6)	0	
<b>0-any duration *</b>			
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) (4) 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
<b>0-16 weeks</b>			
Total exposure, patient years	386.7	122.6	267.2
Patients with thrombotic events, n (rate)	4 (1.0)	0	0
<b>0-52 weeks</b>			
Total exposure, patient years	1694.9	304.8	365.0
Patients with thrombotic events, n (rate)	8 (0.5)	2 (0.7)	0
<b>&gt;52 weeks</b>			
Total exposure, patient years	1300.6	210.2	-
Patients with thrombotic events, n (rate)	8 (0.6)	0	-
<b>0-any duration *</b>			
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†		
<b>Baricitinib 4 mg (16 cases)</b>						
(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		
<b>Baricitinib 2 mg (2 cases)</b>						
(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		
<b>Placebo (no cases)</b>						
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/microL)	0	0.05	0.38
Platelets (thousand cells/microL)	-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.<sup>16</sup>

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.

<sup>16</sup> 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 patent 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 finding 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.

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BADRUL A CHOWDHURY  
02/06/2017

## CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

<b>CLINICAL OUTCOME ASSESSMENT (COA) TRACKING NUMBER</b>	AT-2016-247
<b>IND/NDA/BLA NUMBER</b>	NDA 207924
<b>LETTER DATE/SUBMISSION NUMBER</b>	1/15/16
<b>PDUFA GOAL DATE</b>	1/15/17
<b>DATE OF CONSULT REQUEST</b>	10/11/16
<b>REVIEW DIVISION</b>	DPARP
<b>MEDICAL REVIEWER</b>	Raj Nair/Janet Maynard
<b>REVIEW DIVISION PM</b>	Jessica Lee
<b>PRIMARY COA REVIEWER</b>	Michelle Campbell
<b>SECONDARY COA REVIEWER ASSOCIATE DIRECTOR, COA STAFF</b>	Elektra Papadopoulos
<b>REVIEW COMPLETION DATE</b>	1/7/2017
<b>ESTABLISHED NAME</b>	Baricitinib
<b>TRADE NAME</b>	
<b>SPONSOR/APPLICANT</b>	Eli Lilly
<b>CLINICAL OUTCOME ASSESSMENT TYPE</b>	PRO
<b>ENDPOINT(S) CONCEPT(S)</b>	Worst Tiredness
<b>MEASURE(S)</b>	Severity of Worst Tiredness NRS
<b>INDICATION</b>	Adults with Rheumatoid Arthritis
<b>INTENDED POPULATION(S)</b>	Adults with Rheumatoid Arthritis

## Clinical Outcome Assessment Review

Michelle Campbell, PhD

NDA 207924

Baricitinib

Worst Tiredness

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### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment review is provided as a response to a request for consultation by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) regarding NDA 207924. The applicant used the Severity of Worst Tiredness numeric rating scale (NRS) averaged over seven days for the measurement of worst tiredness as a secondary endpoint in phase 3 clinical trial(s) in adult patients with rheumatoid arthritis (RA). [REDACTED] (b) (4)

Tiredness has been identified by patients with RA as an important symptom they have due to their RA. The applicant developed a single-item NRS asking patients to rate the severity of their worst tiredness in the past 24 hours. The applicant provided qualitative research for agency review supporting the validity of the severity of worst tiredness item from the patient perspective. The applicant also provided quantitative research supporting the psychometric properties of the instrument. The applicant did not use anchor-based methods to establish meaningful change. However, they did conduct supportive analyses on meaningful change, suggesting a meaningful change of 3 points on the Worst Tiredness item, which uses a scale from 0-10. The applicant also determined that RA patients who had a more severe disease state at Week 12 had a significantly smaller improvement in severity of worst tiredness in comparison to RA patients in a less severe disease state.

The review concludes that the evidence submitted by the applicant is adequate to demonstrate that the Severity of Worst Tiredness NRS is sufficient to measure worst tiredness in patients with RA and that a 3-point change appears to be a reasonable threshold for meaningful within-patient change in the population studied.

While not a regulatory requirement, in the spirit of optimizing measurement for future drug development programs, we suggest further work may be conducted to further evaluate meaningful within-patient change using anchor-based methods. The use of a patient global impression of change item and current-state severity of tiredness item using a verbal rating scale of severity may be useful as anchor instruments to use for these methods. The goal of this additional research is to confirm that a 3-point change is meaningful to patients.

## **Clinical Outcome Assessment Review**

Michelle Campbell, PhD

NDA 207924

Baricitinib

Worst Tiredness

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## **B. CLINICAL OUTCOME ASSESSMENT REVIEW**

### **1 CONTEXT OF USE (COU)**

#### **1.1 Target Study Population and Clinical Setting**

Adult patients with moderately to severely active RA

#### **1.2 Clinical Trial Design, Protocol, and Analysis Plan**

Study JADV:

A 52-week, Phase 3, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group, outpatient study which examined the effect of baricitinib (4-mg QD) versus placebo and versus an active comparator, adalimumab, in patients with moderately to severely active RA who had an inadequate response to MTX and who had never been treated with a biologic DMARD.

Study JADX:

A 24-week, Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, outpatient study that enrolled patients with moderately to severely active rheumatoid arthritis who had an inadequate response to at least one cDMARD and who had never been treated with a biologic DMARD.

#### **1.3 Endpoint Positioning**

## Clinical Outcome Assessment Review

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**Table 3. Endpoint Model for the Studies JADV and JADX, 4-mg QD Dose**

Concept		JADV Endpoint	JADX Endpoint
Primary			
Proportion of patients achieving ACR20 at Week 12	→	ACR20	ACR20
Major Secondary			
Change from baseline to Week 24 in structural joint damage as measured by modified Total Sharp Score (mTSS [van der Heijde method]) compared to placebo <sup>a</sup>	→	mTSS	N/A
Change from baseline to Week 12 in HAQ-DI score	→	HAQ-DI	HAQ-DI
Change from baseline to Week 12 in DAS28-hsCRP	→	DAS28	DAS28
Proportion of patients achieving an SDAI score ≤3.3 at Week 12	→	SDAI	SDAI
Proportion of patients achieving ACR20 response at Week 12 compared to adalimumab	→	ACR20	N/A
Change from baseline to Week 12 in DAS28-hsCRP compared to adalimumab	→	DAS28-hsCRP	N/A
Mean duration of morning joint stiffness in the 7 days prior to Week 12, as collected in electronic diaries	→	Morning joint stiffness duration item	Morning joint stiffness duration item
Mean severity of morning joint stiffness numeric rating scale (NRS) in the 7 days prior to Week 12	→	Morning joint stiffness severity NRS	Morning joint stiffness severity NRS
<b>Mean severity of Worst Tiredness NRS in the 7 days prior to Week 12</b>	→	<b>Worst Tiredness NRS</b>	<b>Worst Tiredness NRS</b>
Mean Worst Joint Pain NRS in the 7 days prior to Week 12	→	Worst Joint Pain NRS	Worst Joint Pain NRS

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; HAQ-DI = Health Assessment Questionnaire-Disability Index; hsCRP = high-sensitivity C-reactive protein; N/A = not applicable; SDAI = Simplified Disease Activity Index.

<sup>a</sup> Not applicable as a major secondary endpoint as it was assessed in Study JADX as an exploratory objective.

### 1.4 Labeling or promotional claim(s) based on the COA

(b) (4)

## 2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The Severity of Worst Tiredness item measures the severity of tiredness at its worst in patients with moderately to severely active RA.

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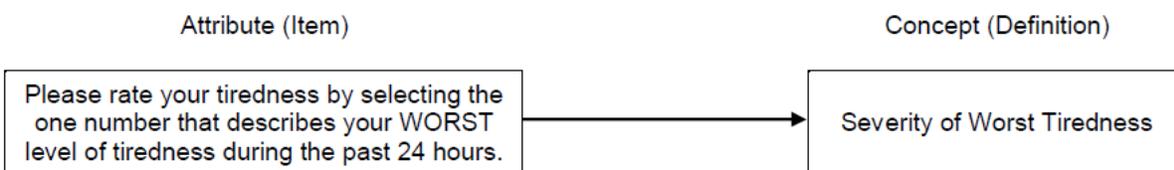
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**Figure 2.** Conceptual framework for the Severity of Worst Tiredness item.

### 3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

The Severity of Worst Tiredness NRS (see appendix) is a single, patient-administered electronic daily diary item, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no tiredness” and 10 representing “as bad as you can imagine.” Patients rate each day’s worst tiredness (using a handheld electronic diary) by selecting an integer in the 0 to 10 range that describes their worst tiredness that day. Data was collected for 12 weeks.

### 4 CONTENT VALIDITY

To document content validity the applicant first conducted a review of the literature, which focused on the etiology of fatigue in RA and recent expert input on the treatment and patients concerns of their RA. From this, the applicant conducted two sets of concept elicitation interviews (Phase 1 and Phase 2) over the course of drug development to understand the patient experience with RA including tiredness. During Phase 1 interviews, 22/23 patients listed fatigue as a symptom of RA. Patients used “tiredness” to define or describe their fatigue.

Phase 2 concept elicitation interviews focused on impact of RA symptoms and patient terminology to describe tiredness. Additionally, cognitive interviews on the understanding of the applicant developed electronic diary including Severity of Worst Tiredness were also conducted. Twenty out of twenty-eight patients used the word tiredness to describe their RA symptom experience with 13/28 used fatigue to describe their RA symptoms. The word tiredness was a common term used by patients when describing tiredness/fatigue/low energy.

During concept elicitation discussions, the majority of participants (n=20; 71%) used the word tiredness to describe their RA symptom experiences, seven (25%) of them spontaneously. Thirteen participants (46%) mentioned fatigue, 5 (18%) of them spontaneously. Lastly, ten participants (36%) mentioned low energy, 6 (21%) of them spontaneously. Phase 2 interviews confirmed the development of the Severity of Worst Tiredness. Cognitive debriefing confirmed that instrument of the daily diary were clear and response options were not difficult for patients to understand. Cognitive debriefing also showed that most patients view fatigue as a more severe form of tiredness.

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## 5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

### *Reliability (test-retest)*

In Studies JADV and JADX, test-retest reliability was assessed in stable patients during the interval between Week 1 and Week 2, and again between Week 4 and Week 8. Stable patients were defined as those with no more than a  $\pm 5$  point difference (DeLoach et al. 1998) on the patient's global assessment of disease activity (PtGA) from Week 1 to Week 2, and again from Week 4 to Week 8. Intra-class correlation coefficients were calculated between the initial (Week 1 or Week 4) and retest (Week 2 or Week 8) scores to evaluate test-retest reliability. The ICCs for weekly mean Severity of Worst Tiredness ranged from 0.89 to 0.91.

### **Construct Validity**

#### Convergent and Discriminant Validity

For Studies JADV and JADX, construct validity was assessed by Pearson correlations at Day 1 and at Week 12 between the scores of Severity of Worst Tiredness and the scores of other clinical/PRO endpoints: SF-36v2 domain scores, HAQ-DI, QIDS-SR16, FACIT-F, patient's assessment of arthritis pain, PtGA, Duration of MJS, Severity of MJS, Worst Joint Pain, Tender Joint Count 28, Swollen Joint Count 28, PhGA, and hsCRP. Cohen's conventions were used to interpret the absolute value of the correlation results, where a correlation  $>0.5$  is large, 0.3 to 0.5 is moderate, 0.1 to  $<0.3$  is small, and  $<0.1$  is insubstantial (Cohen 1988). The applicant hypothesized that moderate or large correlations supporting convergent validity would be demonstrated at Day 1 and Week 12 between Severity of Worst Tiredness and other instruments measuring concepts related to tiredness/fatigue (FACIT-F, SF-36 Vitality) and other RA pain-like symptoms (Severity of MJS, SF-36 Bodily Pain, Worst Joint Pain, patient's assessment of arthritis pain), their impact on functioning (SF-36 Social Functioning, SF-36 Physical Functioning, HAQ-DI), and clinician-reported/laboratory assessments of disease activity (Tender Joint Count 28, Swollen Joint Count 28, PhGA, and hsCRP).

Results from Day 1 in Studies JADV and JADX, moderate-to-large associations between Severity of Worst Tiredness and other assessments measuring similar tiredness-like patient states were demonstrated. These associations were found to be large at Week 12 in Studies JADV and JADX, including the FACIT-F ( $r = -0.60$  in both studies) and SF-36 Vitality ( $r = -0.52$  and  $-0.51$ ). In addition, Severity of Worst Tiredness also demonstrated moderate-to-large associations with measures of other RA symptoms of pain and stiffness at Day 1 that increased at Week 12 in Studies JADV and JADX, respectively, including SF-36 Bodily Pain ( $r = -0.51$  and  $-0.52$ ), Worst Joint Pain ( $r = 0.82$  in both studies), Severity of MJS ( $r = 0.79$  and  $0.77$ ), and patient's assessment of arthritis pain ( $r = 0.69$  and  $0.65$ ).

Discriminant validity was assessed by Pearson correlations at Day 1 and at Week 12 between Severity of Worst Tiredness and PROs measuring distally-related concepts (SF-36 MCS, SF-36 Role Emotional, QIDS-SR16) where small correlations were hypothesized by the applicant. Small-to-moderate correlations were observed between Severity of Worst Tiredness and SF-36

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MCS ( $r = -0.38$  and  $-0.31$ ), and SF-36 Role Emotional ( $r = -0.35$  and  $-0.21$ ) at Day 1, as well as QIDS-SR<sub>16</sub> ( $r = 0.40$  to  $0.37$ ). These associations similarly increased in magnitude at Week 12; however, the association remained weaker than those between Severity of Worst Tiredness and other PROs representing more similar constructs, providing evidence for discriminant validity.

### Known-Groups Validity

In Studies JADV and JADX, known-groups validity of Severity of Worst Tiredness was evaluated using an analysis of variance (ANOVA) model to distinguish mean Severity of Worst Tiredness scores between subgroups defined by the DAS28-ESR thresholds ( $<2.6$ ;  $\geq 2.6$  and  $\leq 3.2$ ;  $>3.2$  and  $\leq 5.1$ ;  $>5.1$ ) measured at Day 1 and Week 4, and CDAI ( $0.0$  to  $\leq 2.8$ ;  $>2.8$  to  $\leq 10$ ;  $>10$  to  $\leq 22$ ; and  $>22$  to  $\leq 76$ ) measured at Day 1 and Week 4. The Scheffé adjustment was used for multiple comparisons. Subgroups were combined in instances of small sample sizes; that is, less than 5% of the total sample size for the subgroup.

**Table 11. Known-groups Validity of Severity of Worst Tiredness Using DAS28-ESR Subgroups at Day 1**

Study	Day 1 DAS28-ESR Category		p-value <sup>a</sup>
	$\leq 5.1$	$> 5.1$	
JADV			
Sample Size	39	496	
Mean (SD) Severity of Worst Tiredness at Day 1	4.7 (2.6)	5.9 (2.1)	0.001
JADX			
Sample Size	36	273	
Mean (SD) Severity of Worst Tiredness at Day 1	5.0 (1.9)	6.2 (2.0)	0.002

Abbreviations: DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count;

ESR = erythrocyte sedimentation rate; SD = standard deviation.

<sup>a</sup> p-value based on a comparison of mean values using ANOVA.

**Table 12. Known-groups Validity of Severity of Worst Tiredness Using DAS28-ESR Subgroups at Week 4**

Study	Week 4 DAS28-ESR Category		p-value <sup>a</sup>
	$\leq 5.1$	$> 5.1$	
JADV			
Sample Size	619	587	
Mean (SD) Severity of Worst Tiredness at Week 4 <sup>b</sup>	3.6 (2.1)	5.3 (1.9)	0.001
JADX			
Sample Size	327	286	
Mean (SD) Severity of Worst Tiredness at Week 4 <sup>b</sup>	3.7 (2.0)	5.5 (2.0)	0.001

Abbreviations: DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count;

ESR = erythrocyte sedimentation rate; SD = standard deviation.

<sup>a</sup> p-value based on a comparison of mean values using ANOVA.

<sup>b</sup> Daily average of seven days preceding visit that contained at least 4 measurements (see Section 15.1.7 for further information).

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**Table 13. Known-groups Validity of Severity of Worst Tiredness Using CDAI Subgroups at Day 1**

Study	Day 1 CDAI Category		p-value <sup>a</sup>
	0.0 to ≤22.0	>22.0 to ≤76.0	
JADV			
Sample Size	36	497	
Mean (SD) Severity of Worst Tiredness at Day 1	4.9 (2.6)	5.9 (2.1)	0.007
JADX			
Sample Size	26	278	
Mean (SD) Severity of Worst Tiredness at Day 1	4.8 (2.1)	6.1 (2.0)	0.002

Abbreviations: CDAI = Clinical Disease Activity Index; SD = standard deviation.

<sup>a</sup> p-value based on a comparison of mean values using ANOVA.

**Table 14. Known-groups Validity of Severity of Worst Tiredness Using CDAI Subgroups at Week 4**

Study	Week 4 CDAI Category			p-value <sup>a</sup>	Comparisons <sup>b</sup>
	0.0 to ≤10.0	>10.0 to ≤22.0	>22.0 to ≤76.0		
JADV					
Sample Size	220	426	567		
Mean (SD) Severity of Worst Tiredness at Week 4 <sup>c</sup>	2.9 (2.0)	4.2 (2.1)	5.1 (2.0)	0.001	a: 0.001 b: 0.001 c: 0.001
JADX					
Sample Size	134	209	275		
Mean (SD) Severity of Worst Tiredness at Week 4 <sup>c</sup>	3.1 (2.0)	4.1 (1.9)	5.6 (2.0)	0.001	a: 0.001 b: 0.001 c: 0.001

Abbreviations: CDAI = Clinical Disease Activity Index; SD = standard deviation.

<sup>a</sup> p-value based on a comparison of mean values using ANOVA.

<sup>b</sup> Note for multiple comparison using Scheffé adjustment: a: 0.0 to ≤10.0 vs. >10.0 to ≤22.0; b: 0.0 to ≤10.0 vs. >22.0 to ≤76.0; c: >10.0 to ≤22.0 vs. >22.0 to ≤76.0.

<sup>c</sup> Daily average of seven days preceding visit that contained at least 4 measurements (see Section 15.1.7 for further information).

### Ability to Detect Change

In Studies JADV and JADX, responsiveness was evaluated using an analysis of covariance (ANCOVA) methodology to assess significant differences in mean change in Severity of Worst Tiredness from Day 1 to Week 12 between ACR20 responders and non-responders at Week 12, controlling for Day 1 Severity of Worst Tiredness. Responsiveness was also assessed using disease activity as measured by DAS28-hsCRP at Week 12, using the following subgroups:

1. DAS28-hsCRP <2.6
2. DAS28-hsCRP ≥2.6 and DAS28-hsCRP ≤3.2
3. DAS28-hsCRP >3.2

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The applicant hypothesized that statistically significant differences in mean change in Severity of Worst Tiredness score would be observed ( $p \leq 0.05$ ) between ACR20 responders versus non-responders, as well as between DAS28-hsCRP groups.

Severity of Worst Tiredness was significantly greater in the ACR 20 responders and lower in the DAS28-hsCRP groups, except for the comparison of DAS28-hsCRP  $< 2.6$  versus  $\geq 2.6$  and  $\leq 3.2$ . These comparisons indicate that patients in a more severe disease state at Week 12 had a significantly smaller improvement in Severity of Worst Tiredness in comparison to patients in a less severe disease state.

**Table 15. Change in Severity of Worst Tiredness from Day 1 to Week 12 Among ACR20 Groups**

Study	ACR20 Responder or Nonresponder at Week 12		p-value
	Responder <sup>a</sup>	Nonresponder <sup>a</sup>	
<b>JADV</b>			
Sample Size	326	211	
Mean (SD) change in Severity of Worst Tiredness	-2.5 (2.5)	-1.0 (2.1)	0.001
Mean (SD) Severity of Worst Tiredness at Week 12 <sup>b</sup>	3.4 (2.1)	4.7 (2.2)	0.001
<b>JADX</b>			
Sample Size	174	137	
Mean (SD) change in Severity of Worst Tiredness	-2.6 (2.6)	-0.9 (2.0)	0.001
Mean (SD) Severity of Worst Tiredness at Week 12 <sup>b</sup>	3.4 (2.1)	5.1 (2.3)	0.001

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; SD = standard deviation.

<sup>a</sup> Responder: Achievement of ACR20 criteria at Week 12; Nonresponder: Failure to achieve ACR20 criteria at Week 12.

<sup>b</sup> Daily average of seven days preceding visit that contained at least 4 measurements (see Section 15.1.7 for further information).

## 6 INTERPRETATION OF SCORES

The applicant used methods that are supportive of meaningful change, however they do not establish meaningful change. We would encourage future work using anchor-based methods to confirm meaningful change. The C-statistic was used to determine the adequacy of a logistic regression model for Severity of Worst Tiredness at Week 12 as a predictor of ACR20 and DAS28-hsCRP, with higher values between 0.5 and 1.0 indicating a better predictive model. Based on this analysis, the Severity of Worst Tiredness PRO had predictive power for predicting ACR20 (0 = non-responder, 1 = responder) and DAS28-hsCRP (0 = moderate/high disease activity, 1 = remission/ LDA), demonstrating a strong association between Severity of Worst Tiredness and both of these endpoints.

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In Studies JADV and JADX, using a ROC curve the optimal cutoff for the Severity of Worst Tiredness is a score of 3 at Week 12, suggesting clinically meaningful change of 3 points. In cognitive debriefing interviews most patients with RA classified 0 to 10 Severity of Worst Tiredness scores in the following manner: a score of 0 indicated no tiredness, 1 to 3 indicated mild tiredness, 4 to 6 indicated moderate tiredness, and 7 or more indicated severe tiredness (when tiredness was at its daily worst).

**Table 22. Interpretation of Week 12 Severity of Worst Tiredness Results: Percentage in Each Clinically Meaningful Category**

	No Tiredness (0)	Mild (1 to 3)	Moderate (4 to 7)	Severe (8 to 10)
Study JADV				
Baricitinib 4 mg	34 (7.1%)	221 (46.1%)	199 (41.5%)	25 (5.2%)
Adalimumab	21 (6.5%)	127 (39.3%)	152 (47.1%)	23 (7.1%)
Placebo	21 (4.4%)	162 (33.8%)	256 (53.4%)	40 (8.4%)
Study JADX				
Baricitinib 2 mg	14 (6.3%)	86 (38.7%)	105 (47.3%)	17 (7.7%)
Baricitinib 4 mg	16 (7.2%)	91 (40.8%)	92 (41.3%)	24 (10.8%)
Placebo	9 (4.1%)	71 (32.1%)	121 (54.8%)	20 (9.0%)

## 7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Translations and cultural adaptations of the Severity of Worst Tiredness item were conducted using methods described in the Principles of Good Practice for Translation and Cultural Adaptation, an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report (Wild et al. 2009). This included two independent forward translations, one harmonized forward translation, a reconciliation of the harmonized translation and source English, a review of the harmonized translation by a survey research expert, a review of the harmonized translation by a clinician reviewer, cognitive debriefing with 5 patients with RA, desktop publishing of the validated translation, and proofreading of the validated translation in each of the languages and countries shown in the table below.

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**Table 23. Languages and Countries Utilizing the Severity of Worst Tiredness Item**

Afrikaans	English	Gujarati	Malayalam	Slovenian
<ul style="list-style-type: none"><li>• South Africa</li></ul>	<ul style="list-style-type: none"><li>• Australia</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>	<ul style="list-style-type: none"><li>• Slovenia</li></ul>
Arabic	<ul style="list-style-type: none"><li>• Canada</li></ul>	Hebrew	Marathi	Spanish
<ul style="list-style-type: none"><li>• Israel</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>	<ul style="list-style-type: none"><li>• Israel</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>	<ul style="list-style-type: none"><li>• Argentina</li></ul>
Bengali	<ul style="list-style-type: none"><li>• South Africa</li></ul>	Hindi	Polish	<ul style="list-style-type: none"><li>• Mexico</li></ul>
<ul style="list-style-type: none"><li>• India</li></ul>	<ul style="list-style-type: none"><li>• United Kingdom</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>	<ul style="list-style-type: none"><li>• Poland</li></ul>	<ul style="list-style-type: none"><li>• Puerto Rico</li></ul>
Chinese	<ul style="list-style-type: none"><li>• United States</li></ul>	Hungarian	Portuguese	<ul style="list-style-type: none"><li>• Spain</li></ul>
<ul style="list-style-type: none"><li>• China</li></ul>	Finnish	<ul style="list-style-type: none"><li>• Hungary</li></ul>	<ul style="list-style-type: none"><li>• Brazil</li></ul>	<ul style="list-style-type: none"><li>• United States</li></ul>
<ul style="list-style-type: none"><li>• Taiwan</li></ul>	<ul style="list-style-type: none"><li>• Finland</li></ul>	Italian	<ul style="list-style-type: none"><li>• Portugal</li></ul>	Swedish
Croatian	French	<ul style="list-style-type: none"><li>• Italy</li></ul>	Punjabi	<ul style="list-style-type: none"><li>• Finland</li></ul>
<ul style="list-style-type: none"><li>• Croatia</li></ul>	<ul style="list-style-type: none"><li>• Belgium</li></ul>	Japanese	<ul style="list-style-type: none"><li>• India</li></ul>	<ul style="list-style-type: none"><li>• Sweden</li></ul>
Czech	<ul style="list-style-type: none"><li>• Canada</li></ul>	<ul style="list-style-type: none"><li>• Japan</li></ul>	Romanian	Tamil
<ul style="list-style-type: none"><li>• Czech Republic</li></ul>	<ul style="list-style-type: none"><li>• France</li></ul>	Kannada	<ul style="list-style-type: none"><li>• Romania</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>
Danish	<ul style="list-style-type: none"><li>• Switzerland</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>	Russian	Telugu
<ul style="list-style-type: none"><li>• Denmark</li></ul>	German	Korean	<ul style="list-style-type: none"><li>• Israel</li></ul>	<ul style="list-style-type: none"><li>• India</li></ul>
Dutch	<ul style="list-style-type: none"><li>• Austria</li></ul>	<ul style="list-style-type: none"><li>• Korea</li></ul>	<ul style="list-style-type: none"><li>• Latvia</li></ul>	Turkish
<ul style="list-style-type: none"><li>• Belgium</li></ul>	<ul style="list-style-type: none"><li>• Belgium</li></ul>	Latvian	<ul style="list-style-type: none"><li>• Lithuania</li></ul>	<ul style="list-style-type: none"><li>• Turkey</li></ul>
<ul style="list-style-type: none"><li>• Netherlands</li></ul>	<ul style="list-style-type: none"><li>• Germany</li></ul>	<ul style="list-style-type: none"><li>• Latvia</li></ul>	<ul style="list-style-type: none"><li>• Russia</li></ul>	Xhosa
	<ul style="list-style-type: none"><li>• Switzerland</li></ul>	Lithuanian	Slovak	<ul style="list-style-type: none"><li>• South Africa</li></ul>
	Greek	<ul style="list-style-type: none"><li>• Lithuania</li></ul>	<ul style="list-style-type: none"><li>• Slovakia</li></ul>	Zulu
	<ul style="list-style-type: none"><li>• Greece</li></ul>			<ul style="list-style-type: none"><li>• South Africa</li></ul>

## 8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

N/A

## 9 REVIEW USER MANUAL

User manuals including instructions for the Diary PRO and electronic data capture device are adequate for capture severity of worst tiredness.

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**D. APPENDIX: WORST TIREDNESS NRS**



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE L CAMPBELL  
01/13/2017

ELEKTRA J PAPADOPOULOS  
01/13/2017

Clinical Review  
Raj Nair  
NDA 207924  
Olumiant (baricitinib)

### CLINICAL REVIEW

<b>Application Type</b>	NDA
<b>Application Number(s)</b>	207924
<b>Priority or Standard</b>	Standard
<b>Submit Date(s)</b>	January 15, 2016
<b>Received Date(s)</b>	January 15, 2016
<b>PDUFA Goal Date</b>	January 15, 2017
<b>Division/Office</b>	Division of Pulmonary, Allergy, and Rheumatology
<b>Reviewer Name(s)</b>	Raj Nair
<b>Review Completion Date</b>	January 9, 2017
<b>Established Name</b>	Baricitinib
<b>(Proposed) Trade Name</b>	Olumiant
<b>Applicant</b>	Eli Lilly and Company
<b>Formulation(s)</b>	Tablets with two dose strengths available: 2 mg and 4 mg
<b>Dosing Regimen</b>	One tablet orally once daily
<b>Applicant Proposed Indication(s)/Population(s)</b>	Rheumatoid arthritis
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response or intolerance to methotrexate

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## Glossary

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AC	advisory committee
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
BARI	baricitinib
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Event
cDMARD	conventional disease modifying anti-rheumatic drug
DMARD	disease modifying anti-rheumatic drug
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HCQ	hydroxychloroquine
Hs-CRP	high sensitivity C-reactive protein
ICH	International Conference on Harmonization

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IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JAK	Janus kinase
LEF	leflunomide
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mTSS	modified total Sharp score
MTX	methotrexate
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAID	nonsteroidal anti-inflammatory drug
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SSZ	sulfasalazine
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TYK	tyrosine kinase

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## 1 Executive Summary

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### 1.1. Product Introduction

Baricitinib (proposed proprietary name Olumiant) is an inhibitor of Janus kinase (Jak) and tyrosine kinase 2 (Tyk 2). Baricitinib is a new molecular entity which will be available in 2 mg and 4 mg tablet oral dosage forms. Another Jak inhibitor, tofacitinib, is approved by the FDA for treatment of rheumatoid arthritis (RA).

The Applicant has proposed baricitinib for the treatment of moderately to severely active RA. The proposed dosing regimen for baricitinib is 4 mg by mouth daily for most patients with some patients able to take 2 mg by mouth daily. All patients with renal impairment are recommended to take the 2 mg daily dose.

Both 2 mg and 4 mg doses of baricitinib provided benefit for the treatment of rheumatoid arthritis. There is ongoing discussion regarding the final recommendation for the dosing regimen.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

To support the efficacy of baricitinib in the treatment of RA patients, Eli Lilly and Company performed 4 independent, phase 3, double-blind, placebo-controlled trials. Two studies, JADX and JADW, evaluated two doses of baricitinib (4 mg daily and 2 mg daily). One study, JADV, studied baricitinib 4 mg daily with an active comparator arm of adalimumab and placebo. One study, JADZ, compared 4 mg of baricitinib monotherapy to methotrexate monotherapy and to combination baricitinib and methotrexate therapy. The primary and key secondary endpoints assessed signs and symptoms (ACR20, DAS28-CRP), physical function, and radiographic progression (mTSS). For a majority of these endpoints baricitinib showed a statistically significant and robust improvement compared to placebo. In conclusion, the data support baricitinib's efficacy towards the treatment of patients with rheumatoid arthritis who are inadequate responders or intolerant of one or more DMARDs. The efficacy results support the efficacy of both 2 mg and 4 mg daily dose of baricitinib for signs and symptoms of RA. There is convincing evidence of efficacy of 4 mg for inhibition of radiographic progression, but uncertainty regarding the 2 mg dose.

### 1.3. 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 there remains unmet need since existing therapies are not effective for all patients with RA and all therapies have potential side effects. Thus, another therapy would be a desirable addition to the therapeutic options for RA.

Baricitinib is an oral, JAK inhibitor. Two doses of baricitinib were studied in two phase 3 trials in patients with RA and additionally, the 4 mg daily dose was studied in two more phase 3 studies with active comparator arms (adalimumab and methotrexate). These trials were adequate and well controlled and provided corroborating evidence of the efficacy of baricitinib for reducing signs and symptoms of RA, based on the proportion of patients experiencing response in American College of Rheumatology (ACR) response criteria. Both of the phase 3 trials using two doses of baricitinib provided corroborating evidence of baricitinib improving physical function, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI). The level of improvement was similar for the 2 mg and 4 mg dose groups. The effect of baricitinib on structural damage progression was assessed by radiographs in two studies, which provided evidence of efficacy on structural damage progression and suggested trends towards more inhibition of radiographic progression with the 4 mg dose as compared to the 2 mg dose.

The safety profile of baricitinib is well characterized within the clinical trials. Based on this profile, the major toxicities of concern are related to significant immunosuppression and are consistent with safety concerns of tofacitinib, which has a similar mechanism of action. Serious infections, including opportunistic infections and tuberculosis, were associated with the use of baricitinib. While no imbalance in malignancy was seen within the trials, treatment with an immunosuppressant may increase the risk of malignancies. Baricitinib treatment was associated with laboratory abnormalities including increases in creatine phosphokinase (CPK), lipid parameters, platelets, and liver function tests and decreases in neutrophils. In general laboratory findings appeared to be dose related. There were elevations in LDL, HDL, and triglycerides on baricitinib but there was no clear evidence of cardiovascular events on baricitinib during the timeframe of the clinical trials. There were few cardiovascular events overall; therefore, there is limited ability to rule out increase in cardiovascular risk based on the currently available data. An additional safety finding was an imbalance in thromboses with multiple pulmonary emboli and deep venous thromboses observed in the baricitinib groups but none in the placebo group. An additional safety concern included gastrointestinal perforations.

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 there is uncertainty with 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
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic symmetric inflammation of joints. It can also cause inflammation outside of the joints in a variety of locations, such as the lungs, heart, and blood vessels.</li> <li>• RA affects 1% of the adult population in the United States (US) and is the most common type of inflammatory arthritis.</li> <li>• RA significantly impacts the lives of patients due to pain and decreased physical function. In addition, patients with RA have higher mortality rates than the general population.</li> <li>• The goal of treatment is early and aggressive use of medications to try to prevent functional impairment and irreversible joint damage.</li> </ul>	<p><b>Rheumatoid arthritis is a serious condition and is the most common type of inflammatory arthritis. Most patients have a chronic progressive disease that is associated with morbidity and increased mortality.</b></p>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>• 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-<math>\alpha</math>) antagonist as add-on or as monotherapy is generally the recommended next line of treatment. However, between 30% and 40% of patients fail to respond or become intolerant to anti-TNF-<math>\alpha</math> therapy. For these patients, additional anti-TNF-<math>\alpha</math> therapies or therapies that target different pathways can</li> </ul>	<p><b>There are multiple current treatment options for patients with RA. However, despite the availability of multiple therapies for RA, there remains unmet medical need for alternative, effective medications.</b></p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>be used.</p> <ul style="list-style-type: none"> <li>• Tofacitinib is approved for the treatment of RA and is also a JAK inhibitor.</li> <li>• There are multiple approved drugs to treat RA, but there remains unmet need since existing therapies are not effective for all patients</li> </ul>	
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>• 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).</li> <li>• 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).</li> <li>• The ACR20 response is calculated as a &gt;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.</li> <li>• 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.</li> <li>• 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.</li> </ul>	<p>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 the study results for the 2 mg dose were inconclusive. 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.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• 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 was inconclusive as to whether baricitinib 2 mg inhibits radiographic progression.</li> <li>• 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.</li> </ul>	
<p><a href="#">Risk</a></p>	<ul style="list-style-type: none"> <li>• A total of 3,464 patients with RA were exposed to baricitinib in RA studies. The drug exposure data are considered adequate.</li> <li>• Major safety concerns:</li> <li>• Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving baricitinib.</li> <li>• Laboratory abnormalities: Baricitinib treatment is associated with neutropenia, lymphopenia, decreases in hemoglobin, and increases in liver enzymes and lipids.</li> <li>• Malignancy: Malignancies were observed in clinical studies with baricitinib.</li> <li>• Gastrointestinal perforations: Events of gastrointestinal perforation have been reported in clinical trials with baricitinib.</li> <li>• Thrombosis: Arterial and venous thromboses were observed in association with baricitinib.</li> </ul>	<p>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.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk Management</u>	<ul style="list-style-type: none"><li>The safety concerns with baricitinib are well-characterized. Healthcare providers are familiar with treatments for RA associated with immunosuppression and lipid elevations.</li></ul>	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 Therapeutic Context

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### 2.1. Analysis of Condition

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.<sup>1,2</sup>

The joints most commonly involved first are the metacarpophalangeal (MCPs), proximal interphalangeal (PIPs), wrist, and metatarsophalangeal (MTPs) joints. The disease onset is usually insidious, with tenderness, warmth, and swelling of many joints. Patients frequently report joint stiffness that is worse in the mornings and after inactivity. Systemic symptoms, such as fatigue, fever, and weight loss can be present. Larger joints generally become symptomatic after small joints. Extra-articular manifestations occur in about 40% of patients with RA.<sup>3</sup> Extra-articular manifestations include rheumatoid nodules, pleurisy, interstitial lung disease, pericarditis, myocarditis, and rheumatoid vasculitis.<sup>4</sup>

RA affects approximately 1% of the adult population in North America and Northern Europe.<sup>5</sup> 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 the exact etiology of RA is unknown, complex interactions between genetic and environmental factors appear to play a role in the development of RA. RA is an autoimmune disease, and certain autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), can precede the clinical manifestations of RA by many years.<sup>6</sup> Cytokines are important contributors in synovial inflammation and proliferation resulting in joint pain and swelling, autoantibody production, bone erosions, joint space narrowing and

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<sup>1</sup> Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.

<sup>2</sup> Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706-14.

<sup>3</sup> Turesson C, et al. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis* 2003;62(8):722-7.

<sup>4</sup> Nyhall-Wahlin BM, et al. High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. *Rheumatology (Oxford)* 2009;48(4):416-20.

<sup>5</sup> Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11(3):229.

<sup>6</sup> Nielen MM, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 2004;50:380-6.

joint destruction. There are multiple cytokines involved, such as interleukin (IL)-1 and IL-6, and tumor necrosis factor (TNF)-alpha.

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. Risk factors for joint damage and disability are rheumatoid factor status and disease activity.<sup>7</sup> One study found that mortality was increased more than two fold in patients with RA as in the general population.<sup>8</sup> Disease activity in RA fluctuates secondary to the disease process itself and therapeutic interventions. Patients with RA can develop radiographic changes, including joint space narrowing and bony erosions. In contrast to clinical symptoms, structural damage is irreversible and cumulative.<sup>9</sup>

The prognosis of RA has improved over the last two decades for a variety of reasons, including changes in drug therapy and approaches to treatment. Specific changes include more aggressive disease management, earlier treatment, and the availability of more therapies, such as targeted biologic agents since the later part of the 1990s. Currently, the course of RA is variable. Approximately 15% of patients have intermittent disease with a relatively good prognosis. However, the majority of patients have progressive disease.

In 2010, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) collaborated to create new classification criteria for RA.<sup>10</sup> The goal of these classification criteria was to facilitate the identification of patients with RA at earlier stages of disease. Recommendations for the treatment of patients with RA have been developed by major professional organizations, including the ACR and EULAR.<sup>11,12,13</sup> Since irreversible structural damage can occur if inflammation persists, early recognition and treatment of RA is key, with a goal of low disease activity or remission.

All patients diagnosed with RA are generally treated with disease-modifying antirheumatic

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<sup>7</sup> Scott DL, et al. Joint damage and disability in rheumatoid arthritis: an updated systematic review. *Clin Exp Rheumatol* 2003;21(5 Suppl 31):S20-7.

<sup>8</sup> Wolfe F, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;37(4):481.

<sup>9</sup> Scott DL. Radiographic progression in established rheumatoid arthritis. *J Rheumatol Suppl* 2004;69:55-65.

<sup>10</sup> Aletaha D, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580-8.

<sup>11</sup> Singh JA, 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 Res (Hoboken)* 2012;64(5):625-39.

<sup>12</sup> Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73(3):492-509.

<sup>13</sup> Singh JA, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016;68(1):1.

drugs (DMARDs). Non-biologic DMARDs, such as methotrexate (MTX), are the first line of therapy for RA.<sup>14</sup> Treatment with a tumor necrosis factor-alpha (TNF- $\alpha$ ) antagonist is generally the next line of treatment for patients with ongoing disease activity. However, between 30% and 40% of patients fail to respond or become intolerant to anti-TNF- $\alpha$  therapy.<sup>15</sup> For patients with ongoing disease activity, the therapeutic strategy usually involves trying another TNF- $\alpha$  antagonist or switching to a medication with a different mechanism of action. Approved alternative therapies include an orally bioavailable Janus kinase (JAK) inhibitor (tofacitinib), and biological DMARDs targeting the B-cell antigen CD-20 (rituximab), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; abatacept), and the pro-inflammatory cytokines IL-1 (anakinra) and IL-6 (tocilizumab).

The goal of treatment is prevention of irreversible joint destruction and functional impairment given the significant impact on patients and public health. RA imposes a substantial economic burden not only on patients but also on family members, employers, and the government. One study estimated a total annual cost of \$19.3 billion and \$39.2 billion (in US 2005 dollars) without and with intangible costs, respectively.<sup>16</sup> Because many RA patients remain inadequately treated or have intolerance to available medications, there remains a continuing unmet medical need for alternative, effective medications for RA.

## 2.2. Analysis of Current Treatment Options

Several therapies have been already approved for the treatment of patients with RA as listed in Table 1 and Table 2. The classes of drugs used for treatment of RA include: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, and disease modifying antirheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful adjunct therapies because of their anti-inflammatory and analgesic effects. Corticosteroids also have anti-inflammatory effects, but their use is limited by long-term toxicity.

DMARDs are therapeutic agents that reduce signs and symptoms of RA and decrease radiographic progression of joint damage. DMARDs are frequently divided into two categories: small molecules and biologics. Methotrexate (MTX) is a small molecule and the most commonly used DMARD because of its well-established safety and efficacy profile. In the

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<sup>14</sup> 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.

<sup>15</sup> Smolen JS, et al. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015;11(5):276-89.

<sup>16</sup> Birnbaum H, et al. Societal cost of rheumatoid arthritis patients in the US. *Curr Med Res Opin* 2010;26(1):77-90.

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treatment of RA, methotrexate is often the initial DMARD used. For patients with ongoing disease activity, other small molecule drugs or biologic DMARDs are frequently added to MTX.

**Table 1. Small Molecule DMARDs Approved for the Treatment of RA in the United States**

Product Name (Trade Name) [Sponsor]	Year of First Approval for RA	Dosing/ Administration	Mechanism of Action in RA
Sulfasalazine (AZULFIDINE) [Pfizer]	1950	Oral	Anti-inflammatory and antimicrobial
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	1988	Oral, SC (autoinjectors)	Anti-metabolite
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	1955	Oral	Interference with antigen processing (?)
Azathioprine (IMURAN) [Prometheus Labs]	1968	Oral	Cytostatic
Penicillamine (CUPRIMINE) [Alton]	1970	Oral	Unknown
Auranofin (RIDAURA) [Prometheus Labs]	1985	Oral	Unknown
Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE) [Novartis]	1995 1990	Oral	T-cell activation inhibitor
Leflunomide (ARAVA) [Sanofi-Aventis]	1998	Oral	Anti-metabolite
Steroids and NSAIDs are approved for the reduction of the signs and symptoms of RA.			

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**Table 2. Biologic DMARDs and JAK Inhibitors Approved for the Treatment of RA in the United States**

Product Name (Trade Name)	Year approved for RA	BLA/NDA (sponsor)	ROA	Description	MOA
Etanercept (ENBREL)	1998	103795 (Immunex/Amgen)	SC	Fusion protein consisting of tumor necrosis factor receptor (TNFR) linked to human IgG1 Fc	TNF inhibitor
Infliximab (REMICADE)	1999	103772 (Centocor)	IV	Chimeric IgG1k mAb	TNF inhibitor
Anakinra (KINERET)	2001	103950 (Amgen)	SC	Recombinant polypeptide	IL-1 receptor antagonist
Adalimumab (HUMIRA)	2002	125057 (Abbott/Abbvie)	SC	Human IgG1k mAb	TNF inhibitor
Abatacept (ORENCIA)	2005 2011	125118 (Bristol-Myers Squibb)	IV SC	Fusion protein consisting of CTLA-4 and human IgG1 Fc	T cell activation inhibitor
Rituximab (RITUXAN)	2006	103705 (Genentech & Biogen Idec)	IV	Chimeric murine/human IgG1k mAb	AntiCD20, B cell depletor
Golimumab (SIMPONI)	2009	125289 (Centocor and Janssen)	SC	Humanized IgG1k mAb	TNF inhibitor
Certolizumab Pegol (CIMZIA)	2009	125160 (UCB Inc)	SC	Humanized Fab fragment	TNF inhibitor
Tocilizumab (ACTEMRA)	2010 2013	125276 125472 (Genentech/Roche)	IV SC	Humanized IgG1k mAb	IL-6 receptor inhibitor
Tofacitinib (XELJANZ)	2012	203214 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Golimumab IV (SIMPONI ARIA)	2013	125433 (Janssen)	IV	Humanized IgG1k mAb	TNF inhibitor
Tofacitinib (XELJANZ XR)	2016	208246 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Infliximab-DYYB (INFLECTRA)	2016	125544 (Celltrion Inc)	IV	Chimeric IgG1k mAb	TNF inhibitor
Etanercept-szszs (ERELZI)	2016	761042 (Sandoz)	SC	Fusion protein consisting of TNFR linked to human IgG1 Fc	TNF inhibitor
Adalimumab-atto (AMJEVITA)	2016	761024 (Amgen)	SC	Human IgG1k mAb	TNF inhibitor

Abbreviations: ROA = Route of administration; MOA= Mechanism of action; TNF=tumor necrosis factor; IL=interleukin; JAK=janus kinase; mAb=monoclonal antibody; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; SC=subcutaneous; IV=intravenous

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Baricitinib is a new molecular entity and is not marketed in the United States.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

May 6, 2008- initial investigational new drug submission

An investigational new drug (IND) application for baricitinib was submitted by the Applicant. After a 30 day safety review, it was determined that the Applicant may proceed with the proposed clinical investigation under IND 102204 on June 5, 2008.

June 26, 2012- End of Phase 2 meeting

An end of phase 2 meeting was held to discuss the phase 3 development program of baricitinib to support a RA indication. Several recommendations were made to the Applicant as follows

- As several doses appeared to be effective in the phase 2 studies, the Applicant was asked to study two doses in their phase 3 program and explore twice daily dosing.
- The Applicant had proposed using linear extrapolation to account for data that was either missing or not recorded due to the design of the study. The Applicant was asked not to impute data using linear extrapolation for radiographic data in their X-ray studies.
- The Applicant was asked to add rescue therapy to study JADZ which was a 52 week study with the primary endpoint measured at week 24 of the study. The Applicant agreed to rescue with baricitinib.

September 23, 2013 - Type C Written Responses only

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.

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July 14, 2014 – initial pediatric study plan submission

The Applicant submitted an initial pediatric study plan (iPSP). There was no agreement with the iPSP due to concerns regarding the timeline of baricitinib development in polyarticular juvenile idiopathic arthritis (pJIA) and as the study needed to be focused on patients with polyarticular juvenile idiopathic arthritis (pJIA) and due to concerns with the proposed patient population to be studied. The Applicant responded with a revised iPSP which the FDA agreed to in December 2014.

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.

January 16, 2015 – Type C Written Responses only

Written responses were sent to the Applicant with concerns that limited conclusions would be available from the extension study JADY regarding durability of effect and step down dosing due to the lack of a control group.

### 3.3. Foreign Regulatory Actions and Marketing History

On December 15, 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medical Association (EMA) adopted a positive position to grant the Applicant the authorization to market baricitinib for the treatment of rheumatoid arthritis. The full indication is "Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Olumiant may be used as monotherapy or in combination with methotrexate".

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

**Table 3** shows the sites that were selected for OSI investigation. Four sites covering three of the four phase 3 trials were selected. All sites enrolled higher numbers of patients as compared to other sites and all sites were located within the United States. In addition, Eli Lilly was inspected.

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**Table 3. Sites identified for Office of Science Investigations Audit**

(Name of investigator, Address)	Site #	Protocol ID	Number of Subjects	Indication
Fleischmann, Roy 8144 Walnut Hill Lane Dallas, TX 75231 USA United States	907	I4V-MC-JADX	8	Randomized, Double-Blind, Placebo-Controlled, Ph3 Study of Baricitinib in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to cDMARDS
Greenwald, Maria 72855 Fred Waring Drive Palm Desert, CA 92260 USA United States	913	I4V-MC-JADV	14	Randomized, Double-Blind, Active-Controlled, Ph3 Study of Baricitinib in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate Therapy
Ludivico, Charles 701 Ostrum St Bethlehem, PA 18015 USA United States	968	I4V-MC-JADW	15	Randomized, Double-Blind, Placebo-Controlled, Ph3 Study of Baricitinib in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to TNFi
Surbeck, William 4619 S Harvard Tulsa, OK 74135 USA United States	958	I4V-MC-JADW	11	Randomized, Double-Blind, Placebo-Controlled, Ph3 Study of Baricitinib in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to TNFi

Source: reviewer generated

In each case, inspection finding support the acceptability of the clinical data submitted.

## 4.2. Product Quality

### Overview

Baricitinib is an inhibitor of Janus kinase.

### Drug Substance

The drug substance is a white to practically white to light pink powder. The molecular formula of the drug substance is  $C_{16}H_{17}N_7O_2S$  and has a molecular weight of 371.42.

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

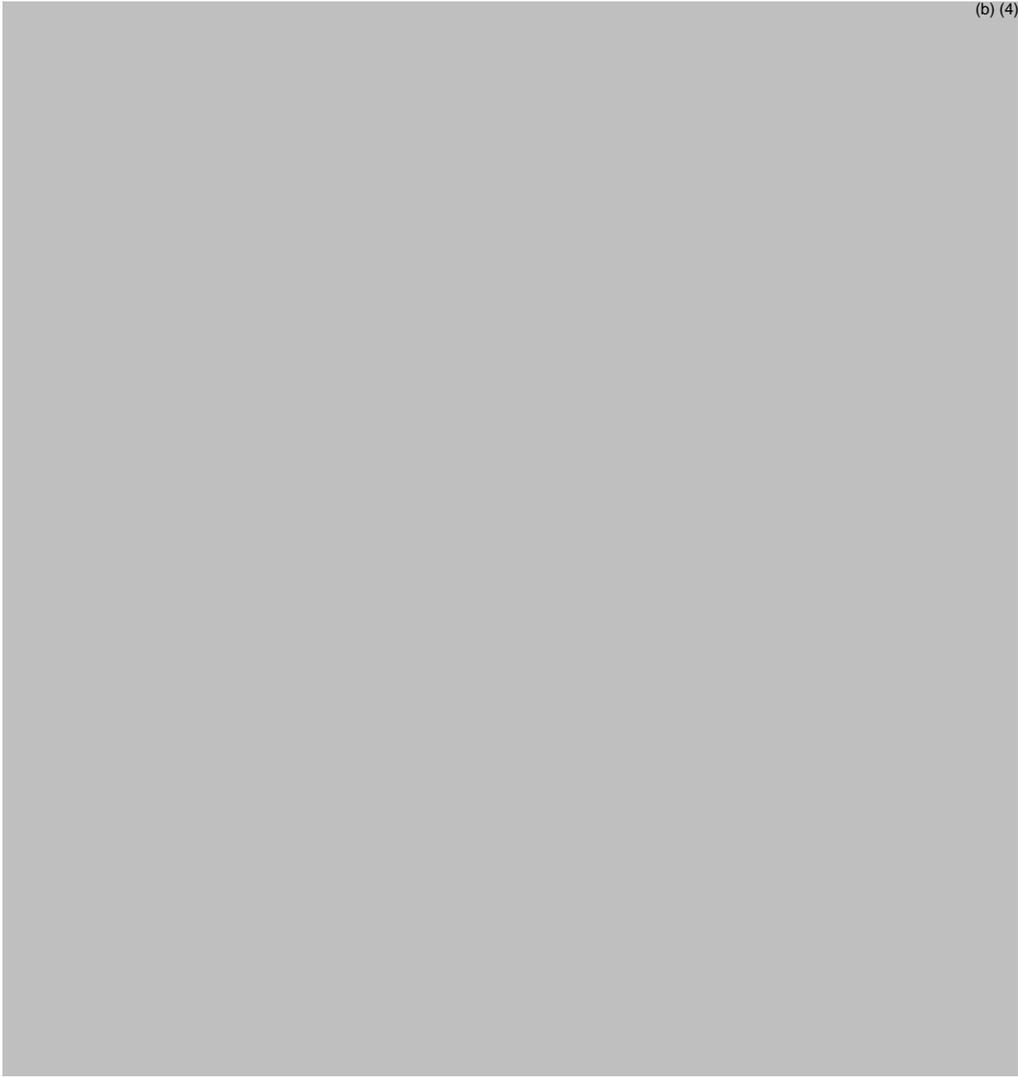
(b) (4)

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Manufacturing consists of [REDACTED] (b) (4)  
[REDACTED]. The manufacturing process of the drug substance is shown in **Figure 1**.

**Figure 1. Baricitinib: manufacturing process for drug substance**

(b) (4)



Source: Applicant's 2.3.S Drug Substance Summary, p. 3

**Drug product**

Baricitinib is available in oblong (2 mg) and round (4 mg), debossed, film-coated, immediate-release tablets. **Table 4** shows the composition of the baricitinib tablets proposed for commercial use. The tablets can be differentiated by shape and by color [REDACTED] (b) (4)



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**Table 4. Composition of baricitinib tablets for commercial use**

Ingredient	Function
<b>Active ingredient</b>	
Baricitinib	Active ingredient
(b) (4)	(b) (4)
Mannitol1, USP-NF, Ph.Eur. D-Mannitol, JP Microcrystalline Cellulose, USP-NF, JP Cellulose, Microcrystalline, Ph.Eur. Croscarmellose Sodium, USP-NF, Ph.Eur., JP Magnesium Stearate, USP-NF, Ph.Eur., JP	
(b) (4)	
<b>Other ingredient- film coating</b>	
(b) (4)	

Source: adapted from Applicant 2.3.P Drug Product Summary

*Reviewer’s comment: The 2 mg and 4 mg tablets are similar in shape and color. There was concern that the tablets may not be differentiated enough in order to distinguish the two strengths from each other; however, for the indication of rheumatoid arthritis, the two dosage forms would not to be prescribed simultaneously to achieve a certain dose so the chance of over or under dosage is small.*

### 4.3. Clinical Microbiology

Clinical microbiology is not applicable for baricitinib.

### 4.4. Nonclinical Pharmacology/Toxicology

General nonclinical pharmacology/toxicology considerations

The non-clinical strategy employed by the Applicant was intended to support the chronic oral administration of baricitinib. The nonclinical species used for pharmacodynamics assessment was the mouse and rat and the nonclinical species used for safety assessment was rat and dog.

Immunosuppression was seen in the 28 day and 6 month rat studies conducted with baricitinib. 7 unscheduled deaths occurred at the high dose (100 mg/kg) in the 6 month rat studies. In 6 of the rats, subacute and chronic inflammation in the myocardium was noted and in the seventh rat, inflammation and necrosis was noted within the liver.

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In the 4 week dog studies, there were findings consistent with immunosuppression including mild hypocellularity in the bone marrow. In the 6 month and 9 month dog studies, there were findings of dermatitis associated with demodicosis resulting in several dogs requiring discontinuation from therapy and euthanization. There were findings of lymphocyte depletion and demodectic mites within the affected animals. In the 9 month dog study, additional findings of liver toxicity were seen in the higher dosed animals (3 mg/kg and 9/6 mg/kg).

#### Carcinogenicity

Baricitinib was not genotoxic in the bacterial mutagenic assay, the in vitro chromosome aberration assay, or the in vivo micronucleus assay in rats. Rat and mouse carcinogenicity studies did not produce neoplasms at any of the administered doses.

#### Reproductive toxicology

In combined male and fertility studies, decreased fertility occurred at the highest doses (50 mg/kg in males; 100 mg/kg in females). No effects on sperm motility, concentration, or sperm morphology were seen.

In embryo-fetal studies, skeletal malformations (bent limbs and rib abnormalities) and other skeletal development variations occurred in rat and rabbit fetuses. Rat pre-and postnatal studies showed similar malformations on the pups as well as lower birth weights and lower postnatal survival. No maternal toxicity was observed.

### 4.5. Clinical Pharmacology

#### 4.5.1. Mechanism of Action

Per the Applicant, baricitinib is an orally administered, selective Janus kinase (JAK) inhibitor intended for treatment of patients with moderate to severely active rheumatoid arthritis.

JAK are 4 protein tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) that are involved in cytokine signal transduction. Baricitinib inhibits JAK1 and JAK2 with lower selectivity for JAK3 and TYK2. This inhibition profile is thought to target multiple RA-associated cytokine pathways and reduce inflammation, cellular activation, and proliferation of immune cells associated with RA pathogenesis.

#### 4.5.2. Pharmacodynamics

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 and Figure 2, which demonstrate a dose-response for efficacy. In 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 C<sub>avg,ss</sub> 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 5. 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 <sup>1</sup>	7 mg <sup>1</sup>	10 mg <sup>1</sup>	
			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 <sup>2</sup>	2 mg <sup>2</sup>	4 mg <sup>2</sup>	8 mg <sup>2</sup>
			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 <sup>2</sup>	2 mg <sup>2</sup>	4 mg <sup>2</sup>	8 mg <sup>2</sup>
			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

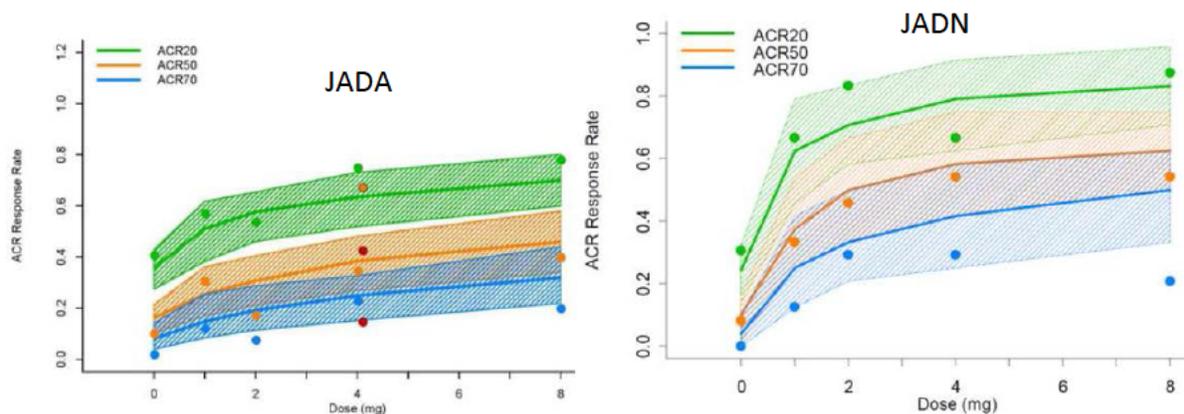
<sup>1</sup> as primary objective

<sup>2</sup> 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 2: 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

### 4.5.3. Pharmacokinetics

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

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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  $AUC_{0-inf}$  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  $AUC_{0-inf}$  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, its use is not recommended in this setting.

In a dedicated drug-interaction study, concomitant probenecid (a strong OAT3 inhibitor) increased  $AUC_{0-inf}$  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.

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 CL<sub>r</sub>/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, and bilirubin), race, and duration of RA were evaluated in the model and not identified as significant covariates.

#### **4.6. Devices and Companion Diagnostic Issues**

Not applicable.

#### **4.7. Consumer Study Reviews**

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Not applicable.

## **5 Sources of Clinical Data and Review Strategy**

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### **5.1. Table of Clinical Studies**

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**Table 6. Baricitinib RA studies: phase 2, phase 3, and extension study**

<b>Trial Identity</b>	<b>Trial Design</b>	<b>Regimen/ schedule/ route</b>	<b>Study Endpoints</b>	<b>Treatment Duration/ Follow Up</b>	<b>No. of patients enrolled</b>	<b>Study Population</b>	<b>No. of Centers and Countries</b>
<b><i>Controlled Studies to Support Efficacy and Safety</i></b>							
JADV Oct 2012- Sept 2015	Phase 3, 24 weeks placebo controlled and 52 weeks active controlled study	Placebo, adalimumab every 2 weeks, BARI 4 mg qday	Week 12: ACR20	52 weeks	1305	RA patients with history of methotrexate and conventional DMARD use	281 study sites in 26 countries
JADX Jan 2013- Dec 2014	Phase 3, 24 weeks placebo controlled study	Placebo, BARI 2 mg qday, BARI 4 mg qday	Week 12: ACR20	24 weeks	684	RA patients with history of methotrexate and conventional DMARD use	182 study sites in 22 countries
JADW Jan 2013- Sept 2014	Phase 3, 24 week placebo controlled study	Placebo, BARI 2 mg qday, BARI 4 mg qday	Week 12: ACR20	24 weeks	527	RA patients with history of TNF inhibitor use	140 sites in 20 countries
JADZ Jan 2013- Aug 2015	Phase 3, 52 week active controlled study	MTX, BARI 4 mg, BARI 4 mg+MTX	Week 24: ACR20	52 weeks	584	RA patients who were naïve to treatment for RA	198 study sites in 18 countries
<b><i>Studies to Support Safety</i></b>							
JADC May 2009- Jul 2010	Phase 2, 24 week, placebo controlled study	Placebo, BARI 4 mg qday, BARI 7 mg qday, BARI 10 mg qday	Week 12: ACR20	24 weeks	125	RA patients with history of conventional DMARD and biologic use	41 study sites in 2 countries
JADA	Phase 2, 128 week, parallel	Placebo, BARI	Week 12:	128 weeks	301	RA patients with	69 study sites

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Nov 2010- Mar 2014	group study	1 mg qday, BARI 2 mg qday, BARI 4 mg qday, BARI 8 mg qday, BARI 2 mg BID	ACR20			history of methotrexate use	in 9 countries
JADN Nov 2011- Dec 2011	Phase 2, 64 week, dose ranging study	Placebo, BARI 1 mg qday, BARI 2 mg qday, BARI 4 mg qday, BARI 8 mg qday	Week 12: ACR20	64 weeks	145	RA patients with history of methotrexate use	25 study sites in 1 country (Japan)
JADY June 2013- current	Extension study that included studies JADZ, JADV, JADX, JADW, and JADA	4 mg, 2 mg baricitinib	NA	ongoing	2539 at data cutoff	Study populations from JADZ, JADV, JADX, JADW, and JADA	398 study sites

Abbreviations: BARI=baricitinib, ACR20=20% improvement in American College of Rheumatology Criteria RA=rheumatoid arthritis, DMARD=disease modifying anti-rheumatic drug, TNF=tumor necrosis factor, MTX=methotrexate  
Source: reviewer generated

## 5.2. Review Strategy

For the review of efficacy, the four phase 3 studies for baricitinib were separately reviewed for evidence of efficacy. Each of the phase 3 studies enrolled different study populations and had differences in study design. Two of the studies had an active comparator arm. JADZ had a treatment arm of baricitinib 4 mg daily that was compared to optimized methotrexate as an active comparator and the combination of optimized methotrexate and baricitinib 4 mg daily. Study JADV compared baricitinib 4 mg daily with placebo and adalimumab 40 mg every other week. Two studies (JADW and JADX) included two treatment arms with baricitinib. Each study had a 2 mg daily dose of baricitinib treatment arm and 4 mg daily dose of baricitinib treatment arm.

As only two of the phase 3 studies included a 2 mg baricitinib treatment arm and all 4 phase studies included a 4 mg baricitinib treatment arm, the exposure with the 2 mg dose of baricitinib was less than the 4 mg dose arm. Studies that included the 2 mg daily dose arm were limited to 24 weeks while the other phase 3 studies were 52 weeks in length. Radiographic data for the 2 mg dose of baricitinib was only available in one study (JADX). In the studies JADX and JADW, patients were rescued or switched to 4 mg daily baricitinib if they were not doing well on placebo or the 2 mg dose of baricitinib; however, if a patient was not doing well in the 4 mg daily dose group, the patient was maintained on a 4 mg daily dose of baricitinib.

For the safety analyses, the phase 2, phase 3, and extension studies were reviewed together with the exception of JADZ which did not have a placebo arm in the study for comparison. For common adverse events at early time points, pre-rescue/pre-switch data was used. For rare adverse events, longer term endpoints were used and additional considerations were necessary to account for switches in therapy due to planned changes in therapy per protocol. The safety analyses had the same limitations as the efficacy analyses in that the number of patients and duration of exposure to 2 mg daily of baricitinib was much smaller than the exposure to 4 mg daily of baricitinib in the pooled phase 2 and phase 3 studies.

Brief summaries of the phase 2 and extension studies used for the safety analysis follow:

### JADA

Title of study: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Parallel-Group, Phase 2b Study of LY3009104 in Patients with Active Rheumatoid Arthritis on Background Methotrexate Therapy

Objective: To evaluate the efficacy of baricitinib as assessed by the aggregate proportion of patients in the 4-mg and 8-mg treatment groups who achieved an ACR20 response compared

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with PBO over 12 weeks in patients with active RA despite ongoing MTX therapy. The efficacy, safety, and PK, of baricitinib over 12, 24, and 52 weeks were also evaluated

Participating Countries: Croatia, Czech Republic, Hungary, India, Mexico, Poland, Romania, Ukraine, United States

Design: Phase 2b, multicenter, randomized, double-blind, parallel-group, multiple-dose, outpatient study in 4 parts:

- Part A: double-blind, PBO-controlled, randomized evaluation of baricitinib or PBO QD for 12 weeks
- Part B: double-blind, randomized evaluation of baricitinib BID or QD for 12 additional weeks
- Part C: optional, open-label extension period to evaluate of baricitinib QD for 52 weeks
- Part D: optional, open-label extension period to evaluate of baricitinib QD for 52 weeks

Enrollment Criteria: Men or women, aged 18 to 75 years, inclusive, with adult-onset, active RA; ACR functional class I, II, or III; a CRP value  $>1.2 \times \text{ULN}$  or ESR  $>\text{ULN}$ ; and prior, regular use of MTX for at least 12 weeks

Treatment: up to 128 weeks duration

- Part A: baricitinib doses of 1-, 2-, 4-, or 8-mg or PBO taken po QD
- Part B: baricitinib doses of 2-mg BID or 2-, 4-, or 8-mg QD taken po
- Part C: baricitinib doses of 4- or 8-mg taken po QD
- Part D: baricitinib doses of 4-mg taken po QD

Number of patients enrolled

- Part A: 301
- Part B: 276
- Part C: 201
- Part D: 144

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**Summary:**

The primary efficacy analysis, comparison of ACR20 response rates adjusted for baseline DAS-hsCRP in the combined 4 mg and 8 mg dose groups compared to placebo at Week 12, found a statistically significantly higher response rate in the combined 4 mg and 8 mg baricitinib groups ( $p < .001$ ), with the placebo group achieving a 41% ACR20 response rate and the combined baricitinib group achieving a 76% response rate.

Key secondary analyses also revealed statistically significant improvements relative to placebo and are shown in Table 7.

**Table 7. JADA: Summary of key secondary endpoints**

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Endpoint	Treatment Groups					
	Placebo	Baricitinib				
		1 mg	2 mg	4 mg	8 mg	4 mg and 8 mg Combined
<b>Week 4</b>						
ACR20 n (%) p-Value <sup>a</sup>	N=98 24 (24%)	N=49 21 (43%)	N=52 19 (37%)	N=52 31 (60%)	N=50 27 (54%)	N=102 58 (57%)
ACR50 n (%) p-Value <sup>a</sup>	N=98 3 (3%)	N=49 5 (10%)	N=52 5 (10%)	N=52 15 (29%)	N=50 11 (22%)	N=102 26 (25%)
ACR70 n (%) p-Value <sup>a</sup>	N=98 0	N=49 1 (2%)	N=52 2 (4%)	N=52 5 (10%)	N=50 3 (6%)	N=102 8 (8%)
ACR-N Mean p-Value <sup>b</sup>	N=93 -7.1	N=47 10.5	N=51 11.6	N=51 28.8	N=50 22.5	N=101 25.7
CDAI ≤2.8 n (%) p-Value <sup>c</sup>	N=94 0 (0%)	N=47 1 (2%)	N=51 3 (6%)	N=51 4 (8%)	N=50 3 (6%)	—
<b>Week 12</b>						
ACR20 n (%) p-Value <sup>a</sup>	N=98 40 (41%)	N=49 28 (57%)	N=52 28 (54%)	N=52 39 (75%)	N=50 39 (78%)	N=102 78 (76%)
ACR50 n (%) p-Value <sup>a</sup>	N=98 10 (10%)	N=49 15 (31%)	N=52 9 (17%)	N=52 18 (35%)	N=50 20 (40%)	N=102 38 (37%)
ACR70 n (%) p-Value <sup>a</sup>	N=98 2 (2%)	N=49 6 (12%)	N=52 4 (8%)	N=52 12 (23%)	N=50 10 (20%)	N=102 22 (22%)
ACR-N Mean p-Value <sup>b</sup>	N=85 3.6	N=44 25.6	N=51 16.0	N=50 34.2	N=49 31.9	N=99 33.0
CDAI ≤2.8 n (%) p-Value <sup>c</sup>	N=98 1 (1%)	N=49 1 (2%)	N=52 3 (6%)	N=51 11 (21%)	N=50 6 (12%)	—
<b>Week 24</b>						
ACR20 n (%)	—	—	N=52 32 (62%)	52 39 (75%)	50 36 (72%)	N=102 75 (74%)
ACR50 n (%)	—	—	N=52 10 (19%)	N=52 24 (46%)	N=50 27 (54%)	N=102 51 (50%)
ACR70 n (%)	—	—	N=52 5 (10%)	N=52 14 (27%)	N=50 12 (24%)	N=102 26 (25%)
ACR-N Mean	—	—	N=50 20.8	N=48 45.1	N=45 48.8	N=93 46.9
CDAI ≤2.8 n (%)	—	—	N=50 4 (8%)	N=48 12 (23%)	N=44 11 (22%)	—

Note: NRI was used for ACR20 and ACR50 values, no imputation was used for ACR-N values, and LOCF was used for CDAI values.

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; ACR50 = 50% improvement in American College of Rheumatology criteria; ACR-N = numeric American College of Rheumatology; ANOVA = analysis of variance; CDAI = Clinical Disease Activity Index; LOCF = last observation carried forward; NRI = nonresponder imputation.

a One-sided Fisher's exact test comparison of the superiority of the baricitinib dose level versus placebo for the 2 levels of response (yes vs no) using nonresponder imputation.

b One-sided ANOVA with treatment as the fixed factor for comparison of the superiority of the baricitinib dose level versus placebo; no imputation.

c Chi-square test.

Source: JADA study synopsis, p. 10

The most commonly reported TEAEs during Weeks 0 to 12 were in the infections and infestations system organ class (SOC), with comparable incidences reported in the placebo group (13% of patients) and in the combined baricitinib groups (15% of patients; range: 10% to 21%). Infections and infestations continued to be the most frequently reported events through

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Week 24 for patients randomized to baricitinib at baseline (range: 25% to 28%), with upper respiratory tract infections being the most frequently reported type of infection.

In Study Parts C and D, the most commonly reported TEAEs were also in the infections and infestations SOC, with comparable incidences reported in the 4/4 mg, 4:8/4 mg, and 8/4 mg treatment groups. Respiratory tract infections were the most frequently reported type of infection. The most frequent TEAEs ( $\geq 2.5\%$  of all patients) listed in Study Part C were urinary tract infection, bronchitis, upper respiratory tract infection, herpes zoster infection, nasopharyngitis, influenza, blood creatine phosphokinase increased, cough, and pharyngitis.

The most frequent TEAEs ( $\geq 2.5\%$  of all patients) listed in Study Part D were nasopharyngitis, bronchitis, alanine aminotransferase (ALT) increase, blood cholesterol increased, dyslipidemia, and urinary tract infection. With the exception of an increase in herpes zoster infections in Study Part C, there were no qualitative differences observed in the incidence rate of TEAEs in the open-label extension portion of the study (Parts C and D) compared to the randomized segment of the trial (Parts A and B).

#### JADC

Objective: To assess the safety, tolerability, efficacy, PK, and PD of baricitinib in patients with RA who had had an inadequate response to any DMARD therapy

Participating countries: Czech Republic, United States

Design: Phase 2a, multicenter, randomized, double-blind, PBO-controlled, dose-ranging, parallel-group study with 5 treatment regimens

Enrollment criteria: Men or women of legal age of consent with a diagnosis of active RA, whose RA was

Inadequately controlled with at least 1 DMARD treatment

Treatment: up to 24 weeks duration

- A: 4-mg baricitinib
- B: 7-mg baricitinib
- C: 10-mg baricitinib
- D: PBO crossing over to 7-mg baricitinib
- E: PBO crossing over to 10-mg baricitinib

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Number of patients enrolled: 127

Summary:

Evidence of efficacy by ACR was seen as early as the first assessment at 2 weeks. The primary efficacy endpoint was the percent of subjects achieving ACR20 improvement at 12 weeks: 52%, 59%, and 53% for the 4 mg, 7 mg and 10 mg groups, respectively, and 32% for placebo. ACR50 responses were 35%, 31% and 30%, respectively, and 13% for placebo. ACR70 responses were 16%, 9%, and 10%, respectively, and 3% for placebo. The result for the primary efficacy analysis, i.e., the Cochran-Armitage trend test for ACR20 responses at Week 12, was not statistically significant ( $p=0.0619$ ).

During the placebo controlled period, the proportions of subjects with at least 1 TEAE increased with increasing dose of baricitinib: 48.4% in the 4 mg group, 62.5% in the 7 mg group, and 74.2% in the 10 mg group, compared with 61.6% in the placebo group. The most frequently reported AEs during the placebo controlled period were headache, upper respiratory tract infection and diarrhea. The frequency of these AEs was similar between active treatment groups and placebo.

A dose-response relationship was noted in anemia. Mean changes (g/L) from baseline in Hgb between Weeks 0 to 12 were -2.4, -4.9, and -11.1 in the 4 mg, 7 mg, and 10 mg groups, respectively, compared with 0 in the placebo group. Anemia (or decreased Hgb) was reported as a TEAE in 1 (3.2%) 10 mg group subject during Weeks 0-12, and in 1 (3.3%) 7 mg subject and 3 (11.1%) 10 mg subjects between Weeks 12 to 24.

Two subjects had at least 1 SAE. One subject (7 mg group) had SAEs of erosive esophagitis, thrombophlebitis, and Mallory-Weiss syndrome. This subject had a prior history of GI bleeds, having had 2 previous gastrointestinal surgeries for that condition, and requiring 2 PPIs and an H2 blocker concomitantly to manage that condition. One subject (10 mg crossover group) had an SAE of right cerebrovascular accident between Weeks 24 and 28. Nine subjects permanently discontinued study medication due to AEs: 2 subjects due to RA, 2 due to hematological toxicity (anemia or decreased Hgb), 2 due to herpes zoster (during the first 12 weeks), 1 due to mouth ulceration, 1 due to subcutaneous abscess, and 1 due to nausea. Five additional subjects developed uncomplicated herpes zoster: 1 subject during the placebo-controlled phase, 3 subjects during the uncontrolled phase, and 1 subject after Week 24. During weeks 0-12, mean increases from baseline were seen in both HDL-C and LDL-C.

JADN

Objective: To evaluate the efficacy, dose-response, PK, safety, and PD of baricitinib in Japanese patients with active RA

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Participating countries: Japan

Design: Phase 2b, outpatient, randomized, PBO-controlled, dose-ranging, and parallel-group study of baricitinib in Japanese patients with active RA, who were on background MTX therapy in 2 treatment periods (Part A, a 12-week double-blind period, and Part B, a 52-week single-blind period)

Enrollment criteria: Ambulatory men or women aged 20 to 75 years, inclusive, with active, adult-onset RA, who had been on background MTX therapy at least 12 weeks

Treatment: up to 64 weeks duration

- Part A: 1-, 2-, 4-, or 8-mg/day baricitinib or PBO
- Part B: 4- or 8-mg/day baricitinib

Number of patients enrolled: 145

Summary:

The primary efficacy analysis of comparing ACR20 response rates between the combined baricitinib 4-mg and 8-mg groups and the placebo group at Week 12 was statistically significantly different ( $p < 0.001$ ), with a higher response rate in the combined 4- and 8-mg groups (77%) than in the placebo group (31%). Results are shown in **Table 8**.

**Table 8. JADN: Efficacy response parameters at week 12**

Efficacy Response Parameter	Baricitinib Treatment Groups				
	Placebo (N=49)	1 mg (N=24)	2 mg (N=24)	4 mg (N=24)	8 mg (N=24)
% ACR20 <sup>a</sup>	31	67 <sup>c</sup>	83 <sup>c</sup>	67 <sup>c</sup>	88 <sup>c</sup>
% ACR50 <sup>a</sup>	8	33 <sup>c</sup>	46 <sup>c</sup>	54 <sup>c</sup>	54 <sup>c</sup>
% DAS28-CRP remission (<2.6) <sup>b</sup>	22	33	33	42	50 <sup>c</sup>
% SDAI remission (≤3.3) <sup>b</sup>	8	4	29 <sup>c</sup>	17	17
% HAQ-DI MCID (change ≤ -0.22) <sup>b</sup>	29	54 <sup>c</sup>	58 <sup>c</sup>	75 <sup>c</sup>	71 <sup>c</sup>

Abbreviations: ACR20/50 = American College of Rheumatology 20/50 responder index; DAS28-CRP = Disease Activity Score 28 using C reactive protein; HAQ-DI = Health Assessment Questionnaire - Disability Index; MCID = minimum clinical important difference; SDAI = Simplified Disease Activity Index.

<sup>a</sup> Nonresponder imputation.  
<sup>b</sup> Last observation.  
<sup>c</sup> p<0.05 vs. placebo (1-sided Fisher exact test).

Source: JADN synopsis, p. 7

The most commonly reported TEAEs, the infections and infestations system organ class, were similar across all the groups, including placebo. The higher TEAE incidence in the 8-mg group was mostly due to higher rates of abnormal laboratory parameters in that group. In Part B, there were no deaths, and the incidence of SAEs and drug discontinuation due to AEs were 14% and 19%, respectively. There were several cases of herpes zoster, pneumocystis jirovecii pneumonia, and 2 cases of malignancies occurred.

JADY (ongoing, data as of August 10, 2015)

Objective: To evaluate the long-term safety and tolerability of baricitinib in patients who have completed a previous baricitinib RA study.

Participating countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States

Design: Phase 3, multicenter, long-term extension study evaluating the safety and efficacy of baricitinib in patients with RA for up to 48 months. Patients could continue to receive the background non-investigational, open-label cDMARD they were receiving at completion of the originating study.

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Enrollment criteria: Patients had completed another Phase 2 or 3 trial of baricitinib. Patients from future baricitinib RA studies may also be enrolled into Study JADY

Treatment: up to 48 months duration  
Number of patients enrolled: 2539

Summary: See section 8 for review of safety from this study.

## **6 Review of Relevant Individual Trials Used to Support Efficacy**

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### **6.1. JADX**

#### **6.1.1. Study Design**

##### **Overview and Objective**

JADX was a phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled study comparing the efficacy of 4 mg and 2 mg daily doses of baricitinib versus placebo. Patient enrollment was approximately 660 patients who had insufficient response to conventional DMARD (including methotrexate) and had moderate to severely active rheumatoid arthritis. Patients were allowed to stay on conventional DMARD while participating in the study.

The primary objective of the study was to determine whether baricitinib 4 mg once daily was superior to placebo in the treatment of patients with moderately to severely active rheumatoid arthritis who had inadequate response to at least one conventional DMARD. Secondary outcomes included patient reported outcome measures and relative efficacy of 2 mg daily baricitinib versus placebo.

##### **Trial Design**

Basic study design

Study JADX consisted of three parts:

- Screening period: 3 to 42 days
- Part A: double blind placebo controlled period lasting 24 weeks. At week 0, patients were randomly assigned to treatment. Patients remained on stable background conventional DMARDs, NSAIDs, analgesics, and/or corticosteroids. Patients who did not adequately respond to investigational product were eligible for rescue therapy at week 16. Primary endpoint was evaluated at week 12.

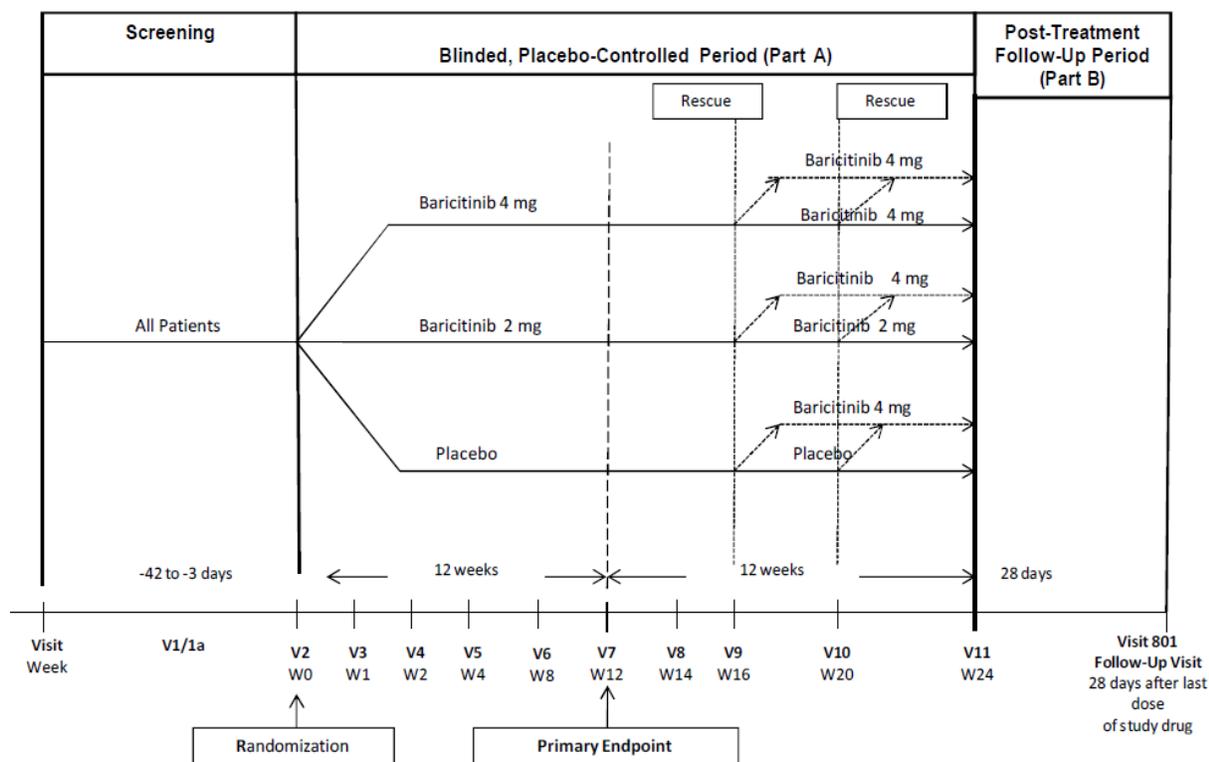
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- Part B: there was post-treatment follow-up period 28 days after last dose. Patients who completed week 24 of JADX were eligible to enter the extension study, JADY.

**Figure 3. JADX study design**



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

Source: JADX study report, p. 85

**Choice of control groups:** In study JADX, the Applicant chose placebo as the control group. In addition to the placebo group, 2 doses of baricitinib (2 mg daily and 4 mg daily) were studied in JADX.

**Diagnostic criteria:** The patient population for JADX consisted of patients with moderately to severely active rheumatoid arthritis who were intolerant or had an inadequate response to conventional DMARDs. Patients were diagnosed with RA based on ACR/EULAR 2010 Criteria for Classification of RA.

**Key Inclusion criteria:**

- Adults diagnosed with adult onset RA defined by ACR/EULAR 2010 Criteria for Classification of Rheumatoid Arthritis

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- Had at least 6 tender and 6 swollen joints
- Had an hsCRP measurement  $\geq 1.2$  times the upper limit of normal
- Had insufficient response to a conventional DMARD

### Key Exclusion Criteria

- Use of any per protocol prohibited RA therapies
- Recent history of infection, positive testing for tuberculosis or other serious infection
- Immunocompromised
- Specific abnormal laboratory testing as defined by protocol
- Comorbidities that put patient at risk when taking investigational product

### Dose selection

Dose selection was based on efficacy, safety, and PK data from the phase 2 studies. The Applicant observed a flat efficacy response at doses higher than 4 mg daily. The Applicant also observed lower rates of improvement in measures such as ACR50, ACR70, low disease activity, and remission rates in patients receiving doses lower than 4 mg daily.

The Applicant decided to study 2 mg daily for patients with renal impairment and to better define the lower end of the dose-response curve.

The following concomitant medications were allowed:

- The following conventional DMARDs at stable doses 8 weeks prior to study entry were allowed: hydroxychloroquine, sulfasalazine, leflunomide, methotrexate, or azathioprine. Dose was to remain stable throughout the study period.
- Concomitant NSAIDs were allowed 2 weeks prior to study entry and for at least 6 weeks prior to randomization. After rescue, change in NSAID dose or switching to another NSAID was allowed
- Analgesics were allowed at a stable dose until a patient received rescue therapy at which time analgesic medications could be increased or switched to a different analgesic
- Prednisone at 10 mg per day were allowed in the study but needed to remain stable 6 weeks prior to randomization.

The following concomitant medications were prohibited after randomization:

- Live vaccines, including herpes zoster vaccination
- Any biologic therapy for any indication
- Any interferon therapy

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- Any parenteral corticosteroid administration administered intramuscular or intravenous
- Any DMARD other than stable background DMARDs used at time of study entry

Study treatments:

Treatment group	Initial treatment administered	Rescue treatment administered
Baricitinib 2 mg	<ul style="list-style-type: none"> <li>• Baricitinib 2 mg daily tablet</li> <li>• Baricitinib 4 mg daily placebo tablet</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> <li>• Baricitinib 2 mg daily placebo tablet</li> </ul>
Baricitinib 4 mg	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> <li>• Baricitinib 2 mg daily placebo tablet</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> <li>• Baricitinib 2 mg daily placebo tablet</li> </ul>
Placebo	<ul style="list-style-type: none"> <li>• Baricitinib 2 mg daily placebo tablet</li> <li>• Baricitinib 4 mg daily placebo tablet</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> <li>• Baricitinib 2 mg daily placebo tablet</li> </ul>

Source: adapted from JADX study report, p. 87

Assignment to treatment

Patients meeting all entry criteria were randomized in a 1:1:1 ratio (baricitinib 4 mg: baricitinib 2 mg: placebo) to double-blind treatment at week 0. Randomization was stratified by region and baseline joint erosion status. Any patient with renal impairment defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m<sup>2</sup> was provided 2 mg of baricitinib if receiving baricitinib. Assignment to treatment groups were determined by computer-generated random sequence using an interactive voice response system.

Blinding

JADX was a double-blind study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. Unblinding did not occur until the reporting database was validated and locked for final statistical analysis.

Dose modification

Study drug was discontinued for significant abnormalities in liver function tests; white blood cell, lymphocyte, and neutrophil counts; and hemoglobin levels. Study drug was also discontinued if the patient developed symptomatic herpes zoster or a serious infection that, in the opinion of the investigator, warranted discontinuation. Patients receiving baricitinib in JADZ with eGFR of >40 mL/min/1.73 m<sup>2</sup> and <60 mL/min/1.73 m<sup>2</sup> were given a dose of 2 mg daily.

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An overview of the criteria for permanent discontinuation is in Table 9. These apply to the 4 phase 3 studies.

**Table 9: Criteria for Permanent Discontinuation of Investigational Product in Phase 3 studies (JADZ, JADV, JADW, and JADX)**

<b>Permanently discontinue if any of the following are observed:</b>
ALT or AST >8x ULN
ALT or AST >5x ULN persisting for more than 2 weeks after temporary interruption of investigational product
ALT or AST >3x ULN and total bilirubin level >2x ULN
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
WBC count <1000 cells/ $\mu$ L
ANC <500 cells/ $\mu$ L
Lymphocyte count <200 cells/ $\mu$ L
Hemoglobin <6.5 g/dL
Symptomatic herpes zoster
Pregnancy
Malignancy
Patient develops a severe infection that, in the opinion of the investigator, merits the investigational product being discontinued

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; HBV DNA = hepatitis B virus deoxyribonucleic acid; ULN = upper limit of normal; WBC = white blood cell.

Administrative structure

Role	Name of responsible company/organization
Sponsor, randomization, study report authors, study master file, statistical analysis, data management, medical and study operations oversight	<ul style="list-style-type: none"> <li><b>Eli Lilly and Company</b></li> </ul>
Statistical analysis (clinical study report tables, figures, and listings)	(b) (4)
Statistical analysis reporting database (ADaM) development	
Data management, data entry and validation, patient narratives	
Study monitoring	

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	(b) (4)
Laboratory assessments	
Manufacturing sites of medicinal product	
Site of release in European Union	<ul style="list-style-type: none"> <li>Eli Lilly European Clinical Trials Services S.A.</li> </ul>
Other contracted services	(b) (4)

Source: adapted from JADX clinical study report, p. 76

Procedures and schedule: See Appendix 13.3.1 for schedule of visits

Concurrent medications: All medications (other than study drug) taken during the study were recorded on the case report form (CRF). Patients were instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements. Any use of excluded medication as stated in the protocol was a violation of the protocol and was documented.

Treatment with concomitant DMARDs was allowed as follows:

- Use of concomitant DMARD for at least 12 weeks with a continuous nonchanging dose for at least 8 weeks prior to study entry
- Concomitant hydroxychloroquine, sulfasalazine, leflunomide, and/or azathioprine allowed
- Stable dose of NSAID for at least 6 weeks allowed
- Concomitant analgesics were permitted
- Prednisone (or equivalent) at doses up to 10-mg per day was allowed during this study but must have been maintained at stable levels from 6 weeks prior to randomization and through the treatment phase of the study unless a patient received rescue therapy

Treatment compliance

Investigators assessed compliance from visit 4 through visit 11. Compliance was measured by direct questioning any by measurement of returned study drug. A patient was considered significantly noncompliant if >20% of study product was missed during the study.

Rescue medication: Rescue medication was available at Weeks 16 and 20 of the study. The option of escape for all arms was 4 mg daily of baricitinib. Thus patients who were already in the baricitinib 4 mg daily arm did not receive a change in treatment upon rescue.

Subject completion, discontinuation, or withdrawal: Patient disposition was summarized using the mITT population. Frequency counts and percentages of patients who completed or discontinued early from the study were summarized separately by treatment group for patients who were not rescued and for patients who were rescued, along with their reason for study discontinuation. Among patients who completed the study, frequency counts and percentages of patients who entered Study JADY, completed the post-treatment follow-up visit, or did not complete the follow-up visit are presented by treatment group. Among patients who discontinued early from the study, frequency counts and percentages of patients who completed the post-treatment follow-up visit or did not complete the follow-up visit are presented by treatment group. Reasons for not completing the post-treatment follow-up visit are also presented.

For handling of dropouts or missing data, the Applicant used several strategies which included non-responder imputation (NRI), modified baseline observation carried forward (mBOCF), modified last observation carried forward (mLOCF), and baseline observation carried forward (BOCF).

All patients who discontinued the study or permanently discontinued the study treatment at any time for any reason were defined as non-responders for the NRI analysis for categorical variables from the time of discontinuation and onward.

The mBOCF method was used for the analysis of key secondary continuous endpoints unless otherwise stated. For patients who discontinued the study or permanently discontinued the study treatment because of an AE, including death, or because of abnormal laboratory results reported as AEs, the baseline observation was carried forward to subsequent time points for evaluation. For patients who discontinued the study or permanently discontinued the study treatment for reason(s) other than an AE, the last non-missing post-baseline observation prior to discontinuation was carried forward to subsequent time points for evaluation.

For all continuous measures that included safety analyses, the mLOCF was a general approach to impute missing data unless otherwise specified. For patients who received rescue therapy starting from Week 24, the last non-missing observation at or before rescue was carried forward to subsequent time points for evaluation. For all other patients who discontinued from the study or permanently discontinued the study treatment for any reason, the last non-missing post-baseline observation before discontinuation was carried forward to subsequent time points for evaluation.

The BOCF method was used for the analysis of key secondary continuous endpoints at Week 24 as a sensitivity analysis to satisfy specific regulatory requests. For patients who discontinued the study or permanently discontinued the study treatment, the baseline observation was carried forward to subsequent time points for evaluation.

### Study Endpoints

The primary efficacy measure was patients achieving ACR20 at week 12 based on change in ACR response from baseline. ACR20 was defined as at least 20% improvement from baseline in the following ACR Core Set variables:

- Tender joint count (68 joint count)
- Swollen joint count (66 joint count)
- An improvement of  $\geq 20\%$  from baseline in at least 3 of the following 5 assessments:
  - Patient's Assessment of Pain (VAS)
  - Patient's Global Assessment of Disease Activity (VAS)
  - Physician's Global Assessment of Disease Activity (VAS)
  - Patient's assessment of physical function as measured by the HAQ-DI
  - Acute phase reactant as measured by hsCRP

The primary efficacy analysis was to test ACR20 at week 12 between the 4 mg baricitinib treatment arm and the placebo arm using the modified intent to treat population.

Assessment of ACR20 as a primary efficacy measure in rheumatoid arthritis is well established and has been used by the FDA as the primary endpoint for approval of several medications used for RA. The composite measure places an emphasis on change in joint counts. Also incorporated into the ACR20 are global measures of assessment by both the patient and provider.

Other Key secondary endpoints measured were:

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*: 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*: 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.<sup>17</sup> An alternative equation 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.
- *Simplified Disease Activity Index (SDAI)*: integrates measures of the physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI ranges from 0.1 to 86. Disease remission has been defined as an SDAI score ≤3.3 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)

## Statistical Analysis Plan

### Sample size determination

The sample size determination was based on 220 patients in the baricitinib 4 mg daily group, 200 patients in the baricitinib 2 mg daily group, and 220 patients in the placebo group. The sample size allowed >95% power to detect a difference in ACR20 response rate at Week 12

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<sup>17</sup> J Fransen and PLCM van Riel, "The Disease Activity Score and the EULAR Response Criteria." Clin Exp Rheumatol 2005; 23 (Suppl 39): S93-S99.

between the baricitinib 4mg group and placebo group. It also provided >90% power to detect a difference between the baricitinib 2 mg group and placebo.

#### Analysis population

There were three main analysis populations which will be described below:

- Modified intent to treat population: This population used the full analysis set and included all randomized patients who received at least one dose of study drug. Efficacy and health outcome analyses were performed on this population unless otherwise specified by the Applicant.
- Per-protocol population: This population included all patients in the modified intent to treat population who were deemed compliant with treatment, did not have important protocol deviations, and whose investigator site did not have significant GCP issues. This population was used to confirm results of the modified intent to treat population.
- Safety population: This population was all randomized patients who received at least one dose of study drug and did not discontinue from the study for the reason of “lost to follow up” at the first post-baseline visit.

#### Primary analysis

The primary efficacy analysis compares ACR20 at week 12 between baricitinib 4 mg daily and placebo using the modified intent-to-treat population. The per protocol population was used for supportive evidence of the modified intent-to-treat results. A logistic regression model was used to test the treatment difference between baricitinib 4 mg daily and placebo in the proportion of patients achieving ACR 20 at week 12 using the Wald test at a 2-sided significance level of 0.05.

#### Handling of dropouts or missing data

The following methods were used in study JADX for handling of missing data:

- Non-responder imputation- For categorical variables, patients who discontinued the study or permanently discontinued study treatment were defined as non-responders. Patients who were rescued from Week 16 onward were also classified as non-responders.
- Modified baseline observation carried forward- This analysis was used for continuous variables and included several key secondary endpoints. For patients who had an adverse event, the baseline observation was carried forward to subsequent time points for evaluation. For patients who discontinued from the study for a reason other than adverse event, the last post-baseline measurement was used for observation.

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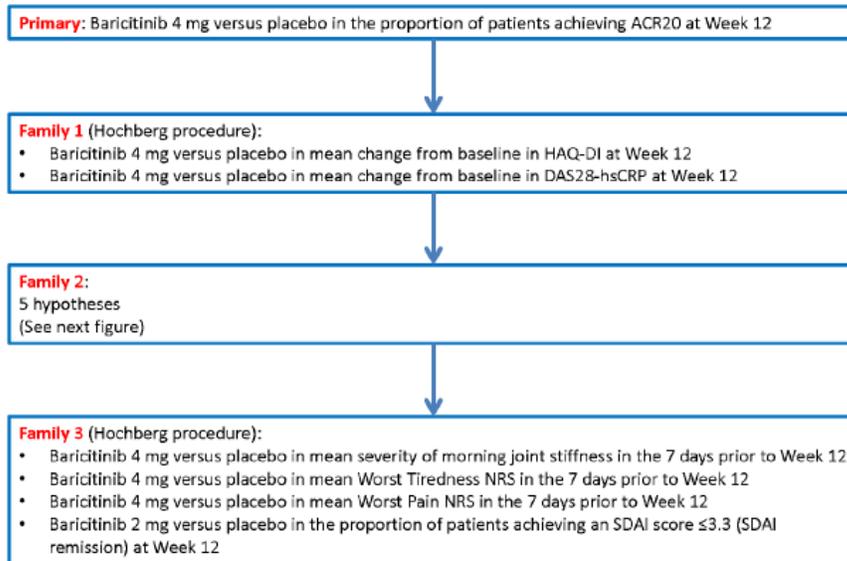
- Modified last observation carried forward- For all continuous measures including the safety analysis, the modified last observation carried forward method was used to impute missing data unless otherwise specified by the Applicant.
- Baseline observation carried forward- This method was used to analyze key secondary continuous endpoints at Week 12 as a sensitivity analysis. For patients who discontinued the study or permanently discontinued the study treatment, the baseline observation was carried forward to subsequent time points for evaluation.

Main statistical model and adjustment of covariates

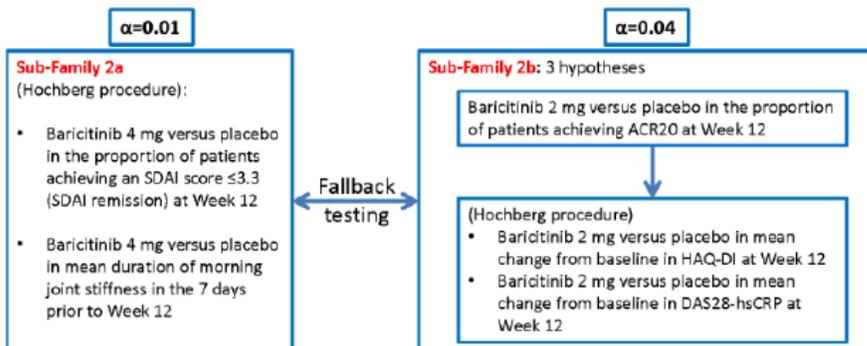
Multiple comparison/multiplicity

The arrangement of gated secondary endpoints was based on the unblinded results of JADW. The primary hypothesis and the families of key secondary hypotheses were tested sequentially. Testing proceeded to the next family only when all the hypotheses in a family had been rejected. **Figure 4** shows the overall gatekeeping design.

**Figure 4. JADX: overall gatekeeping strategy**



## Family 2



Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-hsCRP = Disease Activity Score 28 using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire–Disability Index; NRS = numeric rating scale; SDAI = Simplified Disease Activity Index.

Source: JADX clinical study report, p. 135

### Analysis of secondary endpoints

The key secondary endpoints were for comparisons between baricitinib 4 mg and placebo:

- Change from baseline to week 12 in HAQ-DI
- Change from baseline to week 12 in DAS28-hsCRP
- Proportion of patients achieving an SDAI score of less than or equal to 3.3 at week 12

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- Mean duration of joint stiffness in the 7 days prior to week 12 as collected in electronic diaries
- Mean severity of morning joint stiffness numeric rating scale (NRS) in the 7 days prior to week 12 as collected in electronic diaries
- Mean worst tiredness (NRS) in the 7 days prior to week 12 as collected in electronic diaries
- Mean worst joint pain (NRS) in the 7 days prior to week 12 as collected in electronic diaries

For comparisons between baricitinib 2 mg and placebo:

- Proportion of patients achieving ACR20 at Week 12
- Change from baseline to week 12 in HAQ-DI score
- Change from baseline to week 12 in DAS28-hsCRP score
- Proportion of patients achieving an SDAI of less than or equal to 3.3 at week 12

The key secondary endpoints were measured using the modified intent to treat population and the per protocol population was used to support the modified intent to treat results.

### Analysis of safety data

Safety topics analyzed included adverse events, clinical laboratory evaluations, vital signs/physical characteristics, safety in special groups, investigational product interruptions, and adverse events of special interest.

Safety data was prepared according to 3 formats:

- Week 0 to week 12: exposure to randomized treatments up to week 12
- Week 0 to week 24: censoring data collected after rescue
- Week 0 to week 24: collecting data on all baricitinib exposure including patients who rescue from placebo to baricitinib

### Protocol Amendments

JADX was amended twice

- The first amendment was created in response to queries from the European regulatory authorities to eliminate gender differences in electrocardiogram that would exclude patients from the study.
- The second amendment made several changes
  - Gated secondary objectives and analysis were revised
  - Allowed for retesting of hsCRP and TSH during screening

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- Allowed the tuberculosis test T.SPOT.TB to be used
- Recommended avoidance of hyaluronic acid injections during the study
- Specified gout as an exclusion criteria
- Amended study schedule to include erythrocyte sedimentation rate
- Changed study schedule to provide post-rescue baseline X-rays

### **Data Quality and Integrity: Sponsor's Assurance**

The Applicant states that they took the following steps to ensure data quality:

- Provided necessary instructional materials to study site
- Start-up training session to instruct investigators and study coordinators
- Made periodic visits to study sites
- Available for consultation and stayed in contact with study site personnel
- Reviewed and evaluated eCRF data
- Conducted a quality review of the reporting database

Central laboratories were used to maintain consistency of methods and combine laboratory/diagnostic criteria across study sites.

### **6.1.2. Study Results**

#### **Compliance with Good Clinical Practices**

JADX was conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines including Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- The International Conference of Harmonization (ICH) Good Clinical practices (GCP) Guidelines [E6]
- Applicable laws and regulations

#### **Financial Disclosure**

Eli Lilly and Company has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Appendix section 13.4 for a full review of Eli Lilly's financial disclosure.

#### **Patient Disposition**

**Table 10** shows patient disposition for each group to week 24. Of 1241 patients screened, 684 patients were randomized to study treatment. 24% of patients who were on placebo met rescue criteria and were switched to baricitinib 4 mg daily from Week 16 to Week 24. 145 of the patients who were not rescued in the placebo group completed through week 24. The percent of rescue was numerically lower for the patients in the 2 mg and 4 mg baricitinib arms as compared to the placebo arm.

**Table 10. JADX: patient disposition**

	placebo	BARI 2 mg	BARI 4 mg
Randomized and not treated	0	0	
Randomized and treated	228	229	227
Discontinued prior to week 24	29 (16%)	20 (9%)	24 (11%)
Rescued to BARI 4 mg Week 16-24	55 (24%)	21 (9%)	15 (7%)
Patients not rescued	173 (76%)	208 (91%)	212 (93%)
Completed through week 24	145 (84%)	189 (91%)	189 (90%)

Abbreviations: BARI=baricitinib

Source: adapted from JADX clinical study report, p. 188

*Reviewer's comment: An issue with study JADX was that patients who continued to have active disease were rescued to baricitinib 4 mg daily. Due to the change in therapy, conclusions regarding safety after rescue were difficult to attribute to the initially randomized arm of the study. To account for this study design, multiple different safety analyses were conducted to account for the design.*

### Protocol Violations/Deviations

Table 11 shows protocol deviations that occurred during study JADX. Most of the protocol violations that occurred were due to violating the inclusion criteria of at least one conventional DMARD for at least 12 weeks prior to study entry. 28 (4%) of all patients violated this inclusion criteria. The violations were fairly balanced among treatment groups with 13 (6%) occurring in placebo, 6 (3%) occurring in the 2 mg baricitinib group, and 9 (4%) occurring in the 4 mg baricitinib group.

**Table 11. JADX: protocol deviations**

	Placebo (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	Total (N=684)
Patients with ≥1 important protocol	47 (21)	40 (18)	38 (17)	125 (18)

deviation, n (%)				
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Abbreviations: BARI=baricitinib

Source: adapted from JADX clinical study report, p. 193

### Table of Demographic Characteristics

**Table 12** displays the demographic characteristics of patients who were randomized to treatment in JADX. In general, the demographics of patients were balanced across treatment groups. Patients were predominantly white, under 65 years of age with a mean age of 52 years. Most patients were female (82% overall). 30% of patients enrolled in the study were from the United States. The demographic characteristics in this study were similar to other previous studies performed in rheumatoid arthritis.

**Table 12. JADX: Demographic characteristics**

Demographic Parameters	Control Group placebo (N=228) n (%)	Treatment Group (N=456)		Total (N=684) n (%)
		BARI 2 mg (N=229) n (%)	BARI 4 mg (N=227) n (%)	
<b>Sex</b>				
Male	39 (17)	45 (20)	40(18)	124 (18)
Female	189 (83)	184 (80)	187 (82)	560 (82)
<b>Age</b>				
Mean years (SD)	51 (13)	52 (12)	52 (12)	52 (12)
Median (years)	53	52	53	53
Min, max (years)	21, 79	22, 82	20, 80	20, 82
<b>Age Group</b>				
< 65 years	197 (86)	196 (86)	194 (86)	587 (86)
≥ 65 years	31 (14)	33 (14)	33 (15)	97 (14)
<b>Race</b>				
White	153 (67)	156 (68)	148 (66)	457 (67)
Black or African American	10 (4)	9 (4)	9 (4)	28 (4)
Asian	60 (26)	61 (27)	59 (26)	180 (26)
American Indian or Alaska Native	3 (1)	2 (1)	9 (4)	14 (2)
Native Hawaiian or Other Pacific Islander	1 (0)	0	0	1 (0)
Multiple	1 (0)	1 (0)	1 (0)	3 (0)
<b>Region</b>				
United States & Canada	68 (30)	68 (30)	68 (30)	204 (30)
Rest of the World	31 (13)	30 (13)	32 (14)	93 (14)
Central & South America, Mexico	28 (12)	29 (13)	29 (13)	86 (13)
Europe	61 (27)	61 (27)	59 (26)	181 (26)
Asia	40 (18)	41 (18)	39 (17)	120 (18)

Abbreviations: BARI=baricitinib, SD=standard deviation  
Source: adapted from JADX clinical study report, p. 197-198

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**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

**Table 13** displays the disease baseline characteristics in study JADX. Patients in study JADX had well established RA with an average time from diagnosis of 6 years. They had active disease as reflected in the tender and swollen joint counts. 51% of the overall group was on corticosteroids at baseline.

**Table 13. JADX: Disease baseline characteristics**

Baseline disease Parameters	Control Group Placebo (N=228)	Treatment Group (N=374)		Total (N=684)
		BARI 2 mg (N=229)	BARI 4 mg (N=227)	
<b>Time from RA diagnosis (years)</b>				
Mean (SD)	6 (7)	7 (8)	6 (8)	6 (7)
Median	3	4	4	4
Min, max	0.07, 37	0.3, 53	0.1, 41	0.07, 53
<b>Tender joint count based on 68 joints</b>				
Mean (SD)	24 (15)	24 (14)	24 (14)	24 (14)
Median	21	20	21	20
Min, max	6, 68	6, 68	5, 66	5, 68
<b>Swollen joint count based on 66 joints</b>				
Mean (SD)	13 (7)	14 (9)	14 (7)	13 (8)
Median	12	11	11	11
Min, max	2, 54	3, 62	6, 40	2, 62
<b>Physician's global assessment of disease activity (0-100 mm)</b>				
N-obs	226	225	222	673
Mean (SD)	62 (17)	64 (17)	64 (18)	64 (17)
Median	63	66	66	65
Min, max	14, 100	21, 98	8, 97	8, 100
<b>Patient's global assessment of disease activity (0-100 mm)</b>				
N-obs	225	229	226	680
Mean (SD)	60 (21)	62 (20)	60 (22)	61 (21)
Median	62	63	61	62
Min, max	0, 100	6, 100	1, 100	0, 100
<b>Patient's assessment of pain (0-100 mm)</b>				
N-obs	225	229	226	680
Mean (SD)	57 (23)	60 (21)	57 (22)	58 (22)
Median	58	61	61	60
Min, max	0, 99	7, 100	7, 100	0, 100
<b>High sensitivity C-reactive protein (mg/L)</b>				
Mean (SD)	17 (20)	18 (22)	14 (15)	17 (19)

Median	9	9	10	9
Min, max	1, 118	0, 132	1, 105	0, 132
<b>HAQ-DI</b>				
N-obs	225	229	226	680
Mean (SD)	1.5 (0.6)	1.5 (0.6)	1.6 (0.6)	1.5 (0.6)
Median	1.5	1.5	1.5	1.5
Min, max	0, 2.8	0, 2.9	0, 3	0, 3
<b>Current use of corticosteroid, n (%)</b>				
Yes	114 (50)	117 (51)	115 (51)	346 (51)
<b>Modified total sharp score</b>				
N-obs	197	212	202	611
Mean (SD)	18.5 (31)	25.8 (40)	23.7 (40)	22.8 (38)
Median	6	8.5	6.3	6.5
Min, max	241.5	218	231	241.5

Abbreviations: BARI=baricitinib, N-obs=number observed, SD=standard deviation, min=minimum, max=maximum  
Source: adapted from JADX clinical study report, p. 199-206

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In general, non-compliance was low in study JADX. 4 (1.8%) patients were deemed non-compliant in each study group (placebo, baricitinib 2 mg daily, and baricitinib 4 mg daily).

**Table 14** shows the most commonly used concomitant anti-inflammatory and anti-rheumatic medications used for rheumatoid arthritis in JADX. Over 90% of patients in all groups were taking at least one anti-inflammatory or anti-rheumatic medication. For the most common anti-rheumatic medications, methotrexate was used in 75% of patients in the study and 25% of patients were taking hydroxychloroquine. The most common concomitant anti-inflammatory medication was celecoxib (13% of patients overall) but several other anti-inflammatory medications were with over 10% of the overall patients in the study using diclofenac or naproxen (data not shown).

**Table 14. JADX: Concomitant medications used for RA with data up to rescue**

	Placebo, N=228 n (%)	BARI 2, N=229	BARI 4, N=227
Anti-inflammatory/anti-rheumatic products	209 (92)	216 (94)	214 (94)
Methotrexate	168 (74)	171 (75)	173 (76)
Hydroxychloroquine	54 (24)	63 (28)	54 (24)
celecoxib	33 (15)	30 (13)	27 (12)

Abbreviations: BARI=baricitinib  
Source: adapted from JADX clinical study report, p. 1576

See patient disposition in section 6.4.1 for the patients who were rescued in study JADX.

**Efficacy Results – Primary Endpoint**

**Table 15** shows the percent of patients who had an ACR20 response at week 12. Both the 2 mg and 4 mg doses of baricitinib had a statistically significantly higher percentage of patients who achieved an ACR20 response as compared to placebo.

**Table 15: JADX: percent ACR20 responders at week 12 using non-responder imputation**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
ACR20 response, NRI, n (%)	90 (40)	151 (66)	140 (62)		
Difference in response rate (95% CI)				27 (18, 35)	22 ( 13, 31)
OR (95% CI)				3 (2, 4)	3 (2,4)
p-value for OR				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, ACR20=20% response to American College of Rheumatology Criteria, NRI=non-responder imputation, CI=confidence interval, OR=odds ratio  
Source: adapted from JADX clinical study report, p 224

**Table 16** shows the mean percent change from baseline in tender joint count at week 12. Both the 2 mg and 4 mg doses of baricitinib had a statistically significant improvement in tender joint counts as compared to placebo.

**Table 16. JADX: Tender joint count at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Tender joint count, n	223	228	223		
Mean % change from baseline (SD)	-38 (49)	-55 (42)	-56 (43)		
LSM (SE)	-38.3 (3)	-55.4 (3)	-56.6 (3)		
LSMD (95% CI)				-17.1 (-25.4, -8.8)	-18.3 (-26.7, -10)

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P value				0.001	0.001
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Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADX clinical study report, p. 262

**Table 17** shows the mean percent change from baseline in swollen joint count at week 12. Both the 2 mg and 4 mg doses of baricitinib had a statistically significant improvement in swollen joint counts as compared to placebo.

**Table 17. JADX: Swollen joint count at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Swollen joint count, n	223	228	223		
Mean % change from baseline (SD)	-40 (58)	-60 (42)	-62 (39)		
LSM (SE)	-43.4 (3)	-63.2 (3)	-65.2 (3)		
LSMD (95% CI)				-19.8 (-28.4, -11.1)	-21.8 (-30.5, -13)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from clinical study report, p. 265

**Table 18** shows the mean percent change from baseline in patient assessment of pain using a 100 point visual analogue scale at week 12. Both the 2 mg and 4 mg doses of baricitinib had a statistically significant improvement in patient assessed pain as compared to placebo.

**Table 18. JADX: Patient's assessment of pain at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Patient's assessment of pain, n	216	228	222		
Mean % change from baseline (SD)	-6 (164)	-41 (47)	-30 (74)		
LSM (SE)	-6.6 (8)	-40 (7)	-32.2 (8)		

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LSMD (95% CI)				-33.4 (-52.6, -14.1)	-25.6 (-45, -6.2)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADX clinical study report, p. 268

**Table 19** shows the mean percent change from baseline in patient assessment of disease activity using a 100 point visual analogue scale at week 12. Both the 2 mg and 4 mg doses of baricitinib did not have a statistically significant improvement in patient assessed disease activity as compared to placebo.

**Table 19. JADX: patient’s global assessment of disease activity at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Patient’s global assessment of disease activity, n	217	228	222		
Mean % change from baseline (SD)	0.6 (249)	-38 (50)	-8 (383)		
LSM (SE)	3.2 (19)	-34.9 (18)	-8.7 (19)		
LSMD (95% CI)				-38.1 (-86.2, 9.9)	-11.9 (-60.4, 36.6)
P value				0.12	0.631

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADX clinical study report, p. 271

*Reviewer’s comments: While the patients on baricitinib did not show a statistically significant improvement in patient’s assessment of disease activity, there was a numerical improvement in scores versus placebo. All other ACR core measures showed statistically superior improvement in scores with the baricitinib treatment arms over placebo.*

**Table 20** shows the mean percent change from baseline in the physician’s assessment of disease activity using a 100 point visual analogue scale at week 12. Both the 2 mg and 4 mg doses of baricitinib had a statistically significant improvement in physician assessment of disease activity as compared to placebo.

**Table 20. JADX: Physician’s global assessment of disease activity at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Physician’s global assessment of disease activity, n	221	224	219		
Mean % change from baseline (SD)	-33 (38)	-49 (34)	-52 (35)		
LSM (SE)	-33.8 (3)	-49.9 (3)	-52.8 (3)		
LSMD (95% CI)				-16.1 (-22.7, -9.6)	-19 (-25.7, -12.4)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADX clinical study report, p. 277

**Table 21** shows the mean percent change from baseline in HAQ-DI at week 12. Both the 2 mg and 4 mg doses of baricitinib had a statistically significant improvement in HAQ-DI as compared to placebo.

**Table 21. JADX: mean percent change from baseline in HAQ-DI at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
HAQ-DI, n	215	226	221		
Mean % change from baseline (SD)	-20 (40)	-36 (51)	-35 (45)		
LSM (SE)	-21.9 (3)	-38.2 (3)	-36.6 (3)		
LSMD (95% CI)				-16.2 (-24.8, -7.7)	-14.7 (-23.3, -6)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, HAQ-DI=Health Assessment Questionnaire-Disability Index, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADX clinical study report, p. 280

**Table 22** shows the mean percent change from baseline in hsCRP at week 12. Both the 2 mg and 4 mg doses of baricitinib had a statistically significant improvement in hsCRP as compared to placebo.

**Table 22. JADX: hsCRP at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
hsCRP, n	223	228	223		
Mean % change from baseline (SD)	44 (217)	-15 (184)	-25 (160)		
LSM (SE)	43.6 (12)	-11.6 (12)	-36.7 (12)		
LSMD (95% CI)				-55.2 (-86.4, -23.9)	-80.3 (-111.9, -48.6)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, hs-CRP=high sensitivity C-reactive protein, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADX clinical study report, p. 283

### Data Quality and Integrity – Reviewers’ Assessment

The data quality and integrity appeared adequate. For efficacy, no audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites.

### Efficacy Results – Secondary and other relevant endpoints

Table 23 shows all the primary and gated key secondary endpoints from JADX. All analyses were measured at week 12. For categorical variables, non-responder imputation was used to account for missing data. For continuous variables, mean change from baseline was measured. Both the 2 mg and 4 mg baricitinib doses showed statistically superior improvement in all endpoint tested.

**Table 23. JADX: primary and gated key secondary endpoints at week 12**

	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
ACR20, n (%)	90 (40)		140 (62)		
OR					3
95% CI					(2,3)
p-value					0.001

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HAQ-DI (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	224 -0.3 (0.04)		224 -0.5 (0.04)		-0.2 (0.05) (-0.3, -0.1) 0.001
DAS-28 hsCRP (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	224 -1.1 (0.09)		224 -1.9 (0.09)		-0.8 (0.11) (-1.1, -0.6) 0.001
ACR20, n (%) OR 95% CI p-value	90 (40)	151 (66)		3 (2,4) 0.001	
HAQ-DI (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	224 -0.3 (0.04)	229 -0.5(0.04)		-0.2 (0.05) (-0.3, -0.1) 0.001	
DAS-28 hsCRP (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	224 -1.1 (0.09)	229 -1.8 (0.08)		-0.8 (0.11) (-1, -0.5) 0.001	
SDAI≤3.3, n (%) p-value	2 (1)		20 (9)		0.001
Duration morning joint stiffness n median 95% CI Median difference 95% CI P –value	221 60 (51, 77)		222 35 (24, 51)		-19 (-30, -9) 0.001
Severity morning joint stiffness n LSM (SE) LSM difference (SE) 95% CI p-value	220 4.1 (0.2)		219 3.4 (0.2)		-0.8 (0.2) (-1.2, -0.3) 0.001
Worst tiredness n LSM (SE) LSM difference (SE) 95% CI p-value	220 4.5 (0.2)		219 4 (0.2)		-0.5 (0.2) (-0.9, -0.1) 0.027

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Worst joint pain n	220		219		
LSM (SE)	4.7 (0.2)		3.8 (0.2)		
LSM difference (SE)					-0.9 (0.2)
95% CI					(-1.3, -0.5)
p-value					0.001
SDAI≤3.3, n (%)	2 (1)	21 (9)			
p-value				0.001	

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, SDAI= simplified disease activity index, HAQ-DI=Health Assessment Questionnaire-Disability Index, DAS-28=disease activity scale in 28 joints, PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, OR=odds ratio, CI=confidence interval  
 Source: adapted from JADX clinical study report, p. 245-249

See Section 7 and Section 8 For additional discussion of efficacy and safety results, respectively.

### Dose/Dose Response

Two doses of baricitinib were studied in two studies, JADW and JADX. Please see Section 7.1.4 for additional details regarding dose response.

### Durability of Response

Durability of response was not assessed as JADX was a 24 week study with the primary endpoint assessed at week 12.

### Persistence of Effect

No analysis to determine persistence of effect. It would be expected that baricitinib would be administered chronically for the indication of rheumatoid arthritis.

### Additional Analyses Conducted on the Individual Trial

Information requests were sent to the Applicant to perform efficacy analyses that were requested by the Division prior to submission of the NDA. See Dr. Abugov’s statistical review for details on the additional requested analyses.

## 6.2. JADW

### 6.2.1. Study Design

#### Overview and Objective

JADW was a randomized, double-blind, placebo-controlled phase 3 study in patients with moderate to severe rheumatoid arthritis. The primary objective of JADW was to determine whether baricitinib 4 mg daily was superior to placebo in patients with moderately to severely

active rheumatoid arthritis who had inadequate response to TNF inhibitor as assessed by proportion of patients achieving ACR20 at week 12.

### Trial Design

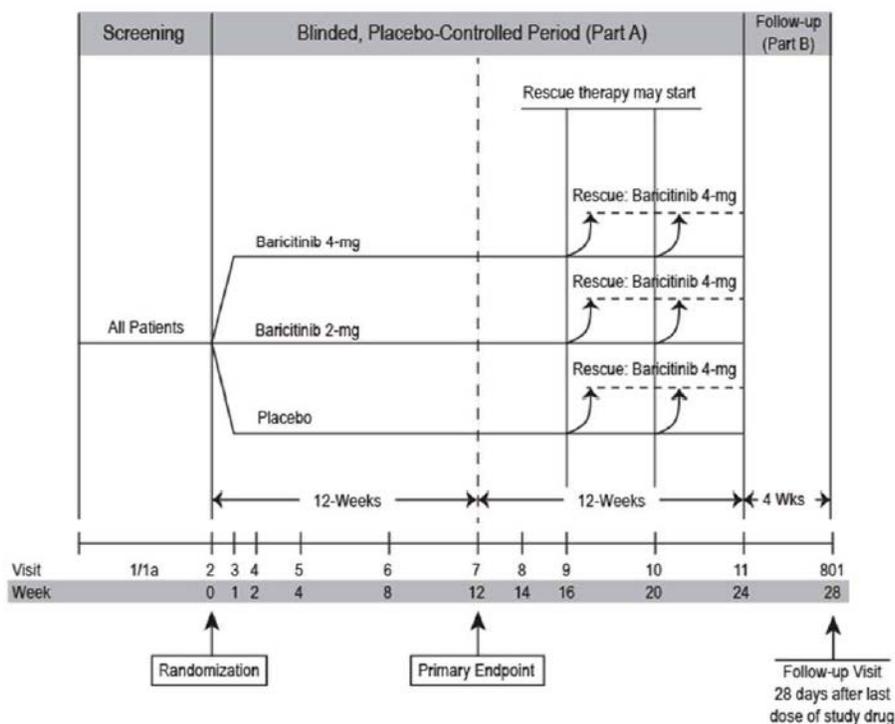
#### Basic Study Design

JADW was a 24 week, randomized, double-blind, placebo-controlled phase 3 study in patients with moderate to severe rheumatoid arthritis. The study compared the efficacy of daily doses of baricitinib at 2 mg and 4 mg daily strengths. Patients had insufficient response or intolerance to at least one tumor necrosis factor (TNF) inhibitor and were taking conventional DMARDs. Patients were randomized in a 1:1:1 ratio. The study consisted of 3 parts:

- Screening period: 3 to 42 days
- Part A: double blind period lasting 24 weeks
- Part B: post-treatment follow up period lasting 4 weeks

The study design is shown in **Figure 5**.

**Figure 5. JADW: Study design**



Source: JADW clinical study report, p. 78

#### Diagnostic Criteria and Key inclusion/exclusion criteria

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Key Inclusion Criteria:

- met ACR/EULAR 2010 Criteria for Classification of Rheumatoid Arthritis
- at least 6 tender joints
- at least 6 swollen joints
- elevated hsCRP
- receiving stable doses of conventional DMARD
- failed treatment with at least one TNF inhibitor

Key exclusion criteria:

- receiving prohibited therapy per protocol
- had a history of serious infection or tuberculosis
- immunocompromised
- protocol defined abnormal laboratory results
- comorbidities that would put patient at risk while taking study drug.

Dose selection

Dose selection was based on efficacy, safety, and PK data from the phase 2 studies. The Applicant observed a flat efficacy response at doses higher than 4 mg daily. The Applicant also observed lower rates of improvement in measures such as ACR50, ACR70, low disease activity, and remission rates in patients receiving doses lower than 4 mg daily.

The Applicant decided to study 2 mg daily for patients with renal impairment and to better define the lower end of the dose-response curve.

Study treatments

Patients received one of 4 study treatments to be given by mouth:

- baricitinib 4 mg tablets to be given daily
- baricitinib 2 mg tablets to be given daily
- placebo to match 4 mg baricitinib tablet to be given daily
- placebo to match 2 mg baricitinib tablet to be given daily

Patients who had renal impairment and were randomized to 4 mg baricitinib daily were given a dose of 2 mg baricitinib daily. In order to maintain blinding, all patients received two tablets. Patients received one strength of their assigned treatment and then placebo of the other strength.

Assignment to treatment

Patients were randomized in a 1:1:1 ratio (baricitinib 4 mg: baricitinib 2 mg: placebo) to double blind treatment at Week 0. Randomization was stratified by region and history of biologic

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DMARD use. A computer generated random sequence using an interactive voice response system was used to determine assignment to treatment.

Administrative Structure

**Table 24** shows the administrative structure used to conduct study JADW. Primary administrative roles and the company/organization responsible are listed in the table. JADW was conducted by 140 investigators at 140 study sites throughout the world.

**Table 24. JADW: Administrative structure**

Role	Name of responsible company/organization
Sponsor, randomization, study report authors, study master file, statistical analysis, data management, medical and study operations oversight	<ul style="list-style-type: none"> <li><b>Eli Lilly and Company</b></li> </ul>
Statistical analysis (clinical study report tables, figures, and listings)	(b) (4)
Statistical analysis reporting database (ADaM) development	
Data management, data entry and validation, patient narratives	
Study monitoring	
Laboratory assessments	
Manufacturing sites of medicinal product	
	<ul style="list-style-type: none"> <li><b>Eli Lilly and Company</b></li> </ul>
Site of release in European Union	<ul style="list-style-type: none"> <li><b>Eli Lilly European Clinical Trials Services S.A.</b></li> </ul>
Other contracted services	(b) (4)

Procedures and schedule: see Appendix 13.3 for schedule of events

Concurrent medications: All medications (other than study drug) taken during the study were recorded on the case report form (CRF). Patients were instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements. Any use of excluded medication as stated in the protocol was a violation of the protocol and was documented.

The following concomitant DMARDs were allowed:

- Stable dose of methotrexate for 8 weeks prior to entry. The patient must have been on methotrexate for at least 12 weeks.
- Stable dose of hydroxychloroquine or sulfasalazine for 8 weeks prior to entry
- Concomitant use of analgesics. Change in dose was not permitted until rescue
- Prednisone up to 10 mg daily, stable for 6 weeks prior to entry

#### Treatment compliance

Investigators assessed compliance from visit 4 through visit 11. Compliance was measured by direct questioning any by measurement of returned study drug. A patient was considered significantly noncompliant if >20% of study product was missed during the study.

#### Subject completion, discontinuation, or withdrawal

JADW used an identical procedure to study JADX. Please see section 6.1.1 for additional details.

#### Study Endpoints

The primary efficacy measure was patients achieving ACR20 at week 12 based on change in ACR response from baseline. ACR20 was defined as at least 20% improvement from baseline in the following ACR Core Set variables:

- Tender joint count (68 joint count)
- Swollen joint count (66 joint count)
- An improvement of  $\geq 20\%$  from baseline in at least 3 of the following 5 assessments:
  - Patient's Assessment of Pain (VAS)
  - Patient's Global Assessment of Disease Activity (VAS)
  - Physician's Global Assessment of Disease Activity (VAS)
  - Patient's assessment of physical function as measured by the HAQ-DI
  - Acute phase reactant as measured by hsCRP

The primary efficacy analysis was to test ACR20 at week 12 between the 4 mg baricitinib

treatment arm and the placebo arm using the modified intent to treat population.

Assessment of ACR20 as a primary efficacy measure in rheumatoid arthritis is well established and has been used by the FDA as the primary endpoint for approval of several medications used for RA. The composite measure places an emphasis on change in joint counts. Also incorporated into the ACR20 are global measures of assessment by both the patient and provider.

Other Key secondary endpoints measured were:

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*: 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*: 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. An alternative equation 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.
- *Simplified Disease Activity Index (SDAI)*: integrates measures of the physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI ranges from 0.1 to 86. Disease remission has been defined as an SDAI score  $\leq 3.3$  and low disease activity has been considered as an SDAI score  $\leq 11$ . 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)

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- 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)

## Statistical Analysis Plan

### Sample size determination

The sample size determination was based on 175 patients in the baricitinib 4 mg daily group, 175 patients in the baricitinib 2 mg daily group, and 175 patients in the placebo group. The sample size allowed >97% power to detect a difference in ACR20 response rate at Week 12 between the baricitinib 4 mg group and placebo group. It also provided >80% power to detect a difference between the baricitinib 2 mg group and placebo.

### Analysis population

There were three main analysis populations which will be described below:

- Modified intent to treat population: This population used the full analysis set and included all randomized patients who received at least one dose of study drug. Efficacy and health outcome analyses were performed on this population unless otherwise specified by the Applicant.
- Per-protocol population: This population included all patients in the modified intent to treat population who were deemed compliant with treatment, did not have important protocol deviations, and whose investigator site did not have significant GCP issues. This population was used to confirm results of the modified intent to treat population.
- Safety population: This population was all randomized patients who received at least one dose of study drug and did not discontinue from the study for the reason of "lost to follow up" at the first post-baseline visit.

### Primary analysis

The primary efficacy analysis compares ACR20 at week 12 between baricitinib 4 mg daily and placebo using the modified intent-to-treat population. The per protocol population was used for supportive evidence of the modified intent-to-treat results. A logistic regression model was used to test the treatment difference between baricitinib 4 mg daily and placebo in the proportion of patients achieving ACR 20 at week 12 using the Wald test at a 2-sided significance level of 0.05.

### Handling of dropouts or missing data

The following methods were used in study JADX for handling of missing data:

- Non-responder imputation- For categorical variables, patients who discontinued the study or permanently discontinued study treatment were defined as non-responders.

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Patients who were rescued from Week 16 onward were also classified as non-responders.

- Modified baseline observation carried forward- This analysis was used for continuous variables and included several key secondary endpoints. For patients who had an adverse event, the baseline observation was carried forward to subsequent time points for evaluation. For patients who discontinued from the study for a reason other than adverse event, the last post-baseline measurement was used for observation.
- Modified last observation carried forward- For all continuous measures including the safety analysis, the modified last observation carried forward method was used to impute missing data unless otherwise specified by the Applicant.
- Baseline observation carried forward- This method was used to analyze key secondary continuous endpoints at Week 12 as a sensitivity analysis. For patients who discontinued the study or permanently discontinued the study treatment, the baseline observation was carried forward to subsequent time points for evaluation.

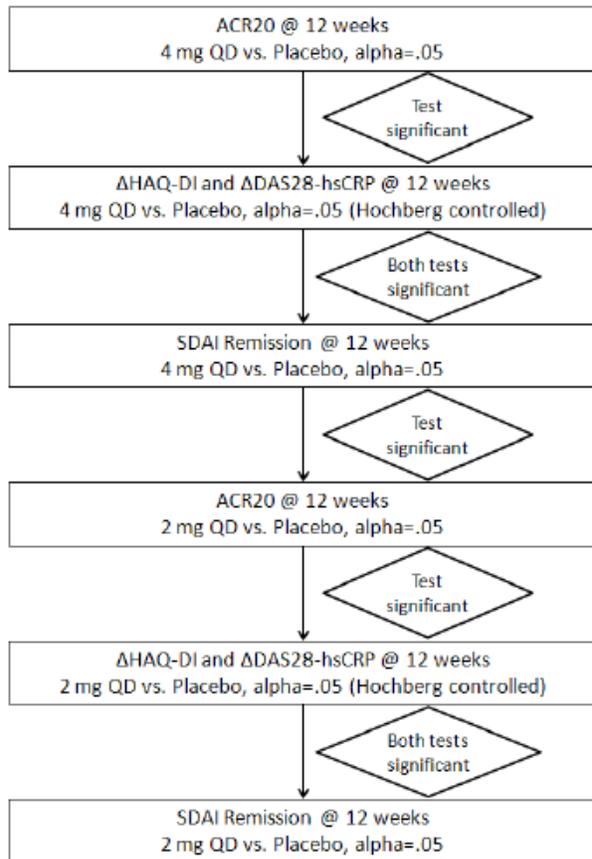
Main statistical model and adjustment of covariates

Multiple comparison/multiplicity

The primary hypothesis and the families of key secondary hypotheses were tested sequentially. Testing proceeded to the next family only when all the hypotheses in a family had been rejected. Figure 6 shows the overall gatekeeping design.

**Figure 6. JADW: overall gatekeeping strategy**

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Abbreviations:  $\Delta$  = change from baseline; ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-hsCRP = Disease Activity Score 28 using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; QD = daily; SDAI = simplified disease activity index; vs = versus.  
All statistical tests were 2-sided at the alpha level indicated in the figure.

Source: JADW clinical study report, p. 127

### Analysis of secondary endpoints

The key secondary endpoints were for comparisons between baricitinib and placebo:

- Change from baseline to week 12 in HAQ-DI and DAS28-hsCRP (baricitinib 4 mg)
- Proportion of patients achieving an SDAI score of less than or equal to 3.3 at week 12 (baricitinib 4 mg)
- Proportion of patients achieving ACR20 at Week 12 (baricitinib 2 mg)
- Change from baseline to week 12 in HAQ-DI and DAS28-hsCRP score (baricitinib 2 mg)
- Proportion of patients achieving an SDAI of less than or equal to 3.3 at week 12 (baricitinib 2 mg)

The key secondary endpoints were measured using the modified intent to treat population and the per protocol population was used to support the modified intent to treat results.

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#### Analysis of safety data

Safety topics analyzed included adverse events, clinical laboratory evaluations, vital signs/physical characteristics, safety in special groups, investigational product interruptions, and adverse events of special interest.

Safety data was prepared according to 3 formats:

- Week 0 to week 12: exposure to randomized treatments up to week 12
- Week 0 to week 24: censoring data collected after rescue
- Week 0 to week 24: collecting data on all baricitinib exposure including patients who rescue from placebo to baricitinib

#### Protocol Amendments

JADW was amended twice

- The first amendment was created in response to queries from the European regulatory authorities to eliminate gender differences in electrocardiogram that would exclude patients from the study, included a minimum duration of treatment with TNF inhibitor, and increased time from previous rituximab before a patient could be enrolled.
- The second amendment made several changes
  - Gated secondary objectives and analysis were revised
  - Allowed for retesting of hsCRP and TSH during screening
  - Allowed the tuberculosis test T.SPOT.TB to be used
  - Recommended avoidance of hyaluronic acid injections during the study
  - Specified gout as an exclusion criteria
  - Clarification to inclusion criteria of minimum duration of treatment with a TNF inhibitor

#### Data Quality and Integrity: Sponsor's Assurance

The Applicant states that they took the following steps to ensure data quality:

- Provided necessary instructional materials to study site
- Start-up training session to instruct investigators and study coordinators
- Made periodic visits to study sites
- Available for consultation and stayed in contact with study site personnel
- Reviewed and evaluated eCRF data
- Conducted a quality review of the reporting database

Central laboratories were used to maintain consistency of methods and combine laboratory/diagnostic criteria across study sites.

## 6.2.2. Study Results

### Compliance with Good Clinical Practices

JADW was conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines including Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- The International Conference of Harmonization (ICH) Good Clinical practices (GCP) Guidelines [E6]
- Applicable laws and regulations

### Financial Disclosure

Eli Lilly and Company has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Appendix section 13.4 for a full review of Eli Lilly's financial disclosure.

### Patient Disposition

JADW was a 24 week study with a 28 day post-treatment follow-up period. At the beginning of the treatment period patients were randomized in a 1:1:1 ratio to placebo, baricitinib 2 mg daily, or baricitinib 4 mg daily.

959 patients were screened of which 527 (56%) were randomized. All patients randomized received at least one dose of therapy.

**Table 25. JADW: Patient disposition**

	Placebo N=176	BARI 2 mg N=174	BARI 4 mg N=177
Randomized and treated, n	176	174	177
Discontinued prior to week 24, n	32	17	19
Rescued to BARI 4 mg Week 16-24, n	56	38	33
Completed through week 24, n	144	157	158

Abbreviations: BARI=baricitinib

Source: adapted from JADW clinical study report, p. 170

### Protocol Violations/Deviations

Table 26 shows the patients who had important protocol deviations in study JADW. Almost 25% of patients had a protocol violation in JADW. The percent of protocol violations was similar among treatment arms with a slightly higher percent occurring in the placebo group (27%) versus the 2 mg baricitinib group (21%) and 4 mg baricitinib group (23%). The most common reasons for discontinuation were due to increasing the dose of steroid or NSAID that violated the protocol. Most of these were due to increase in dose or change of medication prior to the switch/rescue period of the study.

**Table 26. JADW: protocol deviations**

	Placebo (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	Total (N=527)
Patients with ≥1 important protocol deviation, n (%)	48 (27)	36 (21)	41 (23)	125 (24)
Use of any new or change in dose of steroid	24 (14)	9 (5)	12 (7)	45 (9)
Use of any new or increased analgesic or NSAID	12 (7)	10 (6)	7 (4)	29 (6)

Abbreviations: BARI=baricitinib, NSAID=non-steroidal anti-inflammatory drug  
Source: adapted from JADW clinical study report, p. 175-176

**Table of Demographic Characteristics**

Table 27 shows the baseline demographic characteristics of the patients who participated in JADW. The patient population was primarily female and of White race. The majority of patients were enrolled from the United States, Canada, and Europe. The mean age of the group was 56 years of age. The demographic characteristics of this group of patients were consistent with what is seen in other RA trials.

**Table 27. JADW: Demographic characteristics**

Demographic Parameters	Control Group placebo (N=176) n (%)	Treatment Group (N=351)		Total (N=527) n (%)
		BARI 2 mg (N=174) n (%)	BARI 4 mg (N=177) n (%)	
<b>Sex</b>				
Male	31 (18)	37 (21)	28(16)	96 (18)
Female	145 (82)	137 (79)	149 (84)	431 (82)
<b>Age</b>				
Mean years (SD)	56 (11)	55 (11)	56 (11)	56 (11)
Median (years)	57	55	58	57
Min, max (years)	24, 77	21, 82	24, 82	21, 82

<b>Age Group</b>				
< 65 years	136 (77)	139 (80)	136 (77)	411 (78)
≥ 65 years	40 (23)	35 (20)	41 (23)	116 (22)
<b>Race</b>				
White	147 (84)	144 (83)	144 (83)	435 (83)
Black or African American	8 (5)	9 (5)	7 (4)	24 (5)
Asian	11 (6)	9 (5)	12 (7)	32 (6)
American Indian or Alaska Native	9 (5)	12 (7)	11 (6)	32 (6)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Multiple	1 (1)	0	0	1 (0)
<b>Region</b>				
United States & Canada	78 (44)	78 (45)	78 (44)	234 (44)
Rest of the World	18 (10)	18 (10)	18 (10)	54 (10)
Central & South America, Mexico	18 (10)	17 (10)	17 (10)	52 (10)
Europe	52 (30)	52 (30)	53 (30)	157 (30)
Asia	10 (6)	9 (5)	11 (6)	30 (6)

Abbreviations: BARI=baricitinib, SD=standard deviation  
Source: adapted from JADW clinical study report, p. 179-180

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 28 shows the characteristics of the RA and the percent of patients who were taking concomitant prednisone at baseline. On average, patients had a diagnosis of RA for over 10 years. They had active tender and swollen joints and had high disease activity per patient and physician global assessment. The disease characteristics were fairly well balanced between all groups.

**Table 28. JADW: Other baseline characteristics**

Baseline disease Parameters	Control Group placebo (N=176)	Treatment Group (N=351)		Total (N=527)
		BARI 2 mg (N=174)	BARI 4 mg (N=177)	
<b>Time from RA diagnosis (years)</b>				
Mean (SD)	13 (9)	12 (8)	13 (9)	13(9)
Median	10	11	10	11
Min, max	0.6, 51	1, 38	0.6, 38	0.6, 51
<b>Tender joint count based on 68 joints</b>				
Mean (SD)	28 (16)	31(16)	28(16)	30(16)

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Median	24	28	24	26
Min, max	6, 68	7, 68	6, 68	6, 68
<b>Swollen joint count based on 66 joints</b>				
Mean (SD)	17 (11)	19 (12)	16 (9)	17 (11)
Median	14	15	15	14
Min, max	6, 68	7, 68	6, 68	6, 68
<b>Physician's global assessment of disease activity (0-100 mm)</b>				
Mean (SD)	67 (19)	67 (17)	67 (18)	67 (18)
Median	69	69	71	70
Min, max	6, 100	9, 99	5, 100	5, 100
<b>Patient's global assessment of disease activity (0-100 mm)</b>				
Mean (SD)	66 (19)	67 (19)	66 (22)	67(20)
Median	69	72	70	71
Min, max	19, 100	0, 100	1, 100	0, 100
<b>Patient's assessment of pain (0-100 mm)</b>				
Mean (SD)	65 (19)	62 (22)	66 (23)	64(22)
Median	68	65	72	68
Min, max	8, 100	0, 100	0, 100	0, 100
<b>High sensitivity C-reactive protein (mg/L)</b>				
Mean (SD)	21 (25)	20 (22)	20 (25)	20 (24)
Median	10	11	10	10
Min, max	1, 155	0, 132	1, 173	0, 173
<b>HAQ-DI</b>				
Mean (SD)	1.8 (0.6)	1.7 (0.6)	1.7 (0.6)	1.7 (0.6)
Median	1.9	1.8	1.8	1.8
Min, max	0.4, 3	0, 3	0, 3	0, 3
<b>Current use of corticosteroid, n (%)</b>				
Yes	116 (66)	92 (53)	96 (54)	304 (58)

Abbreviations: BARI=baricitinib, SD=standard deviation, HAQ-DI=Health Assessment Questionnaire-disability index  
Source: adapted from JADW clinical study report, p. 181-189

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Table 29 show concomitant medications that were used throughout the 24 weeks of JADW with data censored at the time of switch or rescue. Over 80% of patients were taking methotrexate in the study and the most commonly prescribed NSAID was diclofenac. The concomitant

medications taken by the patients in each treatment arm was balanced among the treatment arms.

**Table 29. JADW: Concomitant medications used for RA with data up to rescue**

	Placebo, N=176 n (%)	BARI 2, N=174	BARI 4, N=177
Analgesics	65 (37)	65 (37)	71 (40)
Anti-inflammatory/anti-rheumatic products	161 (92)	163 (94)	169 (96)
Methotrexate	145 (82)	142 (82)	150 (85)
Hydroxychloroquine	14 (8)	20 (12)	19 (11)
diclofenac	32 (18)	18 (10)	17 (10)

Abbreviations: BARI=baricitinib

Source: adapted from JADW clinical study report, p. 1414-1419

### Efficacy Results - Primary Endpoint

Table 30 shows the percent of patients who had an ACR20 response at week 12 in study JADW. Both the 2 mg and 4 mg treatment arms had a statistically significantly higher percentage of patients who had an ACR20 response compared to placebo.

**Table 30. JADW: Primary endpoint ACR20 percent responders at week 12**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
ACR20 response, NRI, n (%)	48 (27)	85 (49)	98 (55)		
Difference in response rate (95% CI)				22 (12, 32)	28 ( 18, 38)
OR (95% CI)				3 (2, 4)	3 (2,5)
p-value for OR				0.001	0.001

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, PBO=placebo, BARI=baricitinib, OR=odds ratio, CI=confidence interval

Source: adapted from JADW clinical study report, p. 203

Table 31 shows the mean percent change from baseline in tender joint counts at week 12 in study JADW. Both the 2 mg and 4 mg treatment arms had a statistically significantly higher mean percent change from baseline in improved tender joint counts at week 12 compared to placebo.

**Table 31. JADW: mean percent change from baseline in tender joint count at week 12**

	PBO	BARI 2 mg	BARI 4 mg	BARI 2 mg	BARI 4 mg vs PBO
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	(N=176)	(N=174)	(N=177)	vs PBO	
Tender joint count, n	170	173	175		
Mean % change from baseline (SD)	-28 (47)	-44 (42)	-50 (44)		
LSM (SE)	-27.7 (4)	-44.2 (4)	-49.4 (4)		
LSMD (95% CI)				-16.5(-25.8, -7.3)	-21.7 (-30.9, -12.5)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADW clinical study report, p. 229

Table 32 shows the mean percent change from baseline in swollen joint counts at week 12 in study JADW. Both the 2 mg and 4 mg treatment arms had a statistically significantly greater mean percent change from baseline in improved swollen joint counts at week 12 compared to placebo.

**Table 32. JADW: mean percent change from baseline in swollen joint at week 12**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Swollen joint count, n	170	173	175		
Mean % change from baseline (SD)	-28 (57)	-46 (43)	-51 (43)		
LSM (SE)	-26.7 (4)	-45.1 (4)	-50.6 (4)		
LSMD (95% CI)				-18.4 (-28.4, -8.4)	-23.9 (-33.9, -13.9)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADW clinical study report, p. 228

Table 33 shows the mean percent change from baseline in patient's assessment of pain at week 12 in study JADW. Patient's assessment of pain was recorded on a visual analogue scale ranging from 0 to 100. Both the 2 mg and 4 mg treatment arms had a statistically significantly

greater mean percent change from baseline in improved patient’s assessment of pain at week 12 compared to placebo.

**Table 33. JADW: patient’s assessment of pain at week 12 (mean percent change from baseline)**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Patient’s assessment of pain, n	172	171	173		
Mean % change from baseline (SD)	-10 (60)	-21 (59)	-30 (70)		
LSM (SE)	-8.3 (5)	-22.4 (5)	-27.2 (5)		
LSMD (95% CI)				-14.1 (-26.8, -1.3)	-18.9 (-31.6, -6.2)
P value				0.031	0.004

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADW clinical study report, p. 235

Table 34 shows the mean percent change from baseline in patient’s assessment of disease activity at week 12 in study JADW. Patient’s assessment of disease activity was recorded on a visual analogue scale ranging from 0 to 100. Both the 2 mg and 4 mg treatment arms had a statistically significantly greater mean percent change from baseline in improved patient’s assessment of disease activity at week 12 compared to placebo.

**Table 34. JADW: Patient’s global assessment of disease activity at week 12 (mean percent change from baseline)**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Patient’s global assessment of disease activity, n	172	171	175		
Mean % change from baseline (SD)	-12 (42)	-30 (38)	-30 (82)		

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LSM (SE)	-10.2 (5)	-28 (5)	-28 (5)		
LSMD (95% CI)				-17.8 (-29.6, -5.9)	-17.9 (-29.6, -6.1)
P value				0.004	0.004

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADW clinical study report, p. 238

Table 35 shows the mean percent change from baseline in physician’s assessment of disease activity at week 12 in study JADW. Physician’s assessment of disease activity was recorded on a visual analogue scale ranging from 0 to 100. Both the 2 mg and 4 mg treatment arms had a statistically significantly greater mean percent change from baseline in improved physician’s assessment of disease activity at week 12 compared to placebo.

**Table 35. JADW: Physician’s global assessment of disease activity at week 12 (mean percent change from baseline)**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Physician’s global assessment of disease activity, n	171	170	171		
Mean % change from baseline (SD)	-14 (126)	-44 (36)	-50 (39)		
LSM (SE)	-9.7 (7)	-40.2 (7)	-44.9 (7)		
LSMD (95% CI)				-30.5 (-46.7, -14.4)	-35.2 (-51.3, -19.1)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADW clinical study report, p. 241

Table 36 shows the mean percent change from baseline in HAQ-DI at week 12 in study JADW. Both the 2 mg and 4 mg treatment arms had a statistically significantly greater mean percent change from baseline in improved HAQ-DI at week 12 compared to placebo.

**Table 36. JADW: HAQ-DI at week 12 (mean percent change from baseline)**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
HAQ-DI, n	172	171	174		

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Mean % change from baseline (SD)	-10 (33)	-25 (33)	-28 (31)		
LSM (SE)	-7.9 (3)	-22.6 (3)	-25.2 (3)		
LSMD (95% CI)				-14.7 (-21.5, -7.8)	-17.3 (-24.1, -10.5)
P value				0.001	0.001

Abbreviations: HAQ-DI=Health Assessment Questionnaire-Disability Index, PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADW clinical study report, p. 244

Table 37 shows the mean percent change from baseline in hs-CRP at week 12 in study JADW. Both the 2 mg and 4 mg treatment arms had a statistically significantly greater mean percent change from baseline in improved hs-CRP at week 12 compared to placebo.

**Table 37. JADW: hsCRP at week 12 (mean percent change from baseline)**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
Hs-CRP, n	172	173	175		
Mean % change from baseline (SD)	50 (192)	8 (238)	-25 (141)		
LSM (SE)	66.1 (17)	23.4 (17)	-8.7 (17)		
LSMD (95% CI)				-42.7 (-83.2, -2.2)	-74.8 (-115.1, -34.4)
P value				0.039	0.001

Abbreviations: hs-CRP=high sensitivity C-reactive protein, PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from clinical study report, p. 247

**Data Quality and Integrity - Reviewers' Assessment**

The data quality and integrity appeared adequate. For efficacy, no audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites.

**Efficacy Results - Secondary and other relevant endpoints**

Table 38 shows the primary endpoint and key secondary gated endpoints. For most endpoints, the 4 mg dose of baricitinib was superior to placebo in improving the measured endpoints. The

4 mg dose of baricitinib was not statistically significantly superior to placebo in achieving a percent of patients who reached a SDAI equal to or less than 3.3. All the 2 mg baricitinib comparisons to placebo were listed in the hierarchy under the SDAI comparison with the 4 mg of baricitinib. Therefore, the findings with the 2 mg dose of baricitinib were not significant.

**Table 38. JADW: primary and gated secondary endpoints at week 12**

	PBO (N=176)	BARI 2 mg (N=174)	BARI 4 mg (N=177)	BARI 2 mg vs PBO	BARI 4 mg vs PBO
ACR20, n (%) OR 95% CI p-value	48 (27)		98 (55)		3 (2,5) 0.001
HAQ-DI (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	176 -0.2 (0.04)		177 -0.4 (0.04)		-0.2 (0.05) (-0.3, -0.1) 0.001
DAS-28 hsCRP (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	174 -0.8 (0.1)		177 -1.8 (0.1)		-1 (0.14) (-1.4, -0.7) 0.001
<b>SDAI≤3.3, n (%) p-value</b>	<b>3 (2)</b>		<b>9 (5)</b>		<b>0.14</b>
ACR20, n (%) OR 95% CI p-value	48 (27)	85 (49)		3 (2,4) 0.001	
HAQ-DI (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	176 -0.2 (0.04)	172 -0.4 (0.04)		-0.2 (0.05) (-0.3, -0.1) 0.001	
DAS-28 hsCRP (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	174 -0.8 (0.1)	272 -1.5 (0.1)		-0.7 (0.14) (-1, -0.4) 0.001	
SDAI≤3.3, n (%) p-value	3 (2)	4 (2)		<b>0.723</b>	

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, SDAI= simplified disease activity index, HAQ-DI=Health Assessment Questionnaire-Disability Index, DAS-28=disease activity scale in 28 joints, hs-CRP=high sensitivity C-reactive protein, PBO=placebo,

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BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, OR=odds ratio, CI=confidence interval  
Source: adapted from JADW clinical study report, p. 215-216.

See Section 7 and Section 8 for additional discussion of efficacy and safety results, respectively.

### **Dose/Dose Response**

Two doses of baricitinib were studied in two studies, JADW and JADX. Please see Section 7.1.4 for additional details regarding dose response.

### **Durability of Response**

Durability of response was not assessed as JADW was a 24 week study with the primary endpoint assessed at week 12.

### **Persistence of Effect**

No analysis to determine persistence of effect. It would be expected that baricitinib would be administered chronically for the indication of rheumatoid arthritis.

### **Additional Analyses Conducted on the Individual Trial**

Information requests were sent to the Applicant to perform efficacy analyses that were requested by the Division prior to submission of the NDA. See Dr. Abugov's statistical review for details on the additional requested analyses.

## **6.3. JADV**

### **6.3.1. Study Design**

#### **Overview and Objective**

[JADV was a study to assess whether baricitinib was superior to placebo in the treatment of patients with moderately to severely active RA despite methotrexate treatment.

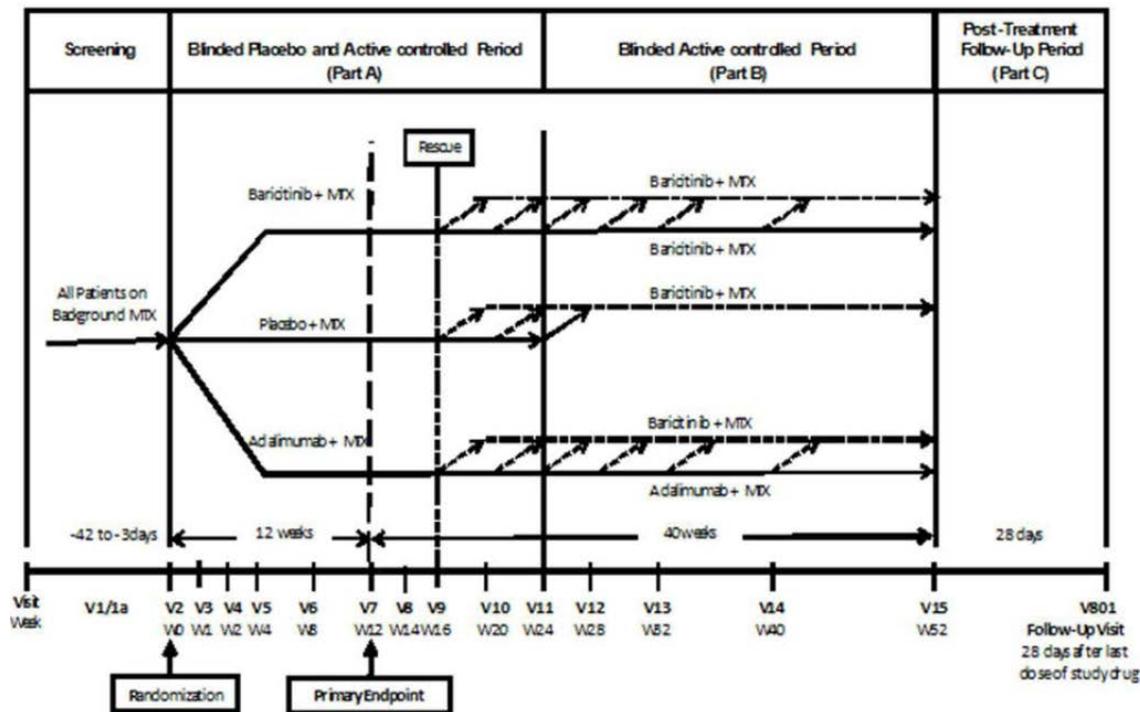
#### **Trial Design**

Basic Study Design: Study JADV was a 52-week, Phase 3, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group, study that compared the efficacy of baricitinib versus placebo on signs and symptoms, function, remission, and structural progression in patients with moderately to severely active RA who had an inadequate response to MTX and who had never been treated with a biologic DMARD. Study JADV also had an active comparator arm using adalimumab as the comparison.

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Source: JADV clinical study report, p. 112

Choice of control groups: JADV was placebo controlled for 24 weeks with the possibility to rescue to baricitinib. Patients randomized to placebo were allowed to be rescued to baricitinib treatment at weeks 16, 20, and 24. JADV had an active comparator arm with adalimumab 40 mg being administered every 2 weeks subcutaneously. Patients could receive adalimumab up to week 52 with opportunity for rescue to baricitinib at weeks 20, 24, 28, 32, and 40. Patients wishing to rescue from the baricitinib group continued to receive baricitinib. All patients participating in JADV received background methotrexate.

Diagnostic criteria: The patient population for Study JADV consisted of patients with moderately to severely active early RA who had previously had limited or no treatment with MTX and were naive to other conventional or biologic DMARDs. Patients were diagnosed with RA based on ACR/EULAR 2010 Criteria for the Classification of RA (see Appendix 13.2).

Additional key inclusion criteria were as follows:

- at least 6 tender joints (of 68 joints examined) and 6 swollen joints (of 66 joints examined)
- hsCRP measurement  $\geq 6$  mg/L
- at least 12 weeks of MTX therapy prior to study entry with 8 weeks being at a stable dose

- at least 3 joint erosions in hand, wrist, or foot joints based on radiographs or have at least 1 joint erosion in hand, wrist, or foot joints based on radiographs and be RF or ACPA antibody positive

Key exclusion criteria were as follows:

- receiving prohibited RA therapies
- had previously received biologic therapies
- recent history of infection including active tuberculosis (TB) or untreated latent TB or other serious infections
- immunocompromised
- certain abnormal laboratory results
- comorbidities that increased the patient’s risk when taking investigational product

Dose selection: The Applicant selected doses for JADV based on efficacy, safety, and PK data from the phase 2 studies JADC and JADA. The Applicant selected the 4 mg daily dose for study JADZ. The Applicant stated that in study JADA, the 1 mg and 2 mg daily doses were biologically active but did not produce adequate response for ACR50 and ACR70 at Week 12 of JADA. Patients with renal impairment defined as eGFR of <60 mL/min/1.73 m<sup>2</sup> were given a dose of 2 mg daily based on previous data that baricitinib exposure increases with decreased renal function.

Study treatments:

**Table 39. JADV: study treatments administered**

Treatment group	Initial treatment administered for Part A	Treatment administered for Part B (patients not rescued)	Treatments administered during Parts A and B (after rescue)
Placebo	<ul style="list-style-type: none"> <li>• Baricitinib placebo daily tablet</li> <li>• Adalimumab placebo by SC injection biweekly</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> <li>• Adalimumab placebo by SC injection biweekly</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> </ul>
Baricitinib 4 mg daily	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> <li>• Adalimumab placebo by SC injection biweekly</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> <li>• Adalimumab placebo by SC injection biweekly</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> </ul>
Adalimumab 40 mg every other week	<ul style="list-style-type: none"> <li>• Baricitinib placebo daily tablet</li> <li>• Adalimumab by SC injection biweekly</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib placebo daily tablet</li> <li>• Adalimumab by SC injection biweekly</li> </ul>	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg daily tablet</li> </ul>

Source: adapted from JADV clinical study report, p. 115

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Assignment to treatment: Patients who met all criteria for enrollment were randomized in a 3:3:2 ratio (baricitinib: placebo: adalimumab) to double-blind treatment at Week 0 (Visit 2). Randomization was stratified by region and the presence of joint erosions. Assignment to treatment groups was determined by a computer-generated random sequence that used an interactive voice-response system (IVRS).

Blinding: This was a double-blind, double-dummy study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. Baricitinib and its placebo and MTX and its placebo were identical in color, shape, smell, and taste. Assignment to treatment groups was determined by a computer-generated random sequence using an IVRS. Emergency unblinding for AEs was performed through an IVRS.

There were 2 planned database locks for this study: a primary database lock after all patients completed Week 24 (Visit 10) and a final data lock at the end of the study. For the primary database lock, by-visit data through Week 24 (Visit 10) were locked; however, ongoing log-type entry forms for ongoing patients with AEs and patients that used concomitant medications remained unlocked. Analyses were conducted on the primary and key secondary endpoints (included in the gatekeeping strategy) except for structure (mTSS), other efficacy measures, health outcomes measures, and safety endpoints that were collected through Week 24 (Visit 10). This analysis was not considered an interim analysis conducted by the data monitoring committee (DMC). Unblinding after the final database lock occurred on October 2, 2015. The final analysis included all data that was collected during the study. All investigators, study site personnel, and patients remained blinded to treatment assignments until the final database lock.

Dose modification, dose discontinuation: Study drug was discontinued for significant abnormalities in liver function tests; white blood cell, lymphocyte, and neutrophil counts; and hemoglobin levels. Study drug was discontinued in the case of a pregnancy or malignancy. Study drug was also discontinued if the patient developed symptomatic herpes zoster or a serious infection that, in the opinion of the investigator, warranted discontinuation. Patients receiving baricitinib in JADZ with eGFR of <60 mL/min/1.73 m<sup>2</sup> were given a dose of 2 mg daily.

Administrative structure: The Sponsor for JADV was Eli Lilly and company. JADV was conducted by 297 investigators at 281 study sites in 26 countries. Table 40 shows the additional organizations involved in the conduct of the study and role.

**Table 40. JADV: Administrative structure**

Role	Name of responsible company/organization
Sponsor, randomization, study report authors,	• <b>Eli Lilly and Company</b>

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study master file, statistical analysis, data management, medical and study operations oversight	
Statistical analysis (clinical study report tables, figures, and listings)	(b) (4)
Statistical analysis reporting database (ADaM) development	
Data management, data entry and validation, patient narratives	
Study monitoring	
Laboratory assessments	
Manufacturing sites of medicinal product	
Site of release in European Union	<ul style="list-style-type: none"> <li>Eli Lilly European Clinical Trials Services S.A.</li> </ul>
Other contracted services	(b) (4)

Source: adapted from JADV study report, p. 102-103

Procedures and schedule: The schedule of events is listed in Appendix 13.3.2.

Concurrent medications: All medications (other than study drug) taken during the study were recorded on the case report form (CRF). Patients were instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements. Any use of excluded medication as stated in the protocol was a violation of the protocol and was documented.

The following concomitant medications were permitted:

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- Concomitant dose of methotrexate for at least 12 weeks with stable dose of at least 8 weeks prior to study entry
- Concomitant use of hydroxychloroquine or sulfasalazine and must have been on stable dose for 8 weeks prior to study entry
- Concomitant use of analgesics
- Concomitant use of NSAIDs was permitted only if the patient was on a stable dose for at least 6 weeks prior to planned randomization
- Prednisone (or equivalent) at doses up to 10-mg per day was allowed during this study but must have been maintained at stable levels from 6 weeks prior to randomization and through the treatment phase of the study unless a patient received rescue therapy.

Treatment compliance:

Patient compliance with study medication was assessed from the randomization visits 5 through Visit 7 and Visits 9 through 15. Compliance was summarized from randomization until rescue or end of treatment using the mITT population. Compliance to baricitinib was measured as the ratio of actual total tablets used divided by expected total tablets used multiplied by 100. Compliance to methotrexate was measured as the ratio of actual total capsules used divided by expected total capsules used multiplied by 100.

A patient was considered noncompliant if he or she missed >20% of the prescribed doses during the study, unless the patient's study drug was withheld by the investigator. For patients who had their treatment temporarily interrupted by the investigator, the periods of time that dose was withheld were taken into account in the compliance calculation as outlined below.

Rescue medication: Rescue medication was available at Weeks 16, 20, 24, 28, 32, and 40 of the study. The option of escape for all arms was baricitinib. Thus patients who were already in the baricitinib arm did not receive a change in treatment upon rescue.

Subject completion, discontinuation, or withdrawal: Patient disposition was summarized using the mITT population. Frequency counts and percentages of patients who completed or discontinued early from the study were summarized separately by treatment group for patients who were not rescued and for patients who were rescued, along with their reason for study discontinuation. Among patients who completed the study, frequency counts and percentages of patients who entered Study JADY, completed the post-treatment follow-up visit, or did not complete the follow-up visit are presented by treatment group. Among patients who discontinued early from the study, frequency counts and percentages of patients who completed the post-treatment follow-up visit or did not complete the follow-up visit are presented by treatment group. Reasons for not completing the post-treatment follow-up visit are also presented.

For handling of dropouts or missing data, the Applicant used several strategies which included  
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non-responder imputation (NRI), modified baseline observation carried forward (mBOCF), modified last observation carried forward (mLOCF), and baseline observation carried forward (BOCF).

All patients who discontinued the study or permanently discontinued the study treatment at any time for any reason were defined as non-responders for the NRI analysis for categorical variables from the time of discontinuation and onward.

The mBOCF method was used for the analysis of key secondary continuous endpoints unless otherwise stated. For patients who discontinued the study or permanently discontinued the study treatment because of an AE, including death, or because of abnormal laboratory results reported as AEs, the baseline observation was carried forward to subsequent time points for evaluation. For patients who discontinued the study or permanently discontinued the study treatment for reason(s) other than an AE, the last non-missing post-baseline observation prior to discontinuation was carried forward to subsequent time points for evaluation.

For all continuous measures that included safety analyses, the mLOCF was a general approach to impute missing data unless otherwise specified. For patients who received rescue therapy starting from Week 16, the last non-missing observation at or before rescue was carried forward to subsequent time points for evaluation. For all other patients who discontinued from the study or permanently discontinued the study treatment for any reason, the last non-missing post-baseline observation before discontinuation was carried forward to subsequent time points for evaluation.

The BOCF method was used for the analysis of key secondary continuous endpoints at Week 12 as a sensitivity analysis to satisfy specific regulatory requests. For patients who discontinued the study or permanently discontinued the study treatment, the baseline observation was carried forward to subsequent time points for evaluation.

## Study Endpoints

The primary efficacy measure was the proportion of patients who achieved ACR20 at Week 12 based on the change in ACR response values from baseline. ACR20 was defined as at least 20% improvement from baseline in the following ACR Core Set variables:

- Tender joint count (68 joint count)
- Swollen joint count (66 joint count)
- An improvement of  $\geq 20\%$  from baseline in at least 3 of the following 5 assessments:
  - Patient's Assessment of Pain (VAS)
  - Patient's Global Assessment of Disease Activity (VAS)
  - Physician's Global Assessment of Disease Activity (VAS)

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- Patient's assessment of physical function as measured by the HAQ-DI
- Acute phase reactant as measured by hsCRP

The primary efficacy analysis was to test the noninferiority of baricitinib to placebo in the proportion (or percentage) of patients that achieved ACR20 at Week 12 using the mITT population.

Assessment of ACR20 as a primary efficacy measure in rheumatoid arthritis is well established and has been used by the FDA as the primary endpoint for approval of several medications used for RA. The composite measure places an emphasis on change in joint counts. Also incorporated into the ACR20 are global measures of assessment by both the patient and provider.

Other Key secondary endpoints measured were:

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*: 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*: 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. An alternative equation 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.

- *Simplified Disease Activity Index (SDAI)*: integrates measures of the physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI ranges from 0.1 to 86. Disease remission has been defined as an SDAI score  $\leq 3.3$  and low disease activity has been considered as an SDAI score  $\leq 11$ . 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)
- *Van der Heijde modified Sharp Score*: 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. 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.

## Statistical Analysis Plan

### Sample size determination

1280 patients (480 in the baricitinib group, 480 in the placebo group, and 320 in the adalimumab group) was estimated to provide:

- $> 95\%$  power to detect a difference between the baricitinib and placebo treatment groups in ACR20 response rate (assuming 60% vs 35%) at Week 12 based on a 2-sided chi-square test at a significance level of 0.05
- approximately 94% power to detect a difference in mTSS between the baricitinib and placebo treatment groups for an effect size of 0.25 (i.e., difference in means divided by common SD), based on a 2-sided t-test at a significance level of 0.04.
- approximately 93% power for the noninferiority analysis of ACR20 response rate at Week 12 between the baricitinib and adalimumab treatment groups, where a common

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response rate of 60% for baricitinib and adalimumab and a 1-sided significance level of 0.025 were assumed. This power calculation adopted a fixed noninferiority margin of 12%

#### Analysis population

JADV had two populations defined for the efficacy analyses.

The modified-intent-to-treat populations included all randomized patients who received at least one dose of study drug. Patients were analyzed according to treatment assigned by random allocation. Primary and secondary analyses were conducted on the modified-intent-to-treat population.

The per-protocol population included all randomized patients who were compliant with treatment, did not have a major protocol violation, and were enrolled at a study site that did not have significant good clinical practices violations. The primary and secondary efficacy analyses were repeated with this population.

#### Safety population

The safety population is defined as all randomized patients who received at least 1 dose of study drug and who did not discontinue from the study for the reason “Lost to Follow-Up” at the first postbaseline visit. Safety analyses up to the end of Part B were conducted on this safety population.

#### Primary analysis

The primary efficacy analysis compared ACR20 at week 12 between baricitinib and placebo using the modified-intent-to-treat population. A logistic regression model was used to test the treatment differences between baricitinib and placebo in the proportion of patients achieving ACR20 response at Week 12 using the Wald test at a 2-sided significance level of 0.05.

#### Multiple comparison/multiplicity

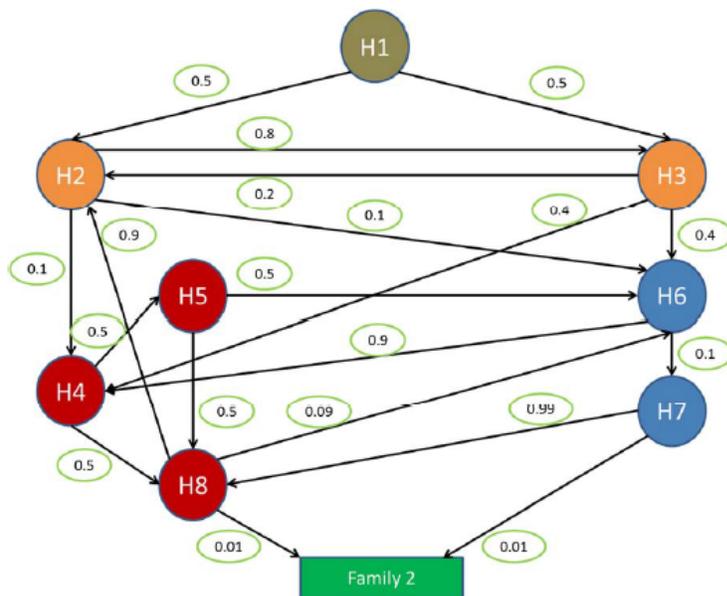
11 hypotheses were tested:

- H1: proportion of patients achieving ACR20 at Week 12, baricitinib versus placebo
- H2: mean change from baseline in mTSS at Week 24, baricitinib versus placebo
- H3: mean change from baseline in HAQ-DI at Week 12, baricitinib versus placebo
- H4: mean change from baseline in DAS28-hsCRP at Week 12, baricitinib versus placebo
- H5: proportion of patients achieving SDAI  $\leq 3.3$  at Week 12, baricitinib versus placebo
- H6: proportion of patients achieving ACR20 at Week 12, baricitinib versus adalimumab (noninferiority)
- H7: mean change from baseline in DAS28-hsCRP at Week 12, baricitinib versus adalimumab

- H8: mean duration of morning joint stiffness (ePRO diary) in the 7 days prior to Week 12, baricitinib versus placebo.
- H9: mean severity of morning joint stiffness (ePRO diary) in the 7 days prior to Week 12, baricitinib versus placebo
- H10: mean Worst Tiredness NRS (ePRO diary) in the 7 days prior to Week 12, baricitinib versus placebo
- H11: mean Worst Joint Pain NRS (ePRO diary) in the 7 days prior to Week 12, baricitinib versus placebo

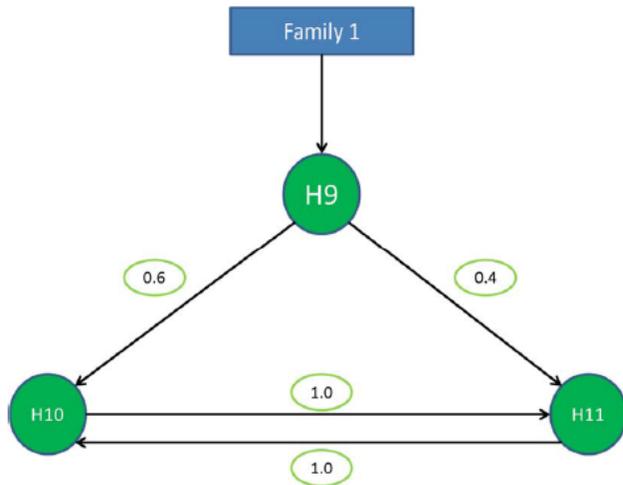
The Applicant replaced a sequential testing strategy with a graphical approach for multiple testing of primary and secondary endpoints. The graphical method did not change the primary endpoint or add or remove any key secondary endpoints. The graphical method began with Family 1 and then Family 2 as shown in Figure 7 and Figure 8.

**Figure 7. JADV: Family 1 graphical testing procedure**



Source: JADV clinical study report, p. 171

**Figure 8. JADV: Family 2 graphical testing procedure**



Source: JADV clinical study report, p. 172

The key secondary efficacy measures were:

- change from baseline to Week 24 in mTSS
- change from baseline to Week 12 in HAQ-DI
- change from baseline to Week 12 in DAS28-hsCRP
- proportion of patients achieving an SDAI score  $\leq 3.3$  at Week 12
- proportion of patients achieving ACR20 at Week 12 with respect to noninferiority of baricitinib to adalimumab
- mean duration of morning joint stiffness (ePRO diary; 7 days prior to Week 12)
- change from baseline to Week 12 in DAS28-hsCRP with respect to superiority of baricitinib to adalimumab
- mean severity of morning joint stiffness (ePRO diary; 7 days prior to Week 12)
- mean Worst Tiredness NRS (ePRO diary; 7 days prior to Week 12)
- mean Worst Joint Pain NRS (ePRO diary; 7 days prior to Week 12).

The key secondary efficacy measures were analyzed using the modified intent to treat population. The per protocol population results were used as supportive to the modified intent to treat results.

#### Handling of dropouts or missing data

The following methods were used in study JADV for handling of missing data:

- Non-responder imputation- For categorical variables, patients who discontinued the study or permanently discontinued study treatment were defined as non-responders. Patients who were rescued from Week 16 onward were also classified as non-responders.
- Modified baseline observation carried forward- This analysis was used for continuous variables and included several key secondary endpoints. For patients who had an

adverse event, the baseline observation was carried forward to subsequent time points for evaluation. For patients who discontinued from the study for a reason other than adverse event, the last post-baseline measurement was used for observation.

- Modified last observation carried forward- For all continuous measures including the safety analysis, the modified last observation carried forward method was used to impute missing data unless otherwise specified by the Applicant.
- Baseline observation carried forward- This method was used to analyze key secondary continuous endpoints at Week 12 as a sensitivity analysis. For patients who discontinued the study or permanently discontinued the study treatment, the baseline observation was carried forward to subsequent time points for evaluation.

### Protocol Amendments

JADW was amended three times

- The first amendment made several changes. Of these, the main changes were:
  - Minimum hsCRP value was listed rather than a multiple of upper limit of normal
  - Dual assessor approach was described
  - Exclusion criteria modified to include a period to avoid pregnancy following administration of adalimumab
  - Serum samples were changed to plasma samples for PK collections
- The second amendment was created in response to queries from the European regulatory authorities to eliminate gender differences in electrocardiogram that would exclude patients from the study
- The third amendment made several changes
  - Gated secondary objectives and analysis were revised
  - Allowed for retesting of hsCRP and TSH during screening
  - Allowed the tuberculosis test T.SPOT.TB to be used
  - Recommended avoidance of hyaluronic acid injections during the study
  - Specified gout as an exclusion criteria
  - Included on site tablets to be used to collect electronic patient reported outcomes
  - Updated duration of period off conventional DMARDs prior to study entry

### Data Quality and Integrity: Sponsor's Assurance

[The Applicant did the following to ensure data quality provided instructional material to the study sites, as appropriate

- sponsored a start-up training session to instruct the investigators and study coordinators
- made periodic visits to the study sites

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- were available for consultation and stayed in contact with study site personnel by mail, telephone, and/or fax
- reviewed and evaluated CRF data and used standard computer edits to detect errors in data collection
- conducted a quality review of the reporting database.

### 6.3.2. Study Results

#### Compliance with Good Clinical Practices

JADV was conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines including Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- The International Conference of Harmonization (ICH) Good Clinical practices (GCP) Guidelines [E6]
- Applicable laws and regulations

#### Financial Disclosure

Eli Lilly and Company has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Appendix section 13.4 for a full review of Eli Lilly and Company's financial disclosure.

#### Patient Disposition

In JADV, 2949 patients were screened and of the screened patients, 1307 patients were randomized to a study medication. Patients were randomized in a 3:3:2 ratio to one of three treatment groups:

- Placebo: 488
- Baricitinib 4 mg daily: 487
- Adalimumab 40 mg every other week: 333

Two patients were randomized but not treated and therefore were not included in analysis populations.

**Table 41** shows patient disposition to week 52 in study JADZ. By protocol, all patients receiving placebo until week 24 were switched to baricitinib 4 mg daily. In addition, patients who met rescue criteria in the baricitinib 4 mg group, continued on baricitinib 4 mg. Adalimumab patients who met rescue criteria were also rescued to 4 mg of baricitinib daily.

**Table 41. JADV: Patient disposition**

	Placebo	BARI 4 mg	ADA
Randomized and not treated	1	1	
Randomized and treated	488	487	330
Discontinued prior to week 24	53	29	24
Rescued to BARI 4 mg Week 16-24	126	35	40
Not rescued	125		290
Completed through week 24	305	458	267
Discontinued week 24 to 52	NA	31	15
Rescued to BARI 4 mg through week 52	NA	8	11
Completed through week 52	NA	427	241

Abbreviations: BARI=baricitinib, ADA=adalimumab  
Source: JADV clinical study report, p. 223

### Protocol Violations/Deviations

Table 42 shows the protocol deviations that occurred during the JADV study. The number of protocol deviations was quite small. Only 6% of patients had a protocol deviation in all treatment arms. The percent of protocol deviations in each treatment arm was well balanced.

**Table 42. JADV: protocol deviations**

	placebo (N=488)	BARI 4 mg (N=487)	Adalimumab (N=330)	Total (N=1305)
Patients with ≥1 important protocol deviation, n (%)	31 (6)	34 (7)	19 (6)	84 (6)

Abbreviations: BARI=baricitinib  
Source: JADV clinical study report, p. 1022

### Table of Demographic Characteristics

Table 43 shows the baseline demographics of patients who participated in study JADV. The patients were predominantly white, female, and had a mean age of 53 years. The study also had approximately 30% of patients who were Asian in origin. The demographic characteristics of the JADV patient population were consistent with other RA studies.

**Table 43. JADV: Baseline demographic characteristics**

Demographic Parameters	Control Group placebo (N=488) n (%)	Treatment Group (N=817)		Total (N=1305) n (%)
		BARI 4 mg (N=487) n (%)	adalimumab (N=330) n (%)	
<b>Sex</b>				
Male	106 (22)	112 (23)	79 (24)	297 (23)
Female	382 (78)	375 (77)	251 (76)	1008 (77)
<b>Age</b>				
Mean years (SD)	53 (12)	54 (12)	53 (12)	53 (12)
Median (years)	55	55	55	55
Min, max (years)	19, 83	23, 80	20, 86	19, 86
<b>Age Group</b>				
< 65 years	406 (83)	384 (79)	274 (83)	1064 (82)
≥ 65 years	82 (17)	103 (21)	56 (17)	241 (19)
<b>Race</b>				
White	302 (62)	312 (64)	204 (62)	818 (63)
Black or African American	4 (1)	2 (0)	4 (1)	10 (1)
Asian	140 (30)	143 (29)	101 (31)	392 (30)
American Indian or Alaska Native	26 (5)	19 (4)	18 (6)	63 (5)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Multiple	7 (1)	11 (2)	3 (1)	21 (2)
<b>Region (optional)</b>				
United States & Canada	39 (8)	40 (8)	26 (8)	105 (8)
Rest of the World	51 (11)	49 (10)	34 (10)	134 (10)
Central & South America, Mexico	141 (29)	143 (29)	96 (29)	380 (29)
Eastern Europe	87 (18)	85 (18)	58 (18)	230 (18)
Western Europe	29 (6)	29 (6)	20 (6)	78 (6)
Japan	93 (19)	93 (19)	63 (19)	249 (19)

Abbreviations: BARI=baricitinib, SD=standard deviation  
Source: adapted from JADV clinical study report, p. 232-233

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 44 shows the baseline disease characteristics of patients who participated in JADV. The patients had well established disease with an average mean time from diagnosis of 9 years. Patients had a mean average of 23 tender joints and 15 swollen joints. The mean Sharp score was 44 which was likely due to the enrollment criteria requiring at least one erosion for entry into the study. The baseline characteristics were balanced among the treatment arms.

**Table 44. JADV: other baseline characteristics**

Baseline disease Parameters	Control Group placebo (N=488)	Treatment Group (N=817)		Total (N=1305)
		BARI 4 mg (N=487)	adalimumab (N=330)	
<b>Time from RA diagnosis (years)</b>				
Mean (SD)	9 (8)	9 (9)	8 (8)	9 (8)
Median	7	6	6	6
Min, max	0, 40	0, 56	0, 35	0, 56
<b>Tender joint count based on 68 joints</b>				
Mean (SD)	23 (14)	23 (13)	23 (14)	23 (13)
Median	21	21	21	21
Min, max	5, 68	5, 68	3, 68	3, 68
<b>Swollen joint count based on 66 joints</b>				
Mean (SD)	16 (9)	15 (8)	15 (9)	15 (9)
Median	12	13	13	13
Min, max	4, 64	3, 54	5, 62	3, 64
<b>Physician's global assessment of disease activity (0-100 mm)</b>				
N-obs	485	483	327	1295
Mean (SD)	64 (17)	66 (17)	65 (17)	65 (17)
Median	66	67	66	66
Min, max	2, 100	14, 100	15, 100	2, 100
<b>Patient's global assessment of disease activity (0-100 mm)</b>				
N-obs	487	486	329	1302
Mean (SD)	61 (23)	63(21)	64 (21)	62 (22)
Median	62	64	67	64
Min, max	1, 100	1, 100	2, 100	1, 100
<b>Patient's assessment of pain (0-100 mm)</b>				
N-obs	487	486	329	1302
Mean (SD)	60 (23)	62 (22)	61 (23)	61 (22)
Median	61	64	61	62
Min, max	0, 100	4, 100	1, 100	0, 100
<b>High sensitivity C-reactive protein (mg/L)</b>				
Mean (SD)	20 (21)	22 (23)	22 (21)	21 (22)

Median	13	14	14	14
Min, max	1, 154	0, 151	1, 121	0, 154
<b>HAQ-DI</b>				
N-obs	487	486	329	1302
Mean (SD)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)
Median	1.5	1.6	1.6	1.6
Min, max	0, 3	0, 3	0, 3	0, 3
<b>Current use of corticosteroid, n (%)</b>				
Yes	290 (59)	275 (57)	201 (61)	766 (59)
<b>Modified total sharp score</b>				
N-obs	458	473	313	1244
Mean (SD)	45 (50)	42 (50)	44 (51)	44 (50)
Median	23	22	26	23
Min, max	0, 301	0, 285	0, 310	0, 310

Abbreviations: BARI=baricitinib, HAQ-DI=health assessment questionnaire-disability index, SD=standard deviation, N-obs=number observed  
Source: adapted from JADV clinical study report, p. 245

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In general, treatment non-compliance was low in study JADV. 1% of placebo patients, 0.6% of baricitinib patients, and 0.6% of adalimumab patients were considered non-compliant.

Table 45 shows common concomitant medications that were used in JADV through week 52. The data is censored at switch or rescue. As per the entry criteria, patients were on methotrexate. Over 10% of patients were taking analgesics and over 50% of patients were taking a systemic corticosteroid.

**Table 45. JADV: Concomitant medications to 52 weeks with data censored at switch or rescue**

	Placebo, N=488 n (%)	BARI 4, N=487 n (%)	ADA, N=330 n (%)
Analgesics	65 (13)	66 (14)	47 (14)
Corticosteroids	299 (61)	276 (57)	205 (62)
Anti-inflammatory/anti-rheumatic products	488 (100)	487 (100)	330 (100)
Methotrexate	487 (100)	488 (100)	330 (100)
Hydroxychloroquine	44 (9)	30 (6)	32 (10)
Diclofenac	94 (19)	106 (22)	74 (22)

Abbreviations: BARI=baricitinib, ADA=adalimumab  
Source: adapted from JADV clinical study report, p. 2259

### Efficacy Results - Primary Endpoint

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Table 46 shows the percent of ACR20 responders at week 12 in JADV. Both the adalimumab and baricitinib treatment arms had a statistically higher percent of ACR20 responders at week 12.

**Table 46. JADV: percent ACR20 responders at week 12 using non-responder imputation**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
ACR20 response, NRI, n (%)	196 (4)	339 (70)	202 (61)		
Difference in response rate (95% CI)				29 (24, 35)	21 ( 14, 28)
OR (95% CI)				4 (3, 5)	2 (2,3)
p-value for OR				0.001	0.001

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, ADA=adalimumab, PBO=placebo, BARI=baricitinib, NRI=non-responder imputation, SD=standard deviation, OR=odds ratio, CI=confidence interval  
Source: adapted from JADV clinical study report, p. 265

Table 47 shows the mean percent change from baseline in tender joint count at week 12. Both the adalimumab and baricitinib treatment arms statistically significantly had improved tender joint counts at week 12 as compared to placebo.

**Table 47. JADV: tender joint count at week 12 (mean percent change from baseline)**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
Tender joint count, n	485	483	328		
Mean % change from baseline (SD)	-33 (53)	-60 (38)	-53 (42)		
LSM (SE)	-31.1 (2)	-57.3 (2)	-50.6 (3)		
LSMD (95% CI)				-26.2(-31.9, -20.6)	-19.6 (-25.8, -13.3)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, ADA=adalimumab, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADV clinical study report, p. 314

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Table 48 shows the mean percent change from baseline in swollen joint count at week 12. Both the adalimumab and baricitinib treatment arms statistically significantly had improved swollen joint counts at week 12 as compared to placebo.

**Table 48. JADV: swollen joint count at week 12 (mean percent change from baseline)**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
Swollen joint count, n	485	483	328		
Mean % change from baseline (SD)	-38 (49)	-65 (35)	-61 (38)		
LSM (SE)	-35.7 (2)	-62.9 (2)	-58.8 (2)		
LSMD (95% CI)				-27.2 (-32.3, -22.1)	-23.1 (-28.8, -17.4)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, ADA=adalimumab, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADV clinical study report, p. 316

Table 49 shows the mean percent change from baseline in patient's assessment of pain on a 100 point visual analogue scale. Baricitinib showed a statistically significant improvement from baseline for patient assessment of pain; however, adalimumab did not.

**Table 49. JADV: Patient assessment of pain at week 12 (mean percent change from baseline)**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
Patient assessment of pain, n	484	482	327		
Mean % change from baseline (SD)	-20 (60)	-46 (71)	-32 (130)		
LSM (SE)	-19.1 (4)	-43.1 (4)	-29.7 (5)		
LSMD (95% CI)				-24 (-34.5, -13.5)	-10.5 (-22.3, 1.2)
P value				0.001	0.079

Abbreviations: PBO=placebo, BARI=baricitinib, ADA=adalimumab, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

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Source: adapted from JADV clinical study report, p. 322

Table 50 shows the percent change from baseline in patient’s global assessment of disease activity at week 12. Both adalimumab and baricitinib showed a statistically significant improvement in patient’s global assessment of disease activity when compared to placebo.

**Table 50. JADV: Patient’s global assessment of disease activity at week 12 (mean percent change from baseline)**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
Patient’s global assessment of disease activity, n	484	482	327		
Mean % change from baseline (SD)	-7 (149)	-42 (143)	-41 (49)		
LSM (SE)	-8.5 (6)	-39.8 (6)	-37 (7)		
LSMD (95% CI)				-31.3 (-47, -15.7)	-28.5 (-46, -11)
P value				0.001	0.002

Abbreviations: PBO=placebo, BARI=baricitinib, ADA=adalimumab, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADV clinical study report, p. 324

Table 51 shows the percent change from baseline in physician’s global assessment of disease activity at week 12. Both adalimumab and baricitinib showed a statistically significant improvement in physician’s global assessment of disease activity when compared to placebo.

**Table 51. JADV: physician’s global assessment at week 12 (mean percent change from baseline)**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
Physician’s global assessment of disease activity, n	482	479	325		
Mean % change from	-38 (40)	-60 (29)	-51 (36)		

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baseline (SD)					
LSM (SE)	-35 (2)	-57.1 (2)	-48 (2)		
LSMD (95% CI)				-22.1 (-26.5, -17.7)	-13 (-17.9, -8.1)
P value				0.001	0.001

Abbreviations: PBO=placebo, BARI=baricitinib, ADA=adalimumab, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADV clinical study report, p. 329

Table 52 shows the percent change from baseline in HAQ-DI at week 12. Both adalimumab and baricitinib showed a statistically significant improvement in HAQ-DI when compared to placebo.  
**Table 52. JADV: HAQ-DI at week 12 (mean percent change from baseline)**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
HAQ-DI, n	479	478	319		
Mean % change from baseline (SD)	-22 (42)	-44 (37)	-36 (38)		
LSM (SE)	-20.5 (2)	-42.8 (2)	-35.4 (2)		
LSMD (95% CI)				-22.3 (-27.3, -17.3)	-14.9 (-20.5, -9.3)
P value				0.001	0.001

Abbreviations: HAQ-DI=Health Assessment Questionnaire-Disability Index, PBO=placebo, BARI=baricitinib, ADA=adalimumab, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADV clinical study report, p. 333

Table 53 shows the percent change from baseline in hs-CRP at week 12. Both adalimumab and baricitinib showed a statistically significant improvement in hs-CRP when compared to placebo.

**Table 53. JADV: hs-CRP at week 12 (mean percent change from baseline)**

	PBO (N=488)	BARI 4 mg (N=487)	ADA (N=330)	BARI 4 mg vs PBO	ADA vs PBO
Hs-CRP, n	485	483	328		
Mean % change from baseline (SD)	56 (328)	-46 (105)	-24 (246)		
LSM (SE)	43.4 (12)	-54.2 (12)	-32.3 (14)		
LSMD (95% CI)				-97.5 (-128.1, -67)	-75.7 (-109.7, -41.7)

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P value				0.001	0.001
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Abbreviations: hs-CRP=high sensitivity C-reactive protein, PBO=placebo, BARI=baricitinib, ADA=adalimumab, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADV clinical study report, p. 337

**Data Quality and Integrity - Reviewers' Assessment**

The data quality and integrity appeared adequate. For efficacy, no audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites.

**Efficacy Results - Secondary and other relevant endpoints**

Table 54 shows the results of the primary endpoint and the gated secondary endpoints. The baricitinib treatment arm showed statistically significant efficacy in all of the secondary endpoints versus placebo. This included a statistically superior mean change from baseline in modified total Sharp score. Baricitinib was also compared to adalimumab in the gated analysis. Baricitinib had a better response in both ACR20 at week 12 and mean change from baseline in DAS20-hsCRP when compared to adalimumab.

**Table 54. JADV: Primary endpoint and key gated secondary endpoints**

	PBO (N=488)	BARI 4 mg (N=487)	adalimumab (N=330)	BARI 4 mg vs PBO	BARI 4 mg vs adalimumab
ACR20, n (%) OR 95% CI p-value	196 (40)	339 (70)		3.6 (2.7, 4.7) 0.001	
mTSS (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	450 0.9 (0.01)	469 0.4 (0.01)		-0.49 (0.12) (-0.7, -0.3) 0.001	
HAQ-DI (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	484 -0.3 (0.03)	485 -0.7 (0.03)		-0.3 (0.03) (-0.4, -0.3) 0.001	
DAS-28 hsCRP (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value	484 -1 (0.06)	485 -2.2 (0.06)		-1.2 (0.07) (-1.4, -1.1) 0.001	
SDAI≤3.3, n (%)	9 (2)	41 (8)			

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p-value				0.001	
ACR20, n (%) OR 95% CI		339 (70)	202 (61)		8.4 (1.7, 15.1)
DAS-28 hsCRP (baseline Δ) n LSM (SE) LSM difference (SE) 95% CI p-value		485 -2.2 (0.06)	326 -1.9 (0.07)		-0.3 (0.08) (-0.4, -0.12) 0.001
Duration morning joint stiffness n median 95% CI Median difference 95% CI P –value	479 60 (60, 75)	479 27 (20, 30)		-20 (-28.6, -12.9) 0.001	
Severity morning joint stiffness n LSM (SE) LSM difference (SE) 95% CI p-value	476 4 (0.1)	478 3 (0.1)		-1 (0.13) (-1.3, -0.8) 0.001	
Worst tiredness n LSM (SE) LSM difference (SE) 95% CI p-value	476 4.3 (0.1)	478 3.6 (0.1)		-0.8 (0.13) (-1, 0.5) 0.001	
Worst joint pain n LSM (SE) LSM difference (SE) 95% CI p-value	476 4.6 (0.1)	478 3.4 (0.1)		-1.2 (0.13) (-1.4, -0.9) 0.001	

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, mTSS=modified total Sharp score, SDAI= simplified disease activity index, HAQ-DI=Health Assessment Questionnaire-Disability Index, DAS-28=disease activity scale in 28 joints, hs-CRP=high sensitivity C-reactive protein, PBO=placebo, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, OR=odds ratio, CI=confidence interval

Source: adapted from JADV clinical study report, p. 295-299

*Reviewer’s comment: The applicant pre-specified several gated analyses for baricitinib against both placebo and adalimumab. Baricitinib achieved a statistically significant response within all the secondary endpoints measured.*

See Section 7 and Section 8 for additional discussion of efficacy and safety results, respectively.

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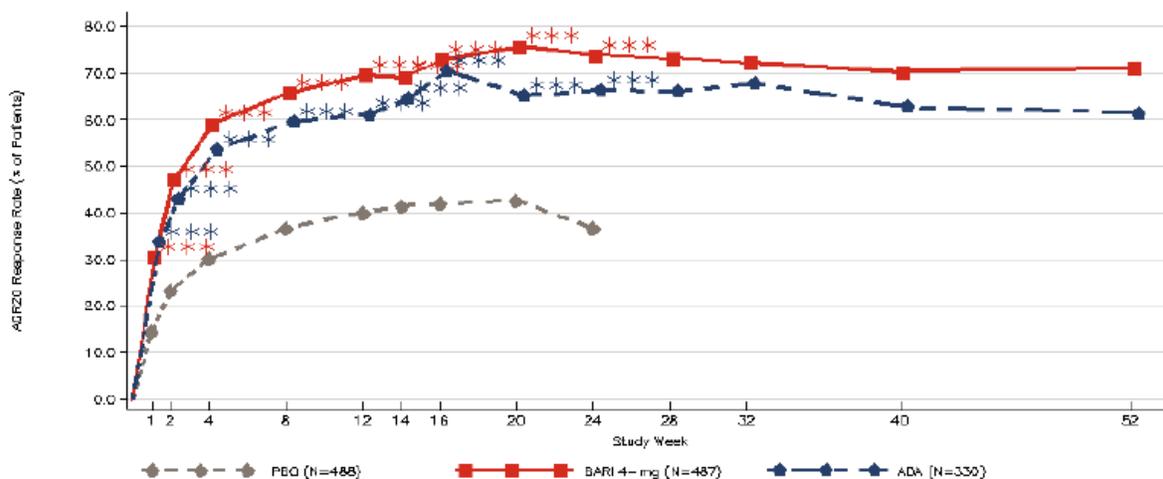
## Dose/Dose Response

Only the 4 mg dose of baricitinib was evaluated in this study.

## Durability of Response

Figure 9 shows the percentage of patients who achieved ACR20 response over the 52 week period. Both the adalimumab and baricitinib study arms separated from placebo as early as week 2 and appeared to maintain response through the 52 week period.

**Figure 9. JADV: percent of ACR20 responders to week 52 using non-responder imputation**



Source: JADV clinical study report, p. 303

*Reviewer's comment: JADV was only placebo controlled for 24 weeks and was an open label study following the 24 week period. Therefore, it is difficult to make conclusions regarding time points beyond the 24 week period.*

## Persistence of Effect

No analysis to determine persistence of effect. It would be expected that baricitinib would be administered chronically for the indication of rheumatoid arthritis.

## Additional Analyses Conducted on the Individual Trial

Information requests were sent to the Applicant to perform efficacy analyses that were requested by the Division prior to submission of the NDA. See Dr. Abugov's statistical review for details on the additional requested analyses.

## 6.4. JADZ

### 6.4.1. Study Design

#### Overview and Objective

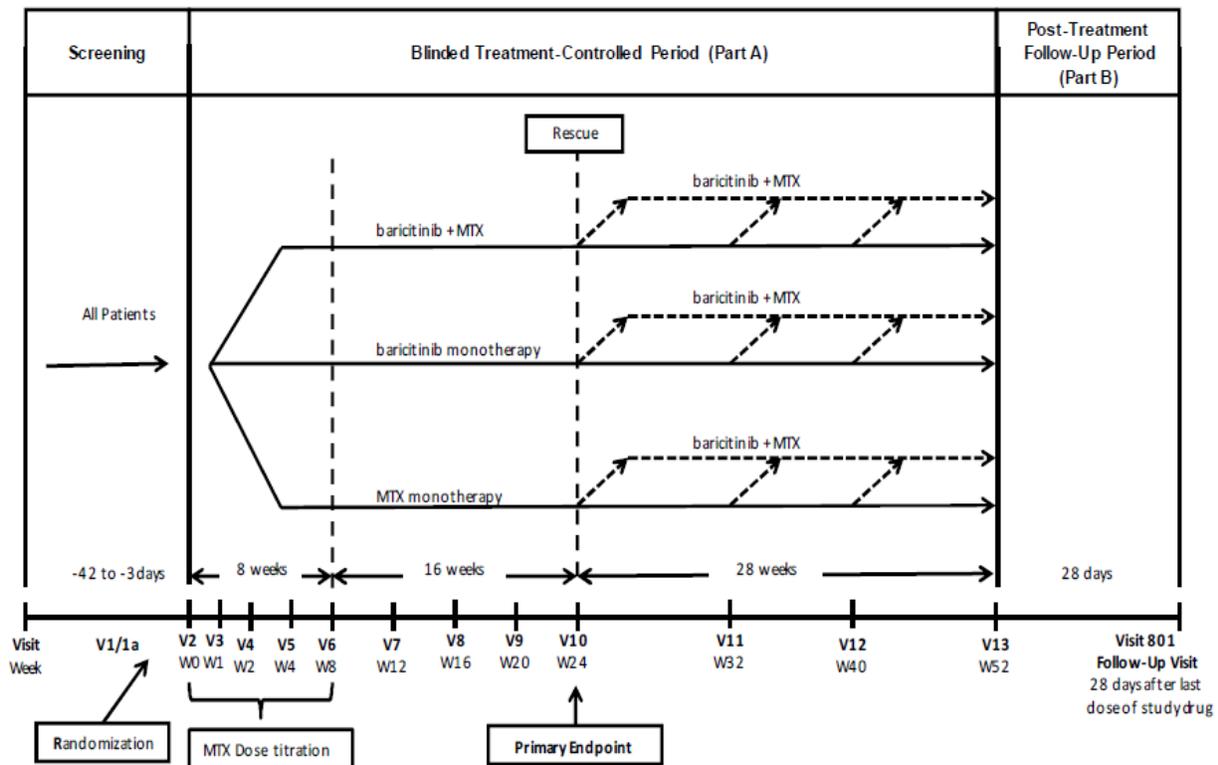
The primary objective of the study was to determine whether baricitinib monotherapy was non-inferior to MTX monotherapy in the treatment of patients with moderately to severely active RA who had limited or no treatment with MTX and were naïve to other conventional or biologic DMARDs, as assessed by the proportion of patients who achieved ACR20 at Week 24.

#### Trial Design

Basic study design: Study JADZ was a phase 3, randomized, double blind, multi-center active comparator study that compared methotrexate monotherapy to baricitinib monotherapy and to the combination of baricitinib and methotrexate. Patients in the study were those who had moderate to severe RA with an insufficient response to methotrexate and who were naïve to the use of a biologic. The study was controlled with methotrexate for 52 weeks with provisions for escape. All arms in the study escaped to combination therapy with baricitinib and methotrexate. The primary endpoint for JADZ was ACR20 response at Week 12.

There were some concerns with the study design. Of note, the patients who were enrolled were patients who had previously had an inadequate response to methotrexate. Therefore the efficacy for methotrexate in this study would be expected to be lower than in patients who are naïve to methotrexate. Provisions to escape to standard of care were not made in this study and the earliest time for escape was 24 weeks. Patients who attempted to escape from the combination baricitinib and methotrexate arm would receive the same baricitinib and methotrexate combination.

#### Figure 10. JADZ Study Design



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

Source: JADZ clinical study report, p. 102

Choice of control groups: In study JADZ, the Applicant chose to use optimized methotrexate with dose titration as the comparator. Methotrexate is a standard initial therapy in the treatment of rheumatoid arthritis. Methotrexate dose was titrated from Week 0 through Week 8 of the study to a maximum dose of 20 mg per week. Initial rescue from therapy occurred at Week 24.

Diagnostic criteria: The patient population for Study JADZ consisted of patients with moderately to severely active early RA who had previously had limited or no treatment with MTX and were naive to other conventional or biologic DMARDs. Patients were diagnosed with RA based on ACR/EULAR 2010 Criteria for the Classification of RA (see Appendix 13.2).

Inclusion criteria: Patients were eligible for participation only if they were adults with a diagnosis of adult-onset RA as defined by the ACR/EULAR 2010 Criteria for the Classification of RA, had documented history of positive rheumatoid factor and/or cyclic citrullinated peptide

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(CCP) antibody test, had moderately to severely active RA defined as the presence of at least 6/68 tender joints and at least 6/66 swollen joints, had a C-reactive protein (or hsCRP) measurement  $\geq 1.2$  x the upper limit of normal (ULN) based on the most recent data (if available), and had previously had limited or no treatment with MTX.

Exclusion criteria: Patients were excluded from participation if they were receiving prohibited RA therapies, had a recent history of infection or tested positive for tuberculosis (TB) or other serious infections, were immunocompromised, had specific abnormal laboratory results, or had comorbidities that put patients at risk when taking study drug.

Dose selection: The Applicant selected doses for JADZ based on efficacy, safety, and PK data from the phase 2 studies JADC and JADA. The Applicant selected the 4 mg daily dose for study JADZ. The Applicant stated that in study JADA, the 1 mg and 2 mg daily doses were biologically active but did not produce adequate response for ACR50 and ACR70 at Week 12 of JADA. Patients with renal impairment defined as eGFR of  $<60$  mL/min/1.73 m<sup>2</sup> were given a dose of 2 mg daily based on previous data that baricitinib exposure increases with decreased renal function.

Study treatments:

**Table 55. JADZ: treatments administered**

Treatment group	Initial treatment administered	Rescue treatment administered
Baricitinib plus methotrexate	<ul style="list-style-type: none"> <li>Baricitinib 4 mg daily tablet</li> <li>Methotrexate oral capsules weekly</li> </ul>	<ul style="list-style-type: none"> <li>Baricitinib 4 mg daily tablet</li> <li>Methotrexate oral capsules weekly</li> </ul>
Baricitinib monotherapy	<ul style="list-style-type: none"> <li>Baricitinib 4 mg daily tablet</li> <li>Methotrexate placebo oral capsules weekly</li> </ul>	<ul style="list-style-type: none"> <li>Baricitinib 4 mg daily tablet</li> <li>Methotrexate oral capsules weekly</li> </ul>
Methotrexate monotherapy	<ul style="list-style-type: none"> <li>Baricitinib placebo daily tablet</li> <li>Methotrexate oral capsules weekly</li> </ul>	<ul style="list-style-type: none"> <li>Baricitinib 4 mg daily tablet</li> <li>Methotrexate oral capsules weekly</li> </ul>

Source: adapted from JADZ clinical study report, p. 104

Assignment to treatment: Patients who met all criteria for enrollment were randomized in a 4:3:4 ratio (baricitinib plus MTX: baricitinib monotherapy: MTX monotherapy) to double-blind treatment at Week 0 (Visit 2). Randomization was stratified by region and the presence of joint erosions at baseline. Assignment to treatment groups was determined by a computer-generated random sequence that used an interactive voice-response system (IVRS).

Blinding: This was a double-blind study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the

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duration of the study. Baricitinib and its placebo and MTX and its placebo were identical in color, shape, smell, and taste. Assignment to treatment groups was determined by a computer-generated random sequence using an IVRS. Emergency unblinding for AEs was performed through an IVRS.

There were 2 planned database locks for this study: a primary database lock after all patients completed Week 24 (Visit 10) and a final data lock at the end of the study. For the primary database lock, by-visit data through Week 24 (Visit 10) were locked; however, ongoing log-type entry forms for ongoing patients with AEs and patients that used concomitant medications remained unlocked. Analyses were conducted on the primary and key secondary endpoints (included in the gatekeeping strategy) except for structure (mTSS), other efficacy measures, health outcomes measures, and safety endpoints that were collected through Week 24 (Visit 10). This analysis was not considered an interim analysis conducted by the data monitoring committee (DMC). Unblinding after the final database lock occurred on 29 September 2015. The final analysis included all data that was collected during the study. All investigators, study site personnel, and patients remained blinded to treatment assignments until the final database lock.

Dose modification, dose discontinuation: Study drug was discontinued for significant abnormalities in liver function tests; white blood cell, lymphocyte, and neutrophil counts; and hemoglobin levels. Study drug was also discontinued if the patient developed symptomatic herpes zoster or a serious infection that, in the opinion of the investigator, warranted discontinuation. Patients receiving baricitinib in JADZ with eGFR of <60 mL/min/1.73 m<sup>2</sup> were given a dose of 2 mg daily.

Administrative structure: The Sponsor for JADZ was Eli Lilly and company. JADZ was conducted by 197 rheumatologists at 198 study sites. One principal investigator conducted the study at 2 separate study sites. **Table 56** shows the additional organizations involved in the conduct of the study and role.

**Table 56. JADZ: Administrative structure**

Role	Name of responsible company/organization
Sponsor, randomization, study report authors, study master file, statistical analysis, data management, medical and study operations oversight	<ul style="list-style-type: none"> <li><b>Eli Lilly and Company</b></li> </ul>
Statistical analysis (clinical study report tables, figures, and listings)	(b) (4)

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Statistical analysis reporting database (ADaM) development	(b) (4)
Data management, data entry and validation, patient narratives	
Study monitoring	
Laboratory assessments	
Manufacturing sites of medicinal product	
Site of release in European Union	
Other contracted services	(b) (4)
	<ul style="list-style-type: none"> <li>• Eli Lilly European Clinical Trials Services S.A.</li> </ul>

Source: adapted from JADZ study report, p. 93

Procedures and schedule: See Appendix 13.3 for schedule of visits

Concurrent medications: All medications (other than study drug) taken during the study were recorded on the case report form (CRF). Patients were instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements. Any use of excluded medication as stated in the protocol was a violation of the protocol and was documented.

Concomitant use of analgesics was permitted. Concomitant use of NSAIDs was permitted only if the patient was on a stable dose for at least 6 weeks prior to planned randomization. Prednisone (or equivalent) at doses up to 10-mg per day was allowed during this study but must have been maintained at stable levels from 6 weeks prior to randomization and through the treatment phase of the study unless a patient received rescue therapy.

Treatment compliance:

Patient compliance with study medication was assessed from the randomization visit (Week 0) to Visit 13 (Week 52) during the treatment period. Compliance was summarized from randomization until rescue or end of treatment using the mITT population. Compliance to

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baricitinib was measured as the ratio of actual total tablets used divided by expected total tablets used multiplied by 100. Compliance to methotrexate was measured as the ratio of actual total capsules used divided by expected total capsules used multiplied by 100.

A patient was considered noncompliant if he or she missed >20% of the prescribed doses during the study, unless the patient's study drug was withheld by the investigator. For patients who had their treatment temporarily interrupted by the investigator, the periods of time that dose was withheld were taken into account in the compliance calculation as outlined below.

Rescue medication: Rescue medication was available at Weeks 24, 30, and 42 of the study. The option of escape for all arms was the combination of baricitinib and methotrexate. Thus patients who were already in the baricitinib and methotrexate combination arm did not receive a change in treatment upon rescue.

Subject completion, discontinuation, or withdrawal: Patient disposition was summarized using the mITT population. Frequency counts and percentages of patients who completed or discontinued early from the study were summarized separately by treatment group for patients who were not rescued and for patients who were rescued, along with their reason for study discontinuation. Among patients who completed the study, frequency counts and percentages of patients who entered Study JADY, completed the post-treatment follow-up visit, or did not complete the follow-up visit are presented by treatment group. Among patients who discontinued early from the study, frequency counts and percentages of patients who completed the post-treatment follow-up visit or did not complete the follow-up visit are presented by treatment group. Reasons for not completing the post-treatment follow-up visit are also presented.

For handling of dropouts or missing data, the Applicant used several strategies which included non-responder imputation (NRI), modified baseline observation carried forward (mBOCF), modified last observation carried forward (mLOCF), and baseline observation carried forward (BOCF).

All patients who discontinued the study or permanently discontinued the study treatment at any time for any reason were defined as non-responders for the NRI analysis for categorical variables from the time of discontinuation and onward.

The mBOCF method was used for the analysis of key secondary continuous endpoints unless otherwise stated. For patients who discontinued the study or permanently discontinued the study treatment because of an AE, including death, or because of abnormal laboratory results reported as AEs, the baseline observation was carried forward to subsequent time points for evaluation. For patients who discontinued the study or permanently discontinued the study treatment for reason(s) other than an AE, the last non-missing post-baseline observation prior

to discontinuation was carried forward to subsequent time points for evaluation.

For all continuous measures that included safety analyses, the mLOCF was a general approach to impute missing data unless otherwise specified. For patients who received rescue therapy starting from Week 24, the last non-missing observation at or before rescue was carried forward to subsequent time points for evaluation. For all other patients who discontinued from the study or permanently discontinued the study treatment for any reason, the last non-missing post-baseline observation before discontinuation was carried forward to subsequent time points for evaluation.

The BOCF method was used for the analysis of key secondary continuous endpoints at Week 24 as a sensitivity analysis to satisfy specific regulatory requests. For patients who discontinued the study or permanently discontinued the study treatment, the baseline observation was carried forward to subsequent time points for evaluation.

### Study Endpoints

The primary efficacy measure was the proportion of patients who achieved ACR20 at Week 24 based on the change in ACR response values from baseline. ACR20 was defined as at least 20% improvement from baseline in the following ACR Core Set variables:

- Tender joint count (68 joint count)
- Swollen joint count (66 joint count)
- An improvement of  $\geq 20\%$  from baseline in at least 3 of the following 5 assessments:
  - Patient's Assessment of Pain (VAS)
  - Patient's Global Assessment of Disease Activity (VAS)
  - Physician's Global Assessment of Disease Activity (VAS)
  - Patient's assessment of physical function as measured by the HAQ-DI
  - Acute phase reactant as measured by hsCRP

The primary efficacy analysis was to test the noninferiority of baricitinib monotherapy to MTX monotherapy in the proportion (or percentage) of patients that achieved ACR20 at Week 24 using the mITT population.

Assessment of ACR20 as a primary efficacy measure in rheumatoid arthritis is well established and has been used by the FDA as the primary endpoint for approval of several medications used for RA. The composite measure places an emphasis on change in joint counts. Also incorporated into the ACR20 are global measures of assessment by both the patient and provider.

Other Key secondary endpoints measured were:

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*: 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*: 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. An alternative equation 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.
- *Simplified Disease Activity Index (SDAI)*: integrates measures of the physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI ranges from 0.1 to 86. Disease remission has been defined as an SDAI score  $\leq 3.3$  and low disease activity has been considered as an SDAI score  $\leq 11$ . 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)
- *Van der Heijde modified Sharp Score*: 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. 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

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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.

### **Statistical Analysis Plan**

#### Sample size

The Applicant estimated that 550 patients (200 on baricitinib plus methotrexate, 150 on baricitinib, 200 on methotrexate monotherapy) would be needed to provide 89% power for a non-inferiority analysis based on a non-inferiority margin of 12% where a response rate of 60% for baricitinib monotherapy and 55% for methotrexate monotherapy was assumed based on a 1-sided significance of 0.025.

The sample size was also 79 to 80% power to test the superiority of baricitinib plus methotrexate versus methotrexate monotherapy in ACR20 response at week 24 based on a 2-sided Chi Square test at a significance level of 0.05 where assumptions were that response rates were 68.5% for baricitinib plus methotrexate versus 55% for methotrexate monotherapy.

#### Analysis populations

The analysis populations were defined in the JADZ protocol as follows:

**Modified-intent-to-treat population:** This population used the full analysis set and included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment group they were randomized or assigned to per protocol. This population was used to conduct the main primary and secondary analyses.

**Per-protocol population:** This population included all modified-intent-to-treat patients who were deemed compliant with the protocol, who did not have important protocol deviations, and whose investigator site did not have significant GCP issues that required a report to regulatory agencies. This population was used to confirm the results of the modified-intent-to-treat population.

**Safety population:** The safety population was defined as all randomized patients who received at least one dose of study drug.

**Demographics and baseline characteristics:** Patient characteristics including demographics used

the modified-intent-to-treat population and included descriptive statistics such as number of patients, mean, standard deviation, median, minimum, and maximum for continuous measures. Frequency counts and percentages were reported for categorical measures.

Prior and concomitant medications: Summaries of previous and concomitant medications used for RA including methotrexate were based on the modified-intent-to-treat population. Previous medications and concomitant medications used for RA were summarized using frequency counts and percentages by WHO drug anatomical therapeutic chemical classification and treatment group. Concomitant therapy was summarized with data up to rescue and after the point of rescue.

#### Primary analysis

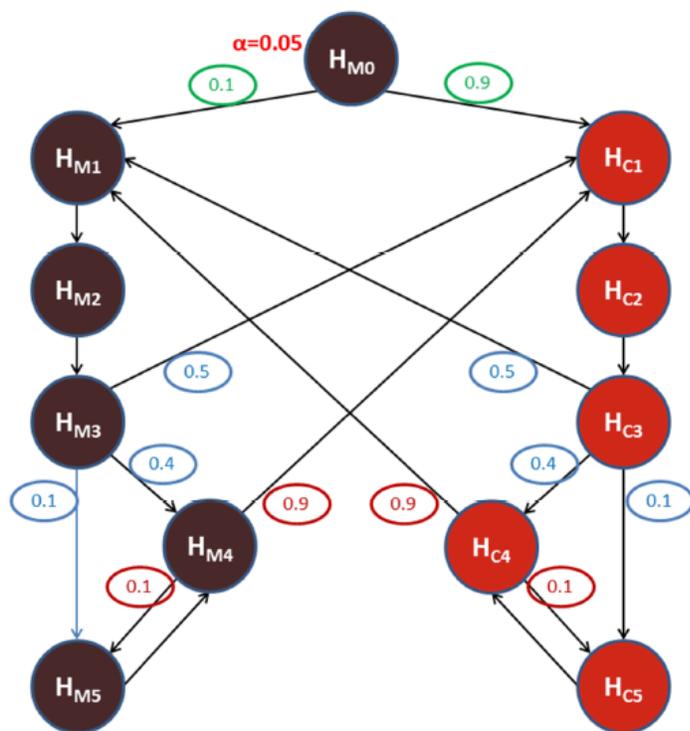
The primary efficacy analysis was to test the noninferiority of baricitinib monotherapy to MTX monotherapy in the proportion (or percentage) of patients achieving ACR20 at Week 24 using the mITT population. The PP population results were used as supportive evidence to the mITT results. A logistic regression model with treatment, region, and baseline joint erosion status (yes/no) in the model was used to test for a treatment difference between baricitinib monotherapy versus MTX monotherapy in the percentage of patients that achieved ACR20 response at Week 24.

There were a total of 11 hypotheses tested:

- 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
- 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  $\leq 3.3$  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  $\leq 3.3$  at Week 24, baricitinib plus MTX vs MTX monotherapy

To account for multiple testing of the 11 hypotheses, a sequentially rejective weighted Bonferroni multiple testing procedure was used as shown in Figure 11.

**Figure 11. JADZ: graphical multiple testing procedure for statistical gatekeeping**



Source: JADZ clinical study report, p. 156

For handling of dropouts or missing data, the Applicant used several strategies which included non-responder imputation (NRI), modified baseline observation carried forward (mBOCF), modified last observation carried forward (mLOCF), and baseline observation carried forward (BOCF).

All patients who discontinued the study or permanently discontinued the study treatment at any time for any reason were defined as non-responders for the NRI analysis for categorical variables from the time of discontinuation and onward.

The mBOCF method was used for the analysis of key secondary continuous endpoints unless otherwise stated. For patients who discontinued the study or permanently discontinued the study treatment because of an AE, including death, or because of abnormal laboratory results reported as AEs, the baseline observation was carried forward to subsequent time points for evaluation. For patients who discontinued the study or permanently discontinued the study

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treatment for reason(s) other than an AE, the last non-missing post-baseline observation prior to discontinuation was carried forward to subsequent time points for evaluation.

For all continuous measures that included safety analyses, the mLOCF was a general approach to impute missing data unless otherwise specified. For patients who received rescue therapy starting from Week 24, the last non-missing observation at or before rescue was carried forward to subsequent time points for evaluation. For all other patients who discontinued from the study or permanently discontinued the study treatment for any reason, the last non-missing post-baseline observation before discontinuation was carried forward to subsequent time points for evaluation.

The BOCF method was used for the analysis of key secondary continuous endpoints at Week 24 as a sensitivity analysis to satisfy specific regulatory requests. For patients who discontinued the study or permanently discontinued the study treatment, the baseline observation was carried forward to subsequent time points for evaluation.

### **Protocol Amendments**

The JADZ protocol was amended 4 times as follows

- The exclusion criteria was modified in order to include the time period to avoid pregnancy after discontinuing methotrexate
- Allowed for folic acid to be administered concomitantly with methotrexate at a dose of 1 mg daily.
- Amendment made through voluntary harmonization procedure at the request of European regulatory authorities
- Several changes with the 4th amendment including
  - Selected gated secondary objectives and analysis were revised
  - Allowed for re-testing of hsCRP and TSH during screening
  - Allowed T.SPOT.TB test to be used for tuberculosis testing
  - Specified gout as an exclusion criteria

### **Data Quality and Integrity: Sponsor's Assurance**

The Applicant did the following to ensure accurate, complete, and reliable data:

- Provide instructional material to the study sites
- Sponsor a start-up session to instruct investigators and study coordinators
- Periodic visits were made to the study sites
- Available for consultation with study site personnel
- Reviewed and evaluated case report form (CRF) data and used standard computer edits to detect errors in data collection

- Quality review of the reporting database was performed

#### 6.4.2. Study Results

##### Compliance with Good Clinical Practices

JADZ was conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines including Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- The International Conference of Harmonization (ICH) Good Clinical practices (GCP) Guidelines [E6]
- Applicable laws and regulations

##### Financial Disclosure

Eli Lilly and Company has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Table Appendix section 13.4 for a full review of Eli Lilly's financial disclosure.

##### Patient Disposition

JADZ was a 52 week study with a 28 day post-treatment follow-up period. At the beginning of the treatment period patients were randomized in a 4:3:4 ratio to methotrexate monotherapy, baricitinib monotherapy, or baricitinib plus methotrexate.

1188 patients were screened of which 588 (50%) were randomized. 210 patients received at least one dose of methotrexate monotherapy, 159 received at least one dose of baricitinib monotherapy and 215 patients received at least one dose of baricitinib plus methotrexate.

**Table 57. JADZ: Disposition of patients**

	Methotrexate monotherapy (N=210)	Baricitinib monotherapy (N=159)	Baricitinib plus methotrexate (N=215)
Discontinued before week 24	28 (13%)	14 (9%)	23 (11%)
Discontinued between week 24-52	44 (24%)	21 (14%)	40 (19%)
Completed through week 52	140 (76%)	131 (86%)	169 (80%)

Source: JADZ clinical study report, p. 202-203

### Protocol Violations/Deviations

Table 58 shows the protocol deviations that occurred during JADZ. Over 20% of patients in each group had protocol deviations. The majority of these deviations were changing dose of analgesic, corticosteroid, or NSAID without an adverse event occurring or prior to rescue.

**Table 58. JADZ: Important Protocol Deviations**

	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	Total (N=584)
Patients with ≥1 important protocol deviation, n (%)	64 (31)	35 (22)	53 (25)	152 (26)
Use of any new or dose change with corticosteroid in absence of AE or prior to rescue	23 (11)	11 (7)	22 (10)	56 (10)
Use of any new or dose change with NSAID/analgesic in absence of AE or prior to rescue	16 (8)	6 (4)	15 (7)	37 (6)

Abbreviations: MTX=methotrexate, BARI=baricitinib, AE=adverse event, NSAID=non-steroidal anti-inflammatory drug  
Source: JADZ clinical study report, p. 208

*Reviewer’s comment: There were several protocol violations in all groups of study JADZ. The patients were not allowed to switch therapy until week 24 of the study which may have led to some of the use of prohibited concomitant medications. The deviations due to change in prohibited concomitant medications appeared similar among study arms.*

### Table of Demographic Characteristics

**Table 59** shows the demographics of patients who participated in study JADZ. The patients were predominantly female, middle aged, and over 50% of patients were Caucasian which was similar to other clinical trials performed in RA. Approximately 20% of the patients enrolled in the study were from the United States and Canada.

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**Table 59. JADZ: Demographics**

Demographic Parameters	Control Group MTX (N=210) n (%)	Treatment Group (N=374)		Total (N=584) n (%)
		BARI 4 mg (N=159) n (%)	BARI 4 mg+MTX (N=215) n (%)	
<b>Sex</b>				
Male	62 (29.5)	38 (23.9)	59 (27.4)	159 (27.2)
Female	148 (70.5)	121 (76.1)	156 (72.6)	425 (72.8)
<b>Age</b>				
Mean years (SD)	50.5 (13.4)	50.9 (13)	48.5 (13.5)	49.9 (13.4)
Median (years)	52	53	50	52
Min, max (years)	18, 79	20, 80	18, 77	18, 80
<b>Age Group</b>				
< 65 years	174 (82.9)	133 (83.6)	194 (90.2)	501 (85.8)
≥ 65 years	36 (17.1)	26 (16.4)	21 (19.8)	83 (14.2)
<b>Race</b>				
White	128 (61)	98 (61.6)	123 (57.2)	349 (59.8)
Black or African American	10 (4.8)	5 (3.1)	10 (4.7)	25 (4.3)
Asian	60 (28.6)	44 (27.7)	61 (28.4)	165 (28.3)
American Indian or Alaska Native	11 (5.2)	10 (6.3)	20 (9.3)	41 (7)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Multiple	1 (0.5)	2 (1.3)	1 (0.5)	4 (0.7)
<b>Region (optional)</b>				
United States & Canada	42 (20)	33 (20.8)	46 (21.4)	121 (20.7)
Rest of the World	40 (19)	30 (18.9)	40 (18.6)	110 (18.8)
Central & South America, Mexico	61 (29)	46 (28.9)	62 (28.8)	169 (28.9)
Europe	31 (14.8)	21 (13.2)	28 (13)	80 (13.7)
Japan	36 (17.1)	29 (18.2)	39 (18.1)	104 (17.8)

Abbreviations: MTX=methotrexate, BARI=baricitinib, SD=standard deviation

Source: adapted from JADZ clinical study report, p. 212-214

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

**Table 60** shows the baseline disease characteristics of patients in study JADZ. The patients had active disease with a mean swollen joint count of 16 in all groups. The time of RA diagnosis was relatively recent with diagnosis within one to two years of screening. Over a third of patients were on corticosteroids.

**Table 60. JADZ: Baseline disease**

Baseline disease Parameters	Control Group MTX (N=210)	Treatment Group (N=374)		Total (N=584)
		BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	
<b>Time from RA diagnosis (years)</b>				
Mean (SD)	1.3 (4.0)	1.9 (4.7)	1.3 (2.7)	1.4 (3.8)
Median	0.2	0.2	0.2	0.2
Min, max	0.02, 37.4	0.03, 30.7	0.02, 20.5	0.02, 37.4
<b>Tender joint count based on 68 joints</b>				
Mean (SD)	26.5 (15)	26.4 (14)	27.7 (15)	26.9 (15)
Median	23	24	26	24
Min, max	5, 68	6, 68	6, 68	5, 68
<b>Swollen joint count based on 66 joints</b>				
Mean (SD)	16.4 (11)	16.1 (9)	16.3 (10)	16.3 (10)
Median	14	14	14	14
Min, max	0, 57	5, 55	6, 49	0, 57
<b>Physician's global assessment of disease activity (0-100 mm)</b>				
N-obs	206	157	213	576
Mean (SD)	66.7 (17)	68.1 (17)	66.4 (17)	67 (17)
Median	68	69	70	69
Min, max	3, 100	20, 99	17, 98	3, 100
<b>Patient's global assessment of disease activity (0-100 mm)</b>				
N-obs	209	159	214	582
Mean (SD)	65.6 (24)	65 (22)	63.1 (24)	64.6

				(23)
Median	67	69	66	67.5
Min, max	0, 100	0, 100	1, 100	0, 100
<b>Patient's assessment of pain (0-100 mm)</b>				
N-obs	209	159	214	582
Mean (SD)	65.2 (24)	64.1 (22)	62.6 (23)	64 (23)
Median	67	68	66	67
Min, max	0, 100	0, 100	0, 100	0, 100
<b>High sensitivity C-reactive protein (mg/L)</b>				
Mean (SD)	22.3 (22)	23.8 (26)	24.3 (29)	23.4 (26)
Median	14.5	15.2	14.3	14.7
Min, max	0.2, 123.5	0.8, 210	0.4, 178.8	0.2, 210
<b>HAQ-DI</b>				
N-obs	209	159	214	582
Mean (SD)	1.67 (0.7)	1.64 (0.7)	1.58 (0.7)	1.63 (0.7)
Median	1.75	1.75	1.5	1.63
Min, max	0, 3	0, 3	0, 3	0, 3
<b>Current use of corticosteroid, n (%)</b>				
Yes	76 (36)	47 (30)	83 (39)	206 (35)
<b>Modified total sharp score</b>				
N-obs	192	154	200	546
Mean (SD)	11.8 (22)	13.3 (27)	11.4 (20)	12.1 (23)
Median	4	3	4	3.5
Min, max	157	172.5	124.5	172.5

Abbreviations: BARI=baricitinib, MTX=methotrexate, SD=standard deviation, N-obs= number observed, HAQ-DI=Health Assessment Questionnaire-Disability Index, hs-CRP=high sensitivity C-reactive protein  
Source: JADZ clinical study report, p. 214-225

*Reviewer's comment: The patients in JADZ had relatively new disease as well as active disease as evidence by hs-CRP, patient and physician reported measures, and tender/swollen joint counts. Over a third of the patients were on corticosteroids. The patients in JADZ were representative of an active RA population.*

#### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Few patients had treatment compliance less than 80% with 9 (4%) patients in the methotrexate group, 4 (3%) in the baricitinib monotherapy group, and 6 (3%) in the baricitinib and methotrexate combination group.

**Efficacy Results - Primary Endpoint**

**Table 61** shows ACR20 response at week 24 in the modified intent to treat population in study JADZ. Patients received either optimized methotrexate therapy, baricitinib 4 mg daily alone, or a combination of optimized methotrexate and baricitinib 4 mg daily. Patients who received baricitinib alone or combination of methotrexate and baricitinib had a higher percentage of patients who had ACR20 response compared to patients who received methotrexate alone. The patients who received baricitinib alone had similar ACR20 response rates compared to patients who received combination of baricitinib and methotrexate.

**Table 61. JADZ: ACR20 response using non-responder imputation at week 24**

	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg+MTX vs BARI 4 mg
ACR20 response, NRI, n (%)	130 (62)	122 (77)	168 (78)			
Difference in response rate (95% CI)				15 (5.5,24.1)	16 (7.7, 24.8)	1.4 (-7.2, 10 )
OR (95% CI)				2 (1.3, 3.2)	2 (1.4, 3.4)	1 (0.7, 1.8)
p-value for OR				0.003	0.001	0.746

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, MTX=methotrexate, BARI=baricitinib, OR=odds ratio, CI=confidence interval

Source: adapted from JADZ clinical study report, p. 248

*Reviewer’s comment: A higher percentage of patients on baricitinib 4 mg daily had ACR20 response as compared to methotrexate. The same was seen with combination therapy of 4 mg baricitinib and methotrexate when compared to methotrexate. The results suggest that baricitinib is non-inferior to methotrexate. The Applicant tested for superiority of baricitinib to methotrexate monotherapy in their secondary analyses.*

**Table 62, Table 63, Table 64, Table 65, Table 66, Table 67, and Table 68** show the components of the ACR20 by core set measure at week 24. **Table 62** shows the mean percent change from baseline in tender joint count. Both baricitinib monotherapy and combination therapy with baricitinib and methotrexate treatment arms improved tender joint counts compared to methotrexate monotherapy. Combination therapy with methotrexate and baricitinib was not superior to baricitinib monotherapy in improving tender joint counts.

**Table 62. JADZ: Percent change in tender joint count at Week 24**

	MTX	BARI 4 mg	BARI 4	BARI 4 mg	BARI 4	BARI 4 mg+MTX vs
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	(N=210)	(N=159)	mg+MTX (N=215)	vs MTX	mg+MTX vs MTX	BARI 4 mg
Tender joint count, n	205	159	210			
Mean % change from baseline (SD)	-55 (49)	-71 (34)	-75 (35)			
LSM (SE)	-54.9 (3)	-71.3 (3)	-75.4 (3)			
LSMD (95% CI)				-16.4 (- 24.8, -8)	-20.5 (- 28.3, -12.7)	-4.1 (-12.5, 4.2)
P value				0.001	0.0001	0.331

Abbreviations: MTX=methotrexate, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADZ clinical study report, p. 281

**Table 63** shows the mean percent change from baseline in swollen joint count. Both baricitinib monotherapy and combination therapy with baricitinib and methotrexate treatment arms improved tender joint counts compared to methotrexate monotherapy. Combination therapy with methotrexate and baricitinib was not superior to baricitinib monotherapy in improving swollen joint counts.

**Table 63. JADZ: Percent change in swollen joint count at week 24**

	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg+MTX vs BARI 4 mg
Swollen joint count, n	204	159	210			
Mean % change from baseline (SD)	-61.4 (48.3)	-78.2 (33.2)	-79.3 (30.1)			
LSM (SE)	-61.6 (2.7)	-78.6 (3.1)	-79.6 (2.7)			
LSMD (95% CI)				-17 (-24.9, - 9.1)	-18 (-25.4, - 10.7)	-1 (-8.9, 6.8)
P value				0.001	0.001	0.797

Abbreviations: MTX=methotrexate, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADZ clinical study report, p. 285

**Table 64** shows the mean percent change from baseline in patient's assessment of pain on a visual analogue scale of 0 to 100. Both baricitinib monotherapy and combination therapy with baricitinib and methotrexate treatment arms improved patient's assessment of pain compared

to methotrexate monotherapy. Combination therapy with methotrexate and baricitinib was not superior to baricitinib monotherapy in improving patient’s assessment of pain.

**Table 64. JADZ: Percent change in patient’s assessment of pain, VAS (0-100) at week 24**

	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg+MTX vs BARI 4 mg
Patients assessment of pain, n	202	158	208			
Mean % change from baseline (SD)	-39.5 (68.6)	-57.4 (44.9)	-55 (95.3)			
LSM (SE)	-42 (5.2)	-61 (5.8)	--59.6 (5.1)			
LSMD (95% CI)				-19 (-33.9, - 4.1)	-17.5 (- 31.4, -3.7)	1.4 (-13.4, 16.3)
P value				0.013	0.014	0.848

Abbreviations: MTX=methotrexate, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source adapted: from JADZ clinical study report, p. 289

**Table 65** shows the mean percent change from baseline in patient’s global assessment of disease activity on a visual analogue scale of 0 to 100. Both baricitinib monotherapy and combination therapy with baricitinib and methotrexate treatment arms improved patient’s assessment of disease activity compared to methotrexate monotherapy. Combination therapy with methotrexate and baricitinib was not superior to baricitinib monotherapy in improving patient’s assessment of disease activity.

**Table 65. JADZ: patient global assessment of disease activity, VAS (0-100) at week 24**

	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg+MTX vs BARI 4 mg
Patient global assessment of disease activity, n	202	158	209			
Mean % change from baseline	-8.8 (330.6)	-54.4 (70.5)	-51.5 (71.4)			

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(SD)						
LSM (SE)	-11.9 (14.2)	-59.8 (16)	--61.6 (14)			
LSMD (95% CI)				-48 (-89, -6.9)	-49.8 (-87.9, -11.6)	-1.8 (-42.6, 38.9)
P value				0.023	0.011	0.931

Abbreviations: MTX=methotrexate, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from clinical study report, p. 293

**Table 66** shows the mean percent change from baseline in physician’s global assessment of disease activity on a visual analogue scale of 0 to 100. Both baricitinib monotherapy and combination therapy with baricitinib and methotrexate treatment arms improved physician’s assessment of disease activity compared to methotrexate monotherapy. Combination therapy with methotrexate and baricitinib was not superior to baricitinib monotherapy in improving physician’s assessment of disease activity.

**Table 66. JADZ: physician global assessment of disease activity, VAS (0-100) at week 24**

	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg+MTX vs BARI 4 mg
Physician global assessment of disease activity, n	201	157	208			
Mean % change from baseline (SD)	-52.9 (67.4)	-73.9 (24)	-72.5 (33.9)			
LSM (SE)	-53 (3.4)	-73.4 (3.8)	--72.9 (3.3)			
LSMD (95% CI)				-20.4 (-30.1, -10.7)	-19.9 (-28.9, -10.9)	0.5 (-9.1, 10.1)
P value				0.001	0.001	0.917

Abbreviations: MTX=methotrexate, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval

Source: adapted from JADZ clinical study report, p. 297

**Table 67** shows the mean percent change from baseline in the Health Assessment Questionnaire and Disability Index (HAQ-DI). Both baricitinib monotherapy and combination therapy with baricitinib and methotrexate treatment arms improved HAQ-DI compared to methotrexate monotherapy. Combination therapy with methotrexate and baricitinib was not superior to baricitinib monotherapy in improving HAQ-DI.

**Table 67. Percent change from baseline in HAQ-DI at week 24**

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	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg+MTX vs BARI 4 mg
HAQ-DI, n	201	155	207			
Mean % change from baseline (SD)	-45.8 (41.8)	-61.5 (52)	-63.5 (35.1)			
LSM (SE)	-46.3 (3.1)	-61.8 (3.5)	-64.1 (3)			
LSMD (95% CI)				-15.5 (- 24.4, -6.6)	-17.8 (- 26.1, -9.6)	-2.3 (-11.2, 6.5)
P value				0.001	0.001	0.605

Abbreviations: HAQ-DI=Health Assessment Questionnaire-Disability Index, MTX=methotrexate, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from JADZ clinical study report, p. 301

**Table 68** shows the mean percent change from baseline in the high sensitivity C reactive protein (hs-CRP). Both baricitinib monotherapy and combination therapy with baricitinib and methotrexate treatment arms improved hs-CRP compared to methotrexate monotherapy. Combination therapy with methotrexate and baricitinib was not superior to baricitinib monotherapy in improving hs-CRP.

**Table 68. Percent change from baseline in hsCRP at week 24**

	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg+MTX vs BARI 4 mg
HsCRP, n	205	159	210			
Mean % change from baseline (SD)	4.6 (257.7)	-50.5 (85.9)	-51.6 (104.9)			
LSM (SE)	3.5 (12.2)	-48.6 (13.8)	-49.5 (12)			
LSMD (95% CI)				-52.1 (- 87.4, -16.8)	-53 (-85.8, - 20.2)	-0.9 (-36, 34.2)
P value				0.004	0.002	0.961

Abbreviations: hs-CRP=high sensitivity C-reactive protein, MTX=methotrexate, BARI=baricitinib, SD=standard deviation, LSM=least square mean, SE=standard error, LSMD=least square mean difference, CI=confidence interval  
Source: adapted from clinical study report, p. 305

**Data Quality and Integrity - Reviewers' Assessment**

The data quality and integrity are adequate. No audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data

or require exclusion of data from any sites.

### Efficacy Results - Secondary and other relevant endpoints

The Applicant tested baricitinib for superiority versus methotrexate and the combination of methotrexate and baricitinib versus methotrexate monotherapy in their key secondary analyses as shown in **Table 69**. The key secondary analyses were measured at Week 24. For categorical variables, non-responder imputation was used to account for missing data. For continuous variables, mean change from baseline was measured. For most endpoints, the baricitinib groups (baricitinib 4 mg daily or baricitinib 4 mg daily in combination with methotrexate) were superior to methotrexate monotherapy; however, baricitinib monotherapy was not statistically significantly superior methotrexate monotherapy on mTSS.

**Table 69. JADZ: Key secondary endpoints**

Week 24	MTX (N=210)	BARI 4 mg (N=159)	BARI 4 mg+MTX (N=215)	BARI 4 vs MTX (P value)	BARI 4+MTX vs MTX (p value)
ACR20, n (%)	130 (61.9)	122 (76.7)	168 (78.1)	0.003	0.001
HAQ-DI, mean (SD)	-0.73 (0.71)	-1.01 (0.74)	-0.92 (0.74)	0.001	0.001
DAS28-hsCRP, mean (SD)	-2.01 (1.51)	-2.74 (1.39)	-2.82 (1.58)	0.001	0.001
SDAI≤3.3, n (%)	22 (10.5)	35 (22)	49 (22.8)	0.003	0.001
mTSS	0.64 (1.81)	0.43 (1.18)	0.32 (1.14)	0.158	0.03

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, SDAI= simplified disease activity index, HAQ-DI=Health Assessment Questionnaire-Disability Index, DAS-28=disease activity scale in 28 joints, hs-CRP=high sensitivity C-reactive protein, mTSS=modified total Sharp score, MTX=methotrexate, BARI=baricitinib, SD=standard deviation, Source: adapted from JADZ clinical study report, p. 248-261

*Reviewer’s comment: For most endpoints, baricitinib monotherapy and baricitinib combination therapy with methotrexate was statistically significantly superior in comparison to methotrexate monotherapy for secondary endpoints measured at Week 24. The exception was the radiographic measure of mTSS which showed baricitinib monotherapy was not superior to methotrexate monotherapy while baricitinib in combination with methotrexate was superior to methotrexate monotherapy in the Applicant’s pre-specified analysis.*

### Dose/Dose Response

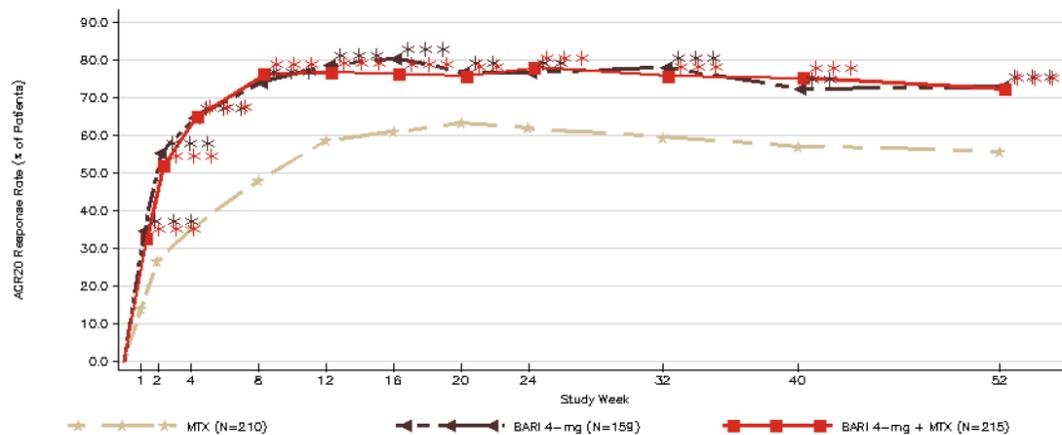
Only the 4 mg daily dose of baricitinib was studied in JADZ. Patients received either baricitinib monotherapy or combination baricitinib and methotrexate therapy Insert text here.

### Durability of Response

**Figure 12** shows the ACR20 response rate to week 52 using non-responder imputation in study JADZ. As early as week 2, the baricitinib monotherapy and baricitinib and methotrexate

combination arms separate from the methotrexate monotherapy arm. The effect appears to persist to week 52.

**Figure 12. JADZ: ACR20 response rate using non-responder imputation at weeks 0-52**

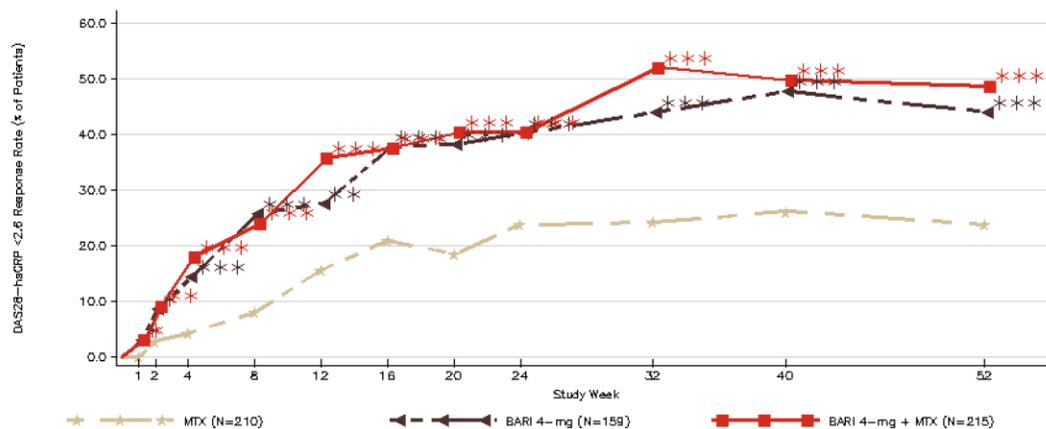


\*p<=.05, \*\*p<=.01, \*\*\*p<=.001 vs MTX.  
 Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; N = number of mITT patients; NRI = non-responder imputation.

Source: JADZ clinical study report, p. 268

**Figure 13** shows the percent of DAS28 responders to week 52 in study JADZ. . As early as week 2, the baricitinib monotherapy and baricitinib and methotrexate combination arms separate from the methotrexate monotherapy arm. The effect appears to persist to week 52.

**Figure 13. JADZ: DAS28-hsCRP<2.6 response rate using non-responder imputation at weeks 0-52**



\*p<=.05, \*\*p<=.01, \*\*\*p<=.001 vs MTX.  
 Abbreviations: DAS28 = Disease Activity Score 28 joints; hsCRP = high sensitivity C-reactive protein; N = number of mITT patients; NRI = non-responder imputation.

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Source: JADZ clinical study report, p. 316

*Reviewer's comments: Both of the endpoints assessed above were based on non-responder imputation. The treatment arms that contained baricitinib appeared to provide efficacy faster than methotrexate arm and maintain that effect over time.*

See Section 7 and Section 8 for additional discussion of efficacy and safety results, respectively.

### **Persistence of Effect**

No analysis to determine persistence of effect. It would be expected that baricitinib would be administered chronically for the indication of rheumatoid arthritis.

### **Additional Analyses Conducted on the Individual Trial**

Information requests were sent to the Applicant to perform efficacy analyses that were requested by the Division prior to submission of the NDA. See Dr. Abugov's statistical review for details on the additional requested analyses.

## **7 Integrated Review of Effectiveness**

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### **7.1. Assessment of Efficacy Across Trials**

#### **7.1.1. Primary Endpoints**

**Table 70** shows the main enrollment criteria that were used for the phase 3 studies of baricitinib in RA. The diagnostic criteria used to enroll patients in all studies were the ACR/EULAR 2010 classification criteria for RA. All patients were required to have active tender and swollen joints. Study JADV required a higher CRP and at least one erosion on X-ray for enrollment so the patients in that study likely had more active RA as compared to the other studies. Further differences in study were based on historical medication that could have been used on patients. In JADZ, patients were to be naïve to both conventional and biologic DMARDs. Patients in JADX and JADV needed to be naïve to biologic DMARDs. JADW required that patients were intolerant to at least one TNF inhibitor and had no requirement on history of conventional DMARD use. JADW would conceivably be a refractory treatment population as well because patients had failed therapy with a biologic DMARD.

#### **Table 70. Enrollment criteria for phase 3 baricitinib studies in RA**

	<b>JADX</b>	<b>JADW</b>	<b>JADV</b>	<b>JADZ</b>
Diagnostic criteria	ACR/EULAR 2010 Criteria	ACR/EULAR 2010 Criteria	ACR/EULAR 2010 Criteria	ACR/EULAR 2010 Criteria
Tender joint count	≥6/68	≥6/68	≥6/68	≥6/68
Swollen joint count	≥6/66	≥6/66	≥6/66	≥6/66
CRP (mg/dL)	≥3.6 mg/L	≥3 mg/L	≥6 mg/L	≥3.6 mg/L
Risk for progression of joint damage	NA	NA	Required at least one baseline erosion at screening	NA
Oral DMARDs	Intolerant to at least one conventional DMARD	NA	Inadequate response to methotrexate	Naïve to conventional DMARDs
Biologic DMARDs	Naïve to biologic DMARDs	Inadequate response to at least one TNF inhibitor	Naïve to biologic DMARDs	Naïve to biologic DMARDs

Abbreviations: ACR=American College of Rheumatology, EULAR=European League Against Rheumatism, CRP=C-reactive protein, DMARD=disease modifying anti-rheumatic drug  
Source: adapted from Applicant's clinical efficacy summary, p. 32-33

In the integrated presentation of efficacy results, the data from the 4 studies are not being pooled. Rather, the results of the primary endpoint and major secondary endpoints will be presented and reviewed alongside each other.

**Table 71** shows the percent responders at the pre-specified time point for each phase 3 study in RA. All dropouts prior to analysis of the primary endpoint were considered non-responders. Both 2 mg and 4 mg treatment arms had significantly higher percent of ACR20 responders as compared to placebo. In study JADZ, the baricitinib 4 mg dose treatment arm and the combination 4 mg dose treatment arm had similar improvement in percent of ACR20 responders. Baricitinib and adalimumab had a higher percent of ACR20 responders as compared to placebo in study JADV.

**Table 71. Phase 3 rheumatoid arthritis studies in baricitinib: ACR20 % responders**

ACR20 % responders	n/N (%)	Comparison	Odds ratio	95% CI	p-value
<b>JADX</b>					
Baricitinib 2 mg	151/229 (66)	Placebo	3	2, 4.4	<0.001
Baricitinib 4 mg	140/227 (62)	Placebo	2.5	1.7, 3.7	<0.001
Placebo	90/228 (39)	NA			
<b>JADW</b>					
Baricitinib 2 mg	85/174 (49)	Placebo	2.7	1.7, 4.2	<0.001
Baricitinib 4 mg	98/177 (55)	Placebo	3.4	2.0, 4.4	<0.001
Placebo	48/176 (27)	NA			
<b>JADV</b>					
Baricitinib 4 mg	339/847 (70)	Placebo	3.6	2.7, 4.7	<0.001
Adalimumab 40 mg	202/330 (61)	Placebo	2.4	1.8, 3.3	<0.001
Placebo	196/488 (40)	NA			

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JADZ					
Baricitinib 4 mg	122/159 (77)	Placebo	2	1.3, 3.2	0.003
Baricitinib 4 mg + MTX	168/215 (78)	Placebo	2.2	1.4, 3.4	0.001
MTX	130/210 (62)	NA			

Abbreviations: ACR=American College of Rheumatology, MTX=methotrexate  
Source: adapted from Dr. Abugov's statistical review

### 7.1.2. Secondary and Other Endpoints

Table 72 shows the p-values for the Applicant's, pre-specified, primary and major gated secondary endpoints in the 4 phase 3 studies. In general, the Applicant showed statistically significant differences between baricitinib and placebo. In JADZ, change in modified total Sharp score did not reach statistical significance

**Table 72. Baricitinib phase 3 RA studies: summary of primary and major gated secondary endpoints**

	JADZ p-value		JADV p-value		JADX p-value		JADW p-value	
	BARI 4 mg vs MTX	BARI 4 mg+MTX vs MTX	BARI 4 mg vs placebo	BARI 4 mg vs ADA	BARI 2 mg vs placebo	BARI 4 mg vs placebo	BARI 2 mg vs placebo	BARI 4 mg vs placebo
ACR20 at primary time point	0.003	≤0.001	0.014	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001
ΔHAQ-DI at wk 12	≤0.001	≤0.001	≤0.001	n/a	≤0.001	≤0.001	≤0.001	≤0.001
ΔmTSS at wk 24	<b>0.158</b>	0.026	≤0.001	n/a	Not gated		n/a	
ΔDAS28-hsCRP at wk 12	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001
SDAI≤3.3 at wk 12	0.003	≤0.001	≤0.001	n/a	≤0.001	≤0.001	<b>0.723</b>	<b>0.140</b>
MJS duration at wk 12	n/a	n/a	≤0.001	n/a	n/a	≤0.001	n/a	n/a
MJS severity at wk 12	n/a	n/a	≤0.001	n/a	n/a	≤0.001	n/a	n/a
Worst tiredness at wk 12	n/a	n/a	≤0.001	n/a	n/a	0.027	n/a	n/a
Worst joint pain at wk 12	n/a	n/a	≤0.001	n/a	n/a	≤0.001	n/a	n/a

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, SDAI= simplified disease activity index, HAQ-DI=Health Assessment Questionnaire-Disability Index, DAS-28=disease activity scale in 28 joints, hs-CRP=high sensitivity C-reactive protein, BARI=baricitinib, MTX=methotrexate, ADA=adalimumab  
Source: adapted from Sponsor clinical efficacy summary, p. 13

In study JADV, the Applicant pre-specified two key secondary endpoints that compared adalimumab to baricitinib ACR 20 responders at week 12 and change from baseline to week 12 in DAS28-hsCRP. **Table 73** shows the percent responders for ACR20, 50, and 70 at week 12 in study JADV. For all measures of ACR response, both adalimumab and baricitinib were statistically significantly superior to placebo. For all measures of ACR response, baricitinib was statistically significantly superior to adalimumab.

**Table 73. JADV: ACR responders at week 12**

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

**Table 74** shows the percent of patient who had a DAS28 response less than or equal to 2.6 in the phase 3 baricitinib studies. Compared to placebo, both the 2 mg and 4 mg dose were superior with statistical significance. In study JADV, both adalimumab and baricitinib were superior to placebo with statistical significance. In the direct comparison of adalimumab and baricitinib, baricitinib had a numerically greater percentage of responders which approached statistical significance (p=0.077). In study JADZ, the baricitinib monotherapy group and combination baricitinib and methotrexate group were statistically superior to methotrexate.

**Table 74. Phase 3 studies: percent of DAS-28 responders**

Study	% Responders (Responders/Total)			Odds Ratio (p-value)		
	B4	A	Pbo	B4:Pbo	A:Pbo	B4:A
At week 12						
JADV	24 (119/487)	19 (63/330)	4 (21/488)	7.6 (<0.001)	5.5 (<0.001)	1.4 (0.077)
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						
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

**Table 75** shows mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI). Both the 2 mg baricitinib and 4 mg doses were statistically significantly superior to placebo for change in HAQ-DI. In study JADV, both baricitinib and adalimumab were

superior to placebo. Baricitinib was statistically significantly superior to adalimumab for mean change in HAQ-DI. In study JADZ, both the combination of methotrexate and baricitinib and baricitinib monotherapy were statistically significantly superior to methotrexate. There was no statistical difference between baricitinib monotherapy and the combination of methotrexate and baricitinib.

**Table 75. Phase 3 studies: mean change from baseline in HAQ-DI**

Study	Mean Change from Baseline (N)			Difference (p-value)		
	B4	A	Pbo	B4-Pbo	A-Pbo	B4-A
<b>At week 12</b>						
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)
<b>At week 24</b>						
	B4MTX	B4	MTX	B4MTX:MTX	B4:MTX	B4MTX:B4
JADZ	-1.03 (209)	-1.04 (159)	-0.74 (204)	-0.29 (<0.001)	-0.3 (<0.001)	0.01 (0.83)

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

Table 76 shows the mean change from baseline in modified total Sharp scores (mTSS). For the 2 mg dose of baricitinib, the type of analysis determined whether the 2 mg dose was statistically significantly superior to placebo. In study JADX, the 2 mg dose of baricitinib was statistically superior to placebo when using linear extrapolation. However, if that assumption is not made and only the observed data is used, the 2 mg dose of baricitinib was not statistically significantly superior to placebo at week 24. Thus, there is some uncertainty regarding the impact of 2 mg on inhibition of radiographic progression. With either type of analysis, the 4 mg dose of baricitinib was statistically significantly superior to placebo at week 24. In study JADV, both adalimumab and baricitinib were statistically significantly superior to placebo. While there was a smaller mean change from baseline in mTSS (suggesting slightly less radiographic progression) for the adalimumab group versus the baricitinib group, this finding was not statistically significant. In study JADZ, when using only observed data, the baricitinib monotherapy arm was not statistically significantly superior to methotrexate at week 24. The combination arm of baricitinib and methotrexate was statistically superior to placebo at week 24. At week 52, both the baricitinib monotherapy arm and the combination baricitinib and methotrexate arm were statistically significantly superior to placebo.

**Table 76. Phase 3 studies: modified total Sharp scores**

	mTSS Mean Change from Baseline (N)			Difference (p-value)		
	B4	A	Pbo	B4-Pbo	A-Pbo	B4-A
<b>At week 24</b>						
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

Table 77 shows the percent of patients who achieved a SDAI response of  $\leq 3.3$ . In study JADX, both the 2 mg and 4 mg baricitinib doses were statistically significantly superior to placebo in the percent of patients who achieved  $\text{SDAI} \leq 3.3$ . In study JADW, neither of the doses achieved a statistically significant improvement over placebo. In study JADV, both adalimumab and baricitinib had a statistically significant improvement in percent responders on SDAI. In JADZ, both baricitinib monotherapy and combination therapy with methotrexate and baricitinib showed an improved response over methotrexate monotherapy.

**Table 77. Phase 3 studies: percent responders of  $\text{SDAI} \leq 3.3$**

Study	% Responders (Responders/Total)			Odds Ratio (p-value)		
<b>At week 12</b>						
	B4	A	Pbo	B4:Pbo	A:Pbo	B4:A
JADV	8 (41/487)	7 (24/330)	2 (9/488)	4.9 (<0.001)	4.2 (<0.001)	1.2 (0.58)
	B4	B2	Pbo	B4:Pbo	B2:Pbo	B4:B2
JADW	5 (9/177)	2 (4/174)	2 (3/176)	3.1 (0.053)	1.4 (0.7)	2.2 (0.14)
JADX	9 (20/227)	9 (21/229)	1 (2/228)	11.7 (0.001)	11.5 (0.001)	1 (0.95)
<b>At week 24</b>						
	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 31, 32, 33, and 34 of Dr. Abugov's statistical review dated 11/17/16

Table 78 shows the mean change from baseline in component scores derived from the SF-36. No significant differences were seen between treatment arms for the mental component score. For the physical component score, both the 2 mg and 4 mg baricitinib treatment arms were statistically significantly superior to placebo. There was no statistical difference between the 4 mg and 2 mg dose groups.

**Table 78. Studies JADV, JADW, and JADX: SF-36 component scores**

Parameter	Study	Change from baseline			Difference (p-value)		
		BARI 4	BARI 2	placebo	BARI 4- placebo	BARI 2- placebo	BARI4- BARI2
Mental component score	JADV	3.27		2.99	0.27 (0.6)		
	JADW	1.84	2.81	1.24	0.6 (0.5)	1.57 (0.1)	-0.98 (0.3)
	JADX	3.48	3.14	3.23	0.25 (0.8)	-0.09 (0.9)	0.34 (0.7)
Physical component score	JADV	8.68		4.25	4.43 (<0.001)		
	JADW	6.37	6.03	2.64	3.73 (<0.001)	3.38 (<0.001)	0.34 (0.7)
	JADX	7.24	7.96	4.29	2.95 (<0.001)	3.67 (<0.001)	-0.72 (0.3)

Source: Dr. Abugov's Statistics review dated 11/17/2016, p. 70

**Table 79** shows the median change from baseline to week 12 for various patient reported outcomes that were measured in studies JADV and JADX. In study JADV, both adalimumab and baricitinib were statistically significantly superior to placebo in median change from baseline scores in morning stiffness duration, morning stiffness severity, worst tiredness, and worst joint pain. Baricitinib was statistically superior to placebo in change from baseline in morning stiffness severity, worst tiredness, and worst joint pain. In study JADX, the 2 mg dose of baricitinib was statistically significantly superior to placebo for all of the patient reported outcomes listed in **Table 79**. The 4 mg dose of baricitinib was numerically better than the 2 mg dose for morning stiffness severity and worst tiredness, but opposite trends were seen for morning stiffness duration and worst joint pain.

**Table 79. JADV and JADX: Morning stiffness duration and severity, worst tiredness, and worst joint pain to week 12**

Study	Δ Minutes (N)/ Δ Severity (N)			Median Difference (p-value)		
	B4	A	Pbo	B4:Pbo	A:Pbo	B4:A
<b>JADV</b>						
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)
<b>JADX</b>						
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

### 7.1.3. Subpopulations

Table 80 shows ACR20 response, DAS28 response, and median change in HAQ-DI by gender age and race in the studies JADV, JADX, JADN, JADA, and JADC. The analysis included the 4 mg treatment arms and placebo arms. For ACR 20 responders, there was no significant interaction between treatment arms for gender, age, or race. The same was true for median change in HAQ-DI. In the subgroup analysis of DAS28-hsCRP responders, there was a significant interaction within the race categories but not for gender or age. This was probably due to the small number of patients enrolled in race that were classified as other.

**Table 80. Pooled Efficacy: Subgroup analyses to week 12**

Efficacy measure	Characteristic	Subgroup	N	Placebo n (%)	N	BARI 4 mg n (%)	OR	Interaction p-value
ACR20	Gender	Female	709	278 (39)	630	417 (66)	3.1	0.3
		Male	172	67 (39)	173	125 (72)	4.1	
	Age	<65	750	289 (39)	650	440 (68)	3.4	0.4
		≥65	131	56 (43)	153	102 (67)	2.7	
	Race	Asian	268	86 (32)	229	149 (65)	3.9	0.07
		White	545	227 (42)	516	360 (70)	3.3	
Other		67	32 (48)	57	33 (58)	1.9		
DAS28-hsCRP≤3.2	Gender	Female	709	119 (17)	630	272 (43)	4	0.5
		Male	172	27 (16)	173	80 (46)	5	
	Age	<65	750	122 (16)	650	278 (43)	4.1	0.9
		≥65	131	24 (18)	153	74 (48)	4.7	
	Race	Asian	268	39 (15)	229	116 (51)	7	0.01
		White	545	92 (17)	516	217 (42)	3.8	
Other		67	15 (22)	57	19 (33)	1.9		
Efficacy measure	Characteristic	subgroup	N	Placebo LSM (SE)	N	BARI 4 mg LSM (SE)	LSMD	Interaction p-value
ΔHAQ-DI	Gender	Female	698	-0.2 (0.03)	622	-0.5 (0.03)	-0.3	0.7
		Male	170	-0.3 (0.06)	170	-0.6 (0.06)	-0.3	
	Age	<65	739	-0.2 (0.03)	641	-0.5 (0.03)	-0.3	1
		≥65	129	-0.2 (0.06)	151	-0.5 (0.06)	-0.3	
	Race	Asian	266	-0.2 (0.03)	226	-0.5 (0.04)	-0.3	0.5
		White	534	-0.3 (0.03)	509	-0.6 (0.03)	-0.3	
Other		67	-0.2 (0.1)	56	-0.4 (0.11)	-0.2		

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, SDAI= simplified disease activity index, HAQ-DI=Health Assessment Questionnaire-Disability Index, DAS-28=disease activity scale in 28 joints, hs-CRP=high sensitivity C-reactive protein, PBO=placebo, BARI=baricitinib, , LSMD=least square mean difference, OR=odds ratio  
Source: adapted from Applicant summary of clinical safety, p. 124

#### 7.1.4. Dose and Dose-Response

**Table 81** shows a comparison of several different efficacy endpoints studied in two of the phase 3 trials, JADW and JADX. The study was not powered to show differences between treatment groups. In general patients who received both baricitinib 2 mg and baricitinib 4 mg daily had better responses than placebo. In direct, pairwise comparisons of baricitinib 2 mg and 4 mg doses, there was only one endpoint that showed a statistically significant difference and that

was for DAS28-hsCRP $\leq$ 3.2 at Week 24 in JADW. The 4 mg baricitinib group showed a statistically significantly improvement in DAS28 responders compared to the 2 mg treatment arm. JADX did not show a similar finding.

**Table 81. Efficacy endpoints for baricitinib 2 mg and 4 mg doses**

Endpoint	Week	Study	% responders (responders/total)		Odds ratio (95% CI)
			<b>BARI4</b>	<b>BARI2</b>	<b>BARI4:BARI2</b>
ACR20	12	JADW	55 (98/177)	49 (85/174)	1.3 (0.8, 2)
		JADX	62 (140/227)	66 (151/229)	0.8 (0.6, 1.2)
	24	JADW	46 (82/177)	45 (78/174)	1 (0.7, 1.6)
		JADX	65 (148/227)	61 (140/229)	1.2 (0.8, 1.8)
ACR50	12	JADW	28 (50/177)	20 (35/174)	1.5 (0.9, 2.5)
		JADX	33 (76/227)	34 (77/229)	1 (0.7, 1.5)
	24	JADW	29 (52/177)	23 (40/174)	1.4 (0.8, 2.3)
		JADX	44 (100/227)	41 (95/229)	1.1 (0.8, 1.6)
ACR70	12	JADW	11 (20/177)	13 (22/174)	0.9 (0.4, 1.6)
		JADX	18 (41/227)	18 (41/229)	1 (0.7, 1.7)
	24	JADW	17 (30/177)	13 (23/174)	1.3 (0.7, 2.4)
		JADX	24 (55/227)	25 (58/229)	1 (0.6, 1.5)
DAS28-hsCRP $\leq$ 3.2	12	JADW	32 (56/177)	24 (42/174)	1.4 (0.9, 2.3)
		JADX	39 (89/227)	36 (82/229)	1.2 (0.8, 1.8)
	24	JADW	33 (59/177)	20 (35/174)	<b>2 (1.3, 3.2)</b>
		JADX	52 (117/227)	46 (106/229)	1.2 (0.8, 1.8)
SDAI $\leq$ 3.3	12	JADW	5 (9/177)	2 (4/174)	2.2 (0.7, 7.4)
		JADX	9 (20/227)	9 (21/229)	1 (0.5, 2)
	24	JADW	9 (16/177)	5 (8/174)	2 (0.8, 4.9)
		JADX	15 (34/227)	17 (38/229)	0.9 (0.5, 1.5)
					<b>Difference (95% CI)</b>
Change in mTSS	24	JADX	0.15	0.33	-0.18 (-0.54, 0.18)
JSN	24	JADX	0.04	0.03	0.01 (-0.15, 0.17)
JSE	24	JADX	0.11	0.3	-0.19 (-0.43, 0.06)

Abbreviations: JSN=joint space narrowing, JSE=joint space erosions, Abbreviations: ACR20/50/70=20%/50%/70% response to American College of Rheumatology Criteria, SDAI= simplified disease activity index, DAS-28=disease activity scale in 28 joints, hs-CRP=high sensitivity C-reactive protein, BARI=baricitinib, CI=confidence interval  
Source: Dr. Abugov's Statistic review

*Reviewer's comments: Overall, the two doses of 2 mg baricitinib daily and 4 mg baricitinib daily appeared similar in regards to efficacy for ACR response. For the ACR components, there were trends towards a higher response for 4 mg than 2 mg in JADW. When comparing the two doses studied in JADX, there was not a consistent trend favoring one dose at Week 12.*

#### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

Table 82 shows the percentage of ACR20 responders, percentage of DAS28 responders, and the mean change from baseline in HAQ-DI for studies JADZ and JADV which had active comparator arms. For both studies, the baricitinib treatment arms appeared to maintain effectiveness through the 52 week period. In study JADZ, both baricitinib monotherapy and the combination of baricitinib and methotrexate were statistically significantly superior to methotrexate monotherapy at week 12, week 24, and week 52. In study JADV, both baricitinib and adalimumab were superior to placebo at week 12 and week 24 for ACR20, DAS28, and change from baseline in HAQ-DI at week 12 and week 24.

The Applicant also reported that baricitinib was superior to adalimumab at week 12, week 24, and week 52 for ACR 20, for DAS28-hsCRP at week 52, and for change in HAQ-DI from baseline at week 12, week 24, and week 52.

**Table 82. Studies JADV and JADZ: maintenance of response**

	JADZ			JADV		
	MTX N=210	BARI 4 N=159	BARI 4+ MTX N=215	placebo N=488	BARI 4 N=487	ADA N=330
<b>ACR20 responders, %</b>						
Week 12	59	79***	77***	40	70***	61***
Week 24	62	77**	78***	37	74***	66***
Week 52	56	73***	73***	NA	71	62
<b>DAS28-hsCRP ≤ 3.2, %</b>						
Week 12	30	47***	56***	14	44***	35***
Week 24	38	57***	60***	19	52***	48***
Week 52	38	57***	63***	NA	56	48
<b>Δ HAQ-DI, change from baseline</b>						
Week 12	-0.61	-0.92***	-0.98***	-0.34	-0.66***	-0.56***
Week 24	-0.74	-1.04***	-1.03***	-0.35	-0.75***	-0.63***
Week 52	-0.71	-0.99***	-1.06***	NA	-0.77	-0.66

Abbreviations: ACR20=20% response to American College of Rheumatology Criteria, HAQ-DI=Health Assessment Questionnaire-Disability Index, DAS-28=disease activity scale in 28 joints, hs-CRP=high sensitivity C-reactive protein, MTX=methotrexate, ADA=adalimumab, BARI=baricitinib  
\*\*p≤0.01, \*\*\*p≤0.001 vs placebo (vs MTX in study JADZ)

Source: adapted from Applicant summary of clinical safety, p.134-135

*Reviewer's comment: The data provided by the Applicant appears to show that efficacy from baricitinib is maintained over the 52 week period. Due to switch and rescue procedures to 4 mg of baricitinib at week 16 in JADV and week 24 in JADZ, there are some limitations to interpretation of the data. However, it does appear that baricitinib is able to maintain efficacy as would be anticipated for a small molecule drug for RA.*

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

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The patient population in the pivotal trials, in the most part, reflected the general RA population in the US. At this point, there are no additional considerations of potential efficacy issues in the postmarket setting.

### 7.2.2. Other Relevant Benefits

Besides the efficacy in rheumatoid arthritis, there are no additional aspects of the drug that may be considered by patients or providers to be a relevant benefit at this time. The dosing schedule and route of administration are similar to what is currently available.

### 7.3. Integrated Assessment of Effectiveness

To support efficacy of baricitinib in the treatment of patients with RA, Eli Lilly and Company has submitted the data 4 phase 3 trials, JADW, JADX, JADV, and JADW. JADW was a 24 week randomized, double-blind placebo controlled trial evaluating 2 doses of baricitinib (4 mg daily and 2 mg daily) in the treatment of moderate to severe RA. JADX was a 24 week randomized, double-blind placebo controlled trial evaluating 2 doses of baricitinib (4 mg daily and 2 mg daily) in the treatment of moderate to severe RA. JADV was a 52 week randomized, double-blind placebo controlled trial comparing baricitinib 4 mg daily with an active comparator, adalimumab 40 mg every other week, for treatment of moderate to severe RA. JADZ was a 52 week randomized, double-blind placebo controlled trial evaluating baricitinib 4 mg daily monotherapy and comparing with optimized methotrexate monotherapy and comparing with the combination of optimized methotrexate and 4 mg daily baricitinib for treatment of moderate to severe RA. The four protocols are described in detail in Sections 6.1, 6.2, 6.3, and 6.4. All studies met evidentiary standard.

The primary and key secondary endpoints are accepted and validated endpoints to assess signs and symptoms (ACR response, DAS28-CRP), physical function (HAQ-DI), and radiographic progression (mTSS) in patients with RA. The results are presented in detail above in Section 7.1. For all these endpoints, baricitinib showed a statistically significant improvement compared to placebo. The primary analysis provided by Eli Lilly and Company was confirmed by sensitivity analyses conducted by the Applicant and Dr. Abugov (FDA statistical review team). The results of the 2 mg dose and 4 mg dose of baricitinib were both superior to placebo.

The current 2015 guidelines recommends use of a conventional DMARD (typically, MTX) with a biologic DMARD for patients with moderate or high disease activity despite DMARD monotherapy. TNF inhibitors are frequently the first biologic used. However, between 20-30% of patients fail to respond or become intolerant to TNF inhibitors. Therefore, options for other therapies are necessary. In study JADW, patients were TNF inadequate responders, in study JADX, patients were intolerant to conventional DMARDs, and in study JADZ, patients were intolerant to methotrexate. Therefore, the data support the use of baricitinib in the treatment of RA for patients who may have had an inadequate response to either conventional DMARDs

(including methotrexate) or TNF inhibitors. The efficacy results appear to support both the 2 mg and 4 mg dose of baricitinib. There is currently another JAK inhibitor on the market for use in RA, tofacitinib. No comparative study was performed between baricitinib and tofacitinib. Baricitinib would offer the RA population another effective JAK inhibitor.

Given the efficacy results, it is reasonable that labeling would convey that baricitinib is effective for the treatment of adult patients with moderately to severely active RA who are inadequate responders or intolerant of one or more DMARDs. Essentially, the reviewer is in agreement with labeling for benefits in signs and symptoms (ACR20 response, DAS28-hsCRP), physical function (HAQ-DI), radiographic response (mTSS), and general health related outcomes (SF-36). Based on the data, there is evidence of inhibition of radiographic progression for 4 mg, but uncertainty regarding 2 mg. Section 10 provides full details regarding labeling recommendations. Additionally see Section 1.3 for a discussion of the dose selection.

## 8 Review of Safety

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### 8.1. Safety Review Approach

The safety review was based on four pivotal phase 3 trials discussed in Section 6, three phase 2 trials, and one long term extension trial. The analysis used for integrated safety through the randomized period was derived from 3 phase 3 studies (JADV, JADW, and JADX) and 3 phase 2 studies (JADC, JADA, and JADN). Study JADZ was not pooled in this integrated safety population because it was an active comparator study with optimized methotrexate, unlike the other studies. An approved JAK inhibitor, tofacitinib, includes integrated safety analyses from the phase 2 and phase 3 studies in the approved labeling. Study JADZ was used for any comparisons to methotrexate and study JADV was used for any comparisons to adalimumab. Studies JADX, JADW, JADA, and JADN were used to make comparisons between 2 mg and 4 mg doses of baricitinib.

In order to assess events that occurred from week 0 to 52 for rare events and adverse events of special interest, a separate analysis that was not included in the initial submission was requested from the Applicant. The studies used to make up this dataset were JADA, JADC, JADN, JADV, JADW, and JADX as well as the long term extension study, JADY. In the analysis, data after randomization was included. In the analysis, adverse events were reported with the study treatment the patient was on at the time of the event and not the treatment the patient was initially randomized to. As placebo data was not available beyond week 24, this caused an imbalance in the exposure to placebo versus baricitinib with a much higher exposure to baricitinib. To help address this concern, exposure adjusted incidence rates (patients per 100 patient years) will be reported, but since there is no way to directly compare placebo at later time points to baricitinib, the conclusions possible from the data are limited in scope.

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FDA requested 2 analytical methodologies of the dataset with studies JADA, JADC, JADN, JADV, JADW, and JADX, and JADY: 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.

Thrombotic events were a focus of scrutiny during the safety review, prompted by an imbalance noted in pulmonary emboli (PE) and deep venous thrombosis (DVT) events between baricitinib treated patients and placebo. A hematology consult was requested to aid in determination of the significance of the imbalance noted in the integrated safety studies. Additional adverse events of special interest were infections, serious infections, tuberculosis and other opportunistic infections, increases in lipids, hematologic parameters (neutropenia, lymphopenia, thrombocytosis), CPK elevations, and malignancies.

The Applicant's approach to determination of a serious adverse event was that all patients who discontinued from drug had a serious adverse event per protocol. Investigators were sent a CDQA form for any patient counted as having a SAE for discontinuation and no other ICH criteria for SAE. The investigator was asked if the SAE was indeed a SAE by GCP standards and for SAEs in which the investigator answered that the SAE was a SAE by GCP standards, those SAEs were considered SAEs by ICH standard. Also any SAEs by discontinuation where the investigator failed to respond via the CDQA were automatically counted as SAEs by ICH criteria.

*Reviewer's comments: There were several challenges to interpreting the Applicant's submitted safety analyses. The Applicant provided an integrated safety analysis of placebo versus baricitinib 4 mg daily and a separate analysis of baricitinib 2 mg daily versus baricitinib 4 mg daily. In the 2 mg versus 4 mg comparison, pairwise comparisons were made between the 2 mg dose and placebo and the 2 mg versus 4 mg doses. However, there were no pairwise comparisons of baricitinib 4 mg versus placebo which made evaluation of a dose response for certain AEs challenging.*

*Multiple information requests were sent to the Applicant to better characterize the safety information. This included the generation of a new dataset and pairwise comparisons between the 4 mg and 2 mg doses, as well as comparisons to placebo. In addition, an information request was sent to the Applicant to provide figures that address the change in laboratory abnormalities over time and to compare the doses of baricitinib.*

*The Applicant performed two different analyses for SAEs. The SAEs were by protocol which included any permanent discontinuations to treatment which is not standard for ICH criteria. The concern regarding this approach was over reporting of SAEs which may have led to a blunting of potential safety signals. An additional information request was sent to the Applicant to determine how many patients were affected by the approach the Applicant used to identify SAEs and reclassify as SAE by ICH criteria.*

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

The overall size and exposure of baricitinib to any indication is presented in **Table 83**. The safety analyses to support the indication of RA used the phase 2 and phase 3 clinical trials in RA. Over 2000 patients exposed to baricitinib and 1000 placebo patients were available for analysis from the controlled trials conducted for rheumatoid arthritis.

**Table 83. Safety database for baricitinib**

	Safety Database for baricitinib Individuals exposed to the study drug in this development program for the indication under review N=5884			
Clinical Trial Groups	Baricitinib (n=4051)	Adalimumab (n=330)	Methotrexate (n=263)	Placebo (n=1240)
Normal Volunteers	454	0	0	109
Controlled trials conducted for this indication	2116	330	263	1070
All other than controlled trials conducted for this indication	662	0	0	0
Controlled trials conducted for other	339	0	0	61

indications				
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Source: adapted from Applicant information request response dated June 24, 2016, p. 118

Table 84 shows the duration of exposure for patients who received baricitinib. More than 4000 patients were exposed to baricitinib and of those patients more than 2000 patients received baricitinib for more than a year.

**Table 84. Baricitinib duration of exposure**

Number of patients exposed to baricitinib: 4051			
>=6 months	>=12 months	>=18 months	>=24 months or longer
N=2674	N=2227	N=1626	N=806

Source: adapted from applicant information request response dated June 24, 2016, p. 119

*Reviewer’s comments: Despite the large sample of RA patients provided, a majority of the long term exposure to baricitinib was with the 4 mg daily dose. Further, baricitinib 4 mg was the only option for patients with ongoing disease activity on either placebo or baricitinib 2 mg and all placebo patients initiated to baricitinib 4 mg when transitioning to the open label extension study, JADY. As the long term exposure with the 2 mg dose of baricitinib was much smaller than the 4 mg dose and patients who escaped to baricitinib 4 mg had more active disease than patients who continued on baricitinib 2 mg, it was difficult to determine whether the increased number of events in the 4 mg baricitinib group were due to a difference in safety, a difference in exposure, or a difference in risk factors. Exposure adjusted incidence rates were calculated to attempt to compare safety of the 2 mg and 4 mg baricitinib doses, but there limitations remain in terms of interpretation of the long-term safety data given the study design and crossover between doses.*

### 8.2.2. Relevant characteristics of the safety population:

**Table 85** shows the baseline demographic characteristics of patients who were on placebo, baricitinib 2 mg, or baricitinib 4 mg daily. The patients in this safety analysis set come from the studies that included 2 mg and 4 mg doses (phase 2 studies JADA and JADN as well as studies JADX and JADW).

Patients were characteristic of a rheumatoid arthritis patient population with a mean age in the 50s and gender that was predominantly female. Almost 70% of patients were Caucasian in the study. Over 20% of patients in each group were Asian. On average, patients enrolled in the study had moderate duration of disease (approximately 9 years since diagnosis of RA).

**Table 85. Integrated Safety: Baseline demographic characteristics of patients on placebo, baricitinib 2 mg, baricitinib 4 mg**

	Placebo (N=551)	BARI 2 mg (N=479)	BARI 2 mg (N=479)
Age Mean (SD)	52.4 (12.1)	53.2 (12)	53.6 (11.7)
Age group, n (%)			
<65	465 (84.4)	397 (82.9)	392 (81.8)
≥65	86 (15.6)	82 (17.1)	87 (18.2)
<75	543 (98.5)	467 (97.5)	467 (97.5)
≥75	8 (1.5)	12 (2.5)	12 (2.5)
Sex, n (%)			
Male	93 (16.9)	93 (19.4)	88 (18.4)
Female	458 (83.1)	386 (80.6)	391 (81.6)
Race, n (%)			
Native American	19 (3.4)	17 (3.5)	23 (4.8)
Asian	135 (24.5)	102 (21.3)	101 (21.3)
Black	24 (4.4)	19 (4)	18 (3.8)
White	370 (67.2)	340 (71)	332 (69.9)
Multiple	2 (0.4)	1 (0.2)	1 (0.2)
Time from symptom onset of RA (yrs) Mean (SD)	8.9 (8.4)	9.6 (8)	9.8 (8.8)

Abbreviations: BARI=baricitinib, SD=standard deviation

Source: adapted from Applicant clinical safety summary Appendix 1, p. 51

*Reviewer's comment: The baseline demographics would represent the US population in regards to gender. However, the high percentage of Asian patients would be different from what would be expected in a study conducted exclusively in the United States. It is not expected that the relative predominance of Asian patients will result in a different safety profile that would not be attributable to the general population of the United States.*

### 8.2.3. Adequacy of the safety database:

The safety database for baricitinib is comprehensive and adequate to assess the safety of baricitinib for the proposed indication, dosage regimen, duration of treatment, and patient population. The phase 3 trials evaluated over 2000 patients with rheumatoid arthritis.

**Figure 14** shows the different safety populations that were generated by the Applicant. The 6 study population was used to study 4 mg of baricitinib versus placebo. Also combined doses of baricitinib were assessed versus placebo but there was no comparison of 2 mg baricitinib versus placebo.

The 4 study population was used to assess baricitinib 2 mg versus placebo as the 4 study population only included studies that used a baricitinib 2 mg treatment arm. Pairwise comparisons were made between 2 mg and placebo and between 2 mg versus 4 mg of baricitinib. There was no comparison between 4 mg baricitinib and placebo.

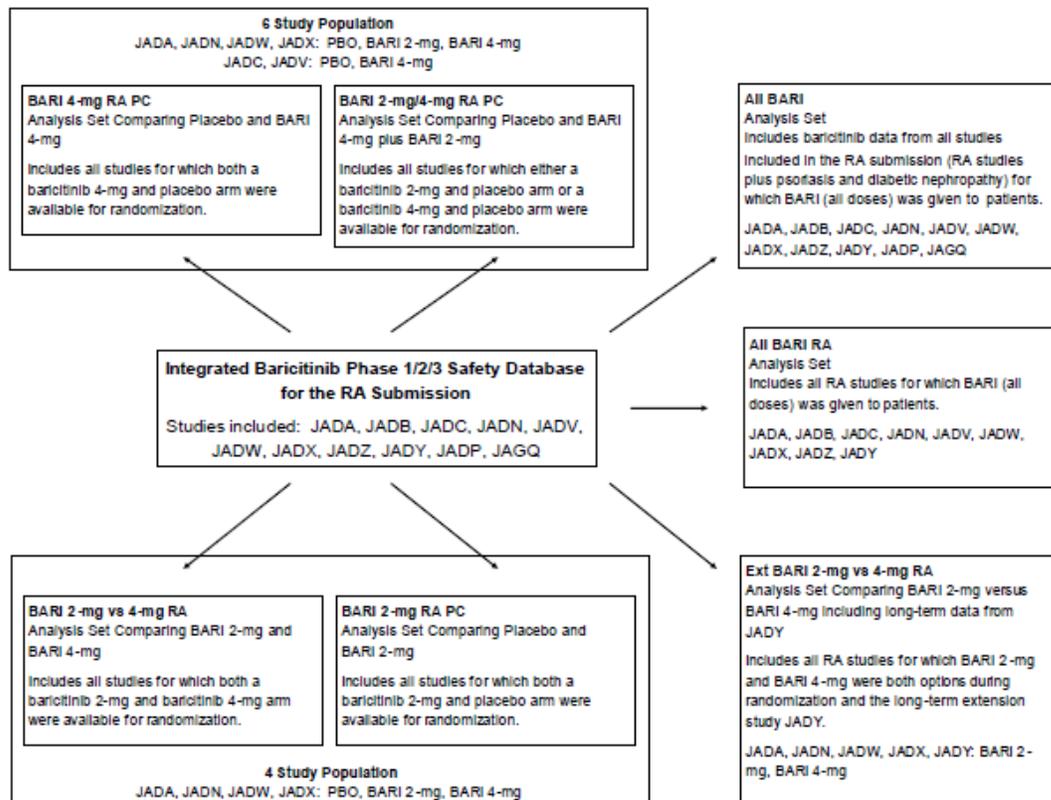
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The extended 2 mg versus 4 mg baricitinib population was used to compare any additional long-term data that was collected from the extension study JADY. Most of the additional exposure was to the 4 mg of baricitinib.

Since JADZ was an active control study (with optimized methotrexate) it was not pooled with the data from the other phase 3 studies, but was pooled in the all BARI and all BARI RA evaluations.

*Reviewer's comments: The comparison to placebo was analyzed in two different populations for 2 mg baricitinib and 4 mg baricitinib; therefore, it was difficult to note any possible dose dependent trends. An information request was sent to the Applicant in order to redo the analysis such that both baricitinib 2 mg and baricitinib 4 mg could be compared against placebo in the same population.*

**Figure 14. Applicant analysis sets submitted for review: Baricitinib in RA**



Source: Applicant's summary of clinical safety, p. 46

*Reviewer's comments: The number of RA patients exposed to baricitinib was adequate;*

*however, the study design provided limitations to conclusions that could be made regarding the safety of the 2 mg baricitinib dose, especially when making comparisons after the controlled period. All patients who were rescued or switched were placed on baricitinib 4 mg daily. Therefore, there was much greater exposure to the baricitinib 4 mg daily dose versus the baricitinib 2 mg daily dose. Of concern, patients who were switched or were rescued to the baricitinib 4 mg daily dose may have been inherently different from patients who were not switched or rescued. Only one study was randomized and controlled to 24 weeks without allowing switch or rescue (JADZ) while all other studies allowed for switching and rescue at week 16 or earlier. However, JADZ did not have a 2 mg baricitinib arm. This made the relative exposure to baricitinib 4 mg daily much greater than baricitinib 2 mg daily. Active comparators were methotrexate (in JADZ) and adalimumab (in JADV). Even within the active comparator studies, due to the switch and rescue design, conclusions regarding relative long term safety between baricitinib and other active comparators was limited.*

### **8.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **8.3.1. Issues Regarding Data Integrity and Submission Quality**

There were concerns regarding whether the submitted data adequately characterized the safety profile, especially comparing 2 mg and 4 mg, during the course of the review. An information request was sent on June 24, 2016, to the Applicant for additional information regarding the safety and efficacy analyses provided by the Applicant. Additional safety analyses were requested to better characterize the long-term safety of baricitinib and compare the 2 mg and 4 mg baricitinib doses.

For long-term 2 mg and 4 mg comparisons, the Applicant was requested to make tables that showed adverse events of special interest and included data after switch/rescue to determine whether additional rare events were occurring. The exposure was greater in the baricitinib 4 mg daily arm as all patients were switched or rescued to 4 mg of baricitinib and the 4 mg daily dose was included in all four phase 3 studies as opposed to only two phase 3 studies for the 2 mg daily dose of baricitinib. The Applicant was to provide exposure adjusted incidence rates to help account for the amount of exposure to the different possible study treatments. The Applicant was asked to provide data for time points of less than 52 weeks and greater than 52 weeks for each adverse event of special interest.

The Applicant was asked to provide mean change from baseline for several labs of interest for each dose including hemoglobin, platelets, lymphocyte count, neutrophil count, leucocyte count, LDL, total cholesterol, triglycerides, HDL, AST, ALT, bilirubin, and creatine phosphokinase. Further, tables to show the number of patients with increased AST/ALT over the upper limit of normal were requested.

A second information request was sent to the Applicant on October 14, 2016 to provide all  
CDER Clinical Review Template 2015 Edition  
*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

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available pre-switch, pre-rescue data to determine adverse events of special interest that occurred during the pre-rescue, pre-switch period. The Applicant was asked to use all 16 week data from studies JADA, JADC, JADN, JADV, JADW, and JADX. The Applicant was asked to adjust for differences among the studies.

Additional safety data was requested including:

- Arterial and venous thrombotic events
- Incidence of common infections organized by preferred term frequency
- Mean change from baseline in creatinine over 12 months
- SAEs organized by decreasing frequency
- Incidence of infections for patients who had low absolute neutrophil or low absolute lymphocyte counts
- Narratives of patients who developed alopecia
- Clarification of SAEs that occurred in the study: per protocol versus ICH criteria and use of Clinical Data Question and answer (CDQA) form
- Narratives of patients who had serious infections

An additional information request was sent to the Applicant with a flow chart to provide numbers on the patients who were classified as having a SAE for “other” reason to gain clarity as to how the use of the CDQA affected the reporting of SAEs in the RA studies.

The review was further complicated by the Applicant’s frequent minimization of safety signals. For example, the Applicant argued that each of the reported opportunistic infection was not actually an opportunistic infection. In addition, the submission emphasized statistical significance rather than rare events, trends, or imbalances. The data were frequently presented in a manner that made interpretation difficult, such as the actual number of events without exposure adjustment. Important data related to tables and figures was frequently included in appendixes, rather than in the body of the submission. These issues greatly complicated the review of the safety data.

### 8.3.2. Categorization of Adverse Events

The Applicant categorized AEs in accordance with standard regulatory definitions. Investigators were asked to rate adverse events as mild, moderate, or severe based upon patient discomfort, health risk, interference with activity, or combination of the aforementioned factors.

The Applicant provided an unusual method for capturing SAEs by protocol in which all patients who permanently discontinued from study drug were considered to have had a SAE by protocol. To determine whether patients who had SAE by protocol had a SAE by ICH criteria, a CDQA form was sent to the investigator asking whether the adverse event was serious by Good

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Clinical Practices standard. If the investigator replied that the adverse event was serious by GCP standards, the SAE was considered a SAE by ICH standard. If the investigator replied that the adverse event was not a SAE by GCP standards, the SAE was considered a SAE by protocol only. If the investigator did not reply to the CDQA, the SAE was considered a SAE by ICH definition.

Treatment emergent AEs were defined as adverse events that either first occurred or worsened in severity after first dose of study treatment. AEs included review of MedDRA preferred terms (PT) and system organ classes (SOC), including uncontrolled data from the entire program.

*Reviewer's comment: The definition used by the Applicant for SAE by protocol was not a standard ICH definition and not consistent with the Code of Federal Regulations. The Applicant further sent a CDQA form to the investigators who permanently discontinued a patient from study treatment or noted the SAE as a discontinuation due to other reason. The investigator was then asked whether the SAE met GCP standards and depending on the investigator's response, the SAE was determined to be a SAE by ICH standards. This method of using the CDQA may have had the unintended consequence of over reporting SAEs that would normally not be reported. An information request was sent to the Applicant to determine the extent of SAEs that were reported as ICH by use of the CDQA form. A concern regarding the potential misclassification of SAEs was a significant consideration during the review.*

### 8.3.3. Routine Clinical Tests

Safety assessment included clinical evaluation of AEs, vital sign measurement, physical examinations, 12-lead ECGs, and standard laboratory safety tests. Screening tests were performed to ensure that a patient did not have evidence of a latent infection such as tuberculosis. Pregnancy tests at screening and periodically throughout the study were conducted. The schedule of assessments were similar among the studies.

## 8.4. Safety Results

### 8.4.1. Deaths

Through November 2015, there were 22 deaths in the phase 2 and phase 3 RA studies. Of the 22 deaths that occurred, 2 patients died during the screening period. 12 patients died during the phase 2 and phase 3 studies. 4 patients died during the extension study.

During the phase 2 and phase 3 studies (excluding deaths that occurred during the screening period), 7 deaths occurred in the combined adalimumab, placebo, and methotrexate monotherapy study arms as compared to 13 deaths in the baricitinib arms.

Table 86 shows the deaths up to week 52 that occurred in the studies that used 2 mg and 4 mg doses of baricitinib. Data was censored at the time the patient changed study treatment but includes all data for patients who stayed on the originally randomized study medication. There were 4 deaths in the baricitinib 4 mg group and 2 deaths in the placebo group. There were no deaths in the 2 mg baricitinib group. The overall incidence rate of deaths was low. There were no significant incidence rate differences between placebo and the baricitinib groups.

**Table 86. Integrated safety analyses: Deaths in BARI 2, BARI 4, and placebo groups to week 52**

				Incidence rate difference	
	Placebo N=1070 PY=406	BARI 2 mg N=479 PY=336	BARI 4 mg N=997 PY=904	Placebo vs BARI 2	Placebo vs BARI 4
Deaths, n	2	0	4		
Incidence rate per 100 PY (95% CI)	0.5 (0.06, 1.78)	0	0.4 (0.12, 1.13)	-1.09 (-2.59, 0.42)	-0.05 (-0.85, 0.75)

Abbreviations: BARI=baricitinib, PY=person years, CI=confidence interval

Source: adapted from Applicant's response to information request received 7/21/16, p. 78

*Reviewer's comments: The overall incidence rate of deaths in the baricitinib studies was low. Pairwise comparisons showed no significant difference between placebo and either baricitinib group. Comparison of incidence rates between the 2 mg and 4 mg dose of baricitinib also did not show a significant incidence rate difference for death (data not shown).*

Table 87 is a listing of deaths that occurred in the baricitinib RA phase 2 and phase 3 studies. The overall number of deaths was low and there did not appear to be unexpected mortality for a population of patients with rheumatoid arthritis.

**Table 87. Listing of deaths in baricitinib program**

Subject Number	Study day of death	Study treatment duration	Cause of death	Comment
(b) (6)	333	333 days of BARI 8 mg	Myocardial infarction	66 year old white female who was thought to have a myocardial infarction
(b) (6)	192	186 days on BARI 4 mg	Pneumonia	68 year old white female who had obstruction of multiple coronary arteries underwent bypass graft surgery and died from post-operative complications of pneumonia
(b) (6)	506	168 days on placebo, 338 days on BARI 4 mg	Pancreatic adenocarcinoma	53 year old white female who had diagnosis of stage IV pancreatic adenocarcinoma developed a DVT and died 8 days later from cardiopulmonary arrest.

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(b) (6)	220	213 days on adalimumab	Respiratory failure	66 year old white female who had trauma to right prosthetic knee and developed coagulase-negative staphylococcus infection within the knee.
	165	165 days on baricitinib 4 mg	Circulatory failure	56 year old white male was hospitalized due to anemia and subsequently due to bleeding duodenal ulcer.
	523	523 days on BARI 4 mg	Pulmonary embolism	65 year old white female who had history of osteoporotic spine fracture had chest CT scan showing obstruction of both right and left pulmonary arteries
	223	192 days on placebo	Pneumonia	74 year old white male who had cholelithiasis and developed complications of pneumonia followed by septic shock.
	47	42 days on BARI 4 mg	Basilar artery thrombosis	76 year old white female who died shortly after having a basilar and left vertebral artery thrombosis.
	480	450 days on BARI 2 mg	Respiratory failure	53 year old white male with history of aortic and mitral valve incompetence had aortic valve surgery. Shortly thereafter, the patient had acute pulmonary edema and malignant cells from a mediastinal node biopsy. The patient died one month after hospitalization.
	324	142 days on placebo, 182 days on BARI 4 mg	Cardio-respiratory arrest	64 year old white female with history of diabetes and aortic valve replacement was found on the bedroom floor and diagnosed with cardiopulmonary arrest
	196	188 days on BARI 4 mg	Abdominal infection	73 year old white female who had 39 degree Celsius fever, abdominal pain and malaise and had abdominal CT scan with multiple bulky confluent mesenteric and retroperitoneal nodes
	63	63 days on placebo	Subarachnoid hemorrhage	51 year old female who had middle cerebral aneurysm and subsequently had extensive sylvian infarction
	27	24 days on placebo	Renal failure	57 year old female hospitalized for bronchopneumonia who developed hypotension and renal failure
	566	566 days on BARI 2 mg	Natural causes	75 year old female who died at home of natural causes. No autopsy was performed.
	498	498 days on BARI 4 mg + MTX	Cardiopulmonary arrest	70 year old female with history of hypertension and smoking was diagnosed with severe hemorrhagic stroke with involvement of brainstem.
	238	234 days on MTX	Pulmonary embolism	79 year old white female who was hospitalized for heart failure and had + d-dimer. No diagnostic imaging was performed for PE. Death following spontaneous rupture of emphysematous bulla
	121	105 days on	Pulmonary	74 year old white male who had CT scan and

(b) (6)		MTX	fibrosis	interstitial lung disease with a BAL negative for infection.
	359	359 days on methotrexate	Drowning	74 year old female who was found dead in her bathtub. No autopsy was performed.
	549	533 days on BARI 4 mg	Lung cancer	77 year old female found to have stage 4 lung cancer with liver metastasis.
	290	140 days on placebo and 150 days on renally dosed BARI (2 mg)	Acute myocardial infarction	59 year old male with history of diabetes, hypertension, and cardiac failure had a fatal acute myocardial infarction

Source: adapted from Applicant clinical safety summary, Appendix 1, p. 934-950

#### 8.4.2. Serious Adverse Events

The primary review will focus on the analyses provided in the Applicant's initial submission as well as responses by the Applicant to information requests that were sent during the review cycle. **Table 88** shows the number of serious adverse events by ICH criteria that occurred in the baricitinib RA studies that used a 2 mg and 4 mg dose during the first 12 weeks. The incidence rates for baricitinib and placebo were similar. Over the first 12 weeks of treatment, serious adverse events were relatively balanced among treatment groups.

**Table 88. Integrated safety analyses: SAEs by SOC in the 2 mg and 4 mg dose groups to week 12**

	Placebo	BARI 2 mg	BARI 4 mg
Total # of pts	551	479	479
Total exposure (PY)	125.3	110.4	111.1
Total # of pts with ≥1 event (%)	19 (3.4)	14 (2.9)	19 (4)
Incidence rates, events per 100 PYs	15.2	12.7	17.1
System organ class	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	2 (0.4)	0	1 (0.2)
Cardiac disorders	3 (0.5)	1 (0.2)	1 (0.2)
Ear and labyrinth disorders	0	0	2 (0.4)
Eye disorders	0	1 (0.2)	1 (0.2)
Gastrointestinal disorders	2 (0.4)	2 (0.4)	1 (0.2)
Hepatobiliary disorders	1 (0.2)	0	0
Infections and infestations	6 (1.1)	6 (1.3)	6 (1.3)
Injury, poisoning, and procedural complications	1 (0.8)	1 (0.2)	1 (0.2)
Investigations	0	0	3 (0.6)
Metabolism and nutrition disorders	1 (0.2)	0	0

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Musculoskeletal and connective tissue disorders	3 (0.7)	1 (0.2)	1 (0.2)
Neoplasms			
Nervous system disorders	1 (0.2)	0	3 (0.6)
Psychiatric disorders	1 (0.2)	1 (0.2)	0
Renal and urinary disorders	2 (0.4)	0	0
Reproductive system and breast disorders			
Respiratory, thoracic, and mediastinal disorders	0	2 (0.4)	3 (0.6)
Skin and subcutaneous tissue disorders	1 (0.2)	1 (0.2)	0
Vascular disorders	2 (0.4)	1 (0.2)	0

Abbreviations: BARI=baricitinib, PY=person years

Source: adapted from Applicant clinical safety summary, Appendix 2, p. 133-141

An information request was sent to the Applicant to include additional SAE analyses.

One of the analyses requested was to determine the number of patients who had adverse events during the 52 week period. The Applicant was asked to account for all time patient was exposed on drug, even after switch or rescue. The Applicant was concerned that this type of analysis would be skewed as the patients with more active disease would be switched to baricitinib 4 mg daily and this is a limitation to the analysis provided. However, in the interest of finding rare adverse events while patients were exposed to baricitinib, the FDA method 2 analysis included adverse events that occurred on the treatment the patient was on at the time of event, regardless of the therapy the patient was randomized to initially. This was a conservative approach to maximizing the number and of adverse events in baricitinib as well as attributing adverse events to baricitinib. However given the study design issues discussed above, there are limitations to comparisons between the two doses.

**Table 89** shows the SAEs that occurred from week 0 to 52 by system organ class in the phase 2 studies JADA, JADC, and JADN and phase 3 studies JADX, JADV, and JADW. The total exposure was much greater in the baricitinib 4 mg daily group due to the additional data that was collected after switch or rescue to baricitinib and the inclusion of a phase 3 study that did not include a baricitinib 2 mg dose treatment arm (JADV).

The number of events in the baricitinib 4 mg dose group was slightly higher than the baricitinib 2 mg dose group. Of note, the placebo group had a higher incidence rate of serious adverse events than the baricitinib groups. No striking differences were seen among the groups by system organ class.

**Table 89. BARI 2 mg vs 4 mg: SAEs by SOC weeks 0-52 (FDA method 2)**

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	placebo	BARI 2 mg	BARI 4 mg
Total # of pts	1070	479	1833
Total exposure (PY)	405.8	335.6	1671.1
Total # of events	100	56	296
Incidence rates, events per 100 PYs	24.6	16.7	17.7
System organ class	N (patient/100 PY)	N (patient/100 PY)	N (patient/100 PY)
Blood and lymphatic system disorders	3 (0.7)	1 (0.3)	10 (0.6)
Cardiac disorders	5 (1.2)	4 (1.2)	15 (0.9)
Ear and labyrinth disorders	0	0	4 (0.2)
Eye disorders	0	1 (0.3)	2 (0.1)
Gastrointestinal disorders	5 (1.2)	4 (1.2)	14 (0.8)
Hepatobiliary disorders	3 (0.7)	3 (0.9)	3 (0.2)
Infections and infestations	17 (4.2)	14 (4.2)	64 (3.8)
Injury, poisoning, and procedural complications	3 (0.7)	3 (0.9)	27 (1.6)
Investigations	1 (0.3)	1 (0.3)	6 (0.4)
Metabolism and nutrition disorders	5 (1.2)	0	5 (0.3)
Musculoskeletal and connective tissue disorders	14 (3.5)	5 (1.5)	30 (1.8)
Neoplasms	2 (0.5)	1 (0.3)	16 (1)
Nervous system disorders	3 (0.7)	2 (0.6)	11 (0.7)
Psychiatric disorders	4 (1)	1 (0.3)	4 (0.2)
Renal and urinary disorders	6 (1.5)	0	4 (0.2)
Reproductive system and breast disorders	0	0	3 (0.2)
Respiratory, thoracic, and mediastinal disorders	2 (0.5)	4 (1.2)	16 (1)
Skin and subcutaneous tissue disorders	1 (0.3)	1 (0.3)	3 (0.2)

Abbreviations: BARI=baricitinib, PY=person years

Adapted from Applicant response to FDA information request, p. 140

*Reviewer's comment: While there were no major differences among the treatment groups by SOC for SAEs, the unusually high number of SAEs in the placebo group was of interest and discussed with the Applicant. The Applicant did not have an explanation for the high number of SAEs. The number of SAEs in the placebo group was partially driven by more SAEs in the Musculoskeletal SOC, but the similar number of SAEs in the Infections and Infestations SOC was unexpected. One possible explanation was that the methods for collecting ICH SAEs was not standard as a CDQA form was sent to every investigator for which a patient discontinued treatment from study drug and asked if the patient had a SAE by GCP criteria. Due to the*

*additional query via the CDQA as to whether an AE due to discontinuation was a SAE, the number of AEs classified as SAEs may have been increased.*

**Table 90** shows the number of patients who had a SAE by the Applicant defined ICH criteria from week 0 to week 24 in the baricitinib 4 mg daily group and the placebo group. Of these patients, roughly 20% in the placebo and baricitinib groups were reported to have SAEs for “other reason serious” only. These SAEs were determined as a SAE via the CDQA form sent to the investigators. A small percentage of SAEs classified as by ICH were due to either no query or no clear response from the investigator.

**Table 90. Patients with SAEs meeting ICH criteria: week 0-24 data from 6-study placebo to BARI 4 mg comparison**

Patients with SAEs meeting ICH criteria	Placebo, N=50 n(%)	Baricitinib 4 mg, N=53 n (%)
Patients with SAEs that were serious only for other reason serious	9 (18%)	12 (23%)
Patients with SAEs that were serious based on no query issued or no/unclear response from investigator	3 (6%)	4 (8%)

Abbreviations: SAE=serious adverse event, ICH=International Conference on Harmonization  
 Source: adapted from Applicant information request response dated October 14, 2016, p. 45

An information request was sent to the Applicant to determine how serious adverse events were classified using the Applicant’s CDQA form. The Applicant initially presented SAEs by protocol and by ICH criteria in their NDA submission. The SAEs by protocol included patients who discontinued therapy permanently. These patients and additional patients who were listed as having a SAE for “other” reason were sent a CDQA form to determine whether the AE was an AE that was consistent with the Good Clinical Practices definition of a SAE. The use of the CDQA form may have resulted in the over counting of SAEs and may have blunted imbalances in the treatment groups due to over reporting of SAEs in each study arm. An information request was sent to the Applicant to determine how many AEs were classified as SAEs using the CDQA form and how many occurred in each treatment arm.

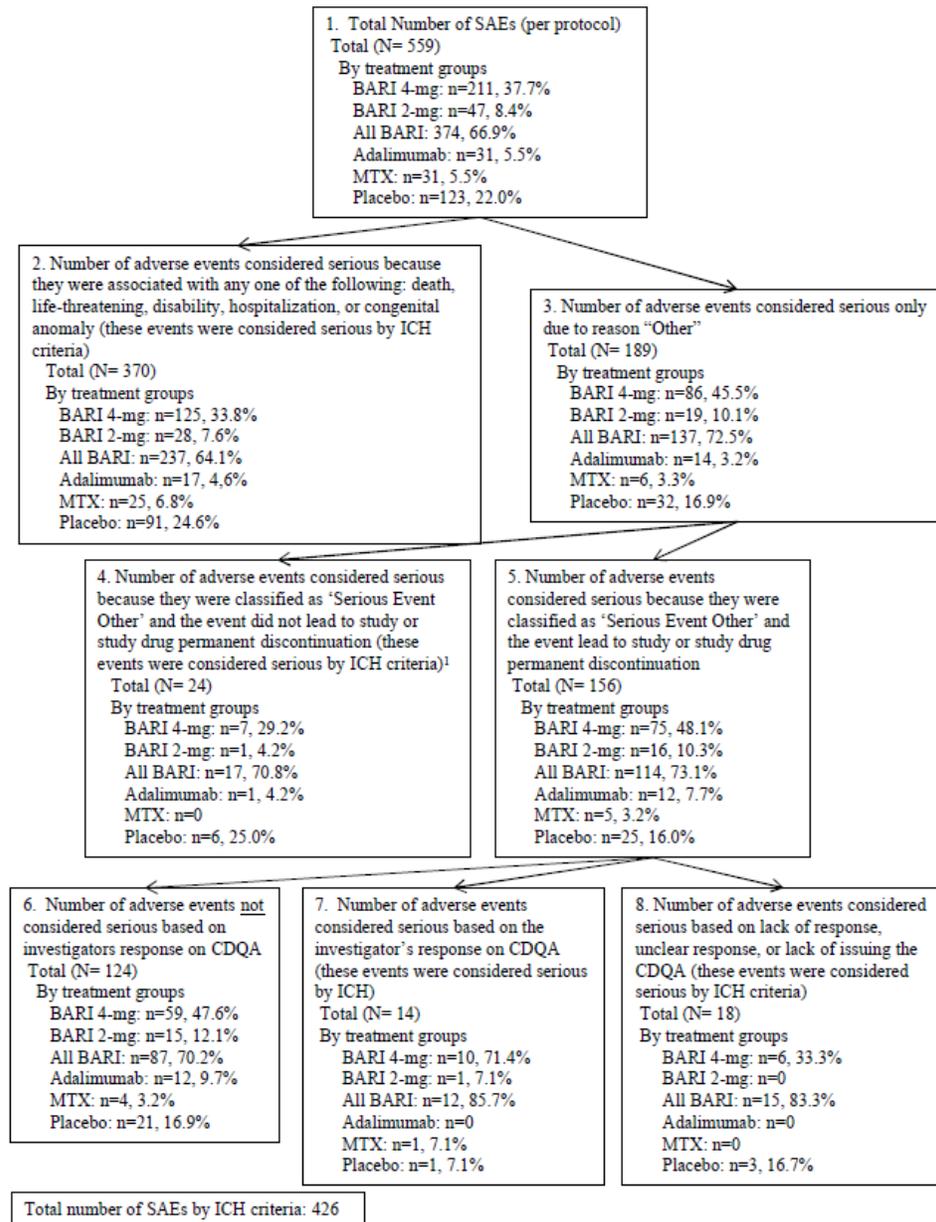
**Figure 15** shows the total number of serious adverse events by protocol that occurred in studies JADA, JADZ, JADW, JADX, and JADV. 559 SAEs per protocol were reported in the studies of which 374 were attributed to baricitinib, 31 were attributed to adalimumab, 31 were attributed to methotrexate and 123 were attributed to placebo. 74% (91/123) of the SAEs in the placebo group were ICH criteria based on death, life-threatening, disability, hospitalization, or congenital anomaly which are all part of the CFR definition for reporting SAEs. 63% (237/374) of the SAEs in the baricitinib groups met ICH criteria based on CFR definition.

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37% (137/374) of the SAEs reported in the baricitinib group were reported as “other”. 12% (17/137) were considered to be serious by ICH criteria due to the investigator declaring the SAE as “other” without a permanent discontinuation having occurred. 9% (12/137) considered serious by ICH criteria after the investigator was queried from a response to the CDQA and responded positively and 15/137 (11%) were considered serious ICH criteria due to a lack of a proper response from the investigator. The remaining 87/137 (64%) “other” SAEs were considered to not be serious.

26% (32/123) of the SAEs reported in the baricitinib group were reported as “other”. 19% (6/32) were considered to be serious by ICH criteria due to the investigator declaring the SAE as “other” without a permanent discontinuation having occurred. 1% (1/32) considered serious by ICH criteria after the investigator was queried from a response to the CDQA and responded positively and 3/32 (9%) were considered serious ICH criteria due to a lack of a proper response from the investigator. The remaining 21/32 (66%) “other” SAEs were considered to not be serious.

**Figure 15. Total number of serious adverse events by protocol in JADA, JADZ, JADW, JADX, and JADV)**



Source: Applicant's response to information request dated November 14, 2016

*Reviewer's comment: The additional query by the Applicant to the investigator via the CDQA form may have contributed to an increased percent of SAEs noted in the placebo group but also affected the baricitinib group. Therefore, re-analysis of the SAEs by removing SAEs that were classified as ICH due to query via CDQA would not be expected to reveal any further imbalances in SAEs between the 4 mg baricitinib group and placebo group.*

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

**Table 91** shows the adverse events leading to permanent discontinuation that occurred in the phase 2 and phase 3 RA trials. The events are from studies JADA, JADC, JADN, JADV, JADW, and JADX to week 16 of follow up. The exposure to baricitinib 2 mg was much smaller than the 4 mg and placebo groups as fewer studies had a 2 mg dose treatment arm. The overall percentage of permanent discontinuations due to adverse event was small in all dose groups. The overall rate of discontinuations in the baricitinib groups were nearly identical between the 2 doses (14 events per 100 patient years for BARI 2 mg, 14.8 events per 100 patient years for BARI 4 mg) and slightly higher than placebo (11.6 events per 100 patient years)

**Table 91. Integrated safety analysis to week 16: Adverse events leading to permanent discontinuation**

	Placebo	BARI 2 mg	BARI 4	Incidence rate difference (95% CI)	
				Placebo vs BARI 2 mg	Placebo vs BARI 4 mg
Total pts	1070	479	997	1.4 (-6.9, 9.8)	3.5 (-2.5, 9.4)
Person year exposure	308	140	298		
Patients with events, n	35	19	42		
Rate per 100 patient years (95% CI)	11.6 (8.1, 16.1)	14 (8.4, 21.8)	14.8 (10.7, 20)		

Abbreviations: BARI=baricitinib, CI=confidence interval

Source: adapted from Applicant response to information request dated November 14, 2016, p. 22

**Table 92** shows the adverse events leading to permanent discontinuation by system organ class. The most common system organ class leading to permanent discontinuation was infections and infestations. The percent of patients who had infections and infestations leading to permanent discontinuation were 0.6% in placebo, 1.5% in the 2 mg baricitinib group, 1.6% in the 4 mg baricitinib group. The baricitinib groups had a numerically higher percentage of infections and infestations leading to permanent discontinuation compared to the placebo group at week 16. The most common infection leading to discontinuation in infections and investigations were herpes zoster infections (4 events in placebo, 5 events in baricitinib 2 mg, and 10 events in baricitinib 4 mg).

Laboratory abnormalities leading to permanent discontinuation appeared to occur numerically more frequently in the baricitinib groups versus placebo. Anemia (3 events in baricitinib groups versus 0 in placebo) and alanine aminotransferase elevation (2 events in the baricitinib group versus 0 in placebo) were the most common reported preferred terms. Overall, laboratory abnormalities leading to permanent discontinuation were uncommon.

A numerically higher number of musculoskeletal and gastrointestinal events occurred in the placebo groups as compared to placebo. Of the musculoskeletal events, the most common preferred term was rheumatoid arthritis (5 in placebo, 0 in the baricitinib groups). Most of the discontinuations were balanced among groups. 5 gastrointestinal disorders were noted in the placebo group versus 1 in the baricitinib groups. There was no predominance of gastrointestinal preferred terms leading to permanent discontinuation in the placebo group (1 celiac disease, 2 diarrhea, 1 gastrointestinal hemorrhage, and 1 acute pancreatitis).

**Table 92. Integrated safety analyses to week 16: Adverse events leading to permanent discontinuation by system organ class**

System organ class, n (%)	PBO	BARI 2	BARI 4
Infections and infestations	6 (0.6)	7 (1.5)	16 (1.6)
Investigations	3 (0.3)	2 (0.4)	7 (0.7)
Blood and lymphatic	0	3 (0.6)	2 (0.2)
General disorders and administration site conditions	0	1 (0.2)	3 (0.3)
Hepatobiliary	1 (0.1)	1 (0.2)	3 (0.3)
Neoplasms	2 (0.2)	1 (0.2)	2 (0.2)
Immune system	0	0	2 (0.2)
Musculoskeletal and connective tissue	6 (0.6)	1 (0.2)	1 (0.1)
Skin and subcutaneous	2 (0.2)	1 (0.2)	1 (0.1)
Cardiac	1 (0.1)	0	1 (0.1)
Ear and labyrinth	0	0	1 (0.1)
Gastrointestinal	5 (0.5)	1 (0.2)	0
Nervous system	1 (0.1)	0	1 (0.1)
Reproductive system and breast	0	0	1 (0.1)
Respiratory, thoracic, and mediastinal	1 (0.1)	0	1 (0.1)
Vascular	1 (0.1)	1 (0.2)	0
Eye	1 (0.1)	0	0
Injury, poisoning, and procedural	1 (0.1)	0	0
Psychiatric	2 (0.2)	0	0
Renal and urinary	2 (0.2)	0	0

Abbreviations: BARI=baricitinib

Source: adapted from Applicant response to information request dated November 14, 2016, p. 22-27

*Reviewer's comments: In general, discontinuations were balanced among the placebo and baricitinib groups. The greatest difference was between the number of infections and infestations that led to discontinuation between the placebo and baricitinib groups. The infections that appeared to cause most of the discontinuations were herpes zoster infections.*

#### 8.4.4. Significant Adverse Events

The severity of adverse events was not a major aspect of the safety assessment for baricitinib. Rather, for each AE and particularly, for AESIs, severity was assessed and described based on the event being analyzed. Therefore, as part of this review, the grading of adverse events will not be described separately. See the individual AEs of special interest.

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

**Table 93** shows the most common adverse events that occurred in the first 16 weeks of studies JADA, JADC, JADN, JADV, JADW, and JADX. Preferred terms are listed for adverse events that occurred in at least 1.0% of the patients who received baricitinib. For most adverse events reported by system organ class and preferred terms, the number of adverse events were fairly balanced. Approximately 30% of baricitinib patients had an infection in the first 16 weeks compared to approximately 25% in the placebo group. The most common infections were upper respiratory tract infections and urinary tract infections.

There were several cases of herpes zoster infection with a numerically higher amount of infections occurring in the baricitinib groups (19 cases) versus placebo (4 cases). Herpes zoster was an adverse event of special interest and will be further described in the adverse events of special interest section.

Laboratory abnormalities such as creatine phosphokinase increase, dyslipidemia, and liver function test increases were noted in the week 16 analysis. The laboratory data provided by the Applicant confirmed that increases in liver function tests and creatine phosphokinase occurred more frequently in the patients treated with baricitinib as compared to placebo. Further details regarding these findings are available in the section on adverse events of special interest.

*Reviewer's comments: Overall, the common adverse events that occurred in the placebo group and baricitinib were similar. There were imbalances in the number of infections that occurred between placebo and the baricitinib treatment arms. Of the infections noted in the first 16 weeks of treatment, a vast majority of them were upper respiratory infections.*

*An increased number of laboratory abnormalities in the baricitinib arms were noted by preferred term in the first 16 weeks. These included liver function abnormalities, creatine phosphokinase abnormalities, and hyperlipidemia. Other findings that were noted in the Applicant's submission that were not evident in the analysis by preferred term were thrombocytosis and neutropenia. These laboratory abnormalities will be discussed in more detail in the adverse events of special interest.*

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**Table 93. Integrated safety analyses to week 16: most common adverse events by system organ class and preferred term**

System organ class, n (%) <i>Preferred term, n (%)</i>	Placebo	BARI 2	BARI 4
<b>Infections and infestations</b>	<b>253 (24)</b>	<b>138 (29)</b>	<b>298 (30)</b>
<i>Upper respiratory infection</i>	39 (4)	28 (6)	46 (5)
<i>Nasopharyngitis</i>	52 (5)	16 (3)	53 (5)
<i>Urinary tract infection</i>	31 (3)	18 (4)	34 (3)
<i>Bronchitis</i>	30 (3)	12 (3)	31 (3)
<i>Pharyngitis</i>	14 (1)	10 (2)	23 (2)
<i>Influenza</i>	10 (1)	6 (1)	18 (2)
<i>Gastroenteritis</i>	9 (1)	7 (2)	16 (2)
<i>Sinusitis</i>	12 (1)	10 (2)	10 (1)
<i>Herpes zoster</i>	4 (0)	5 (1)	14 (1)
<b>Gastrointestinal</b>	<b>128 (12)</b>	<b>85 (18)</b>	<b>145 (15)</b>
<i>Nausea</i>	17 (2)	13 (3)	28 (3)
<i>Diarrhea</i>	35 (3)	16 (3)	24 (2)
<i>Vomiting</i>	6 (1)	11 (2)	14 (1)
<i>Upper abdominal pain</i>	5 (1)	10 (2)	14 (1)
<i>Constipation</i>	15 (1)	8 (2)	13 (1)
<i>Abdominal pain</i>	9 (1)	8 (2)	8 (1)
<i>Dyspepsia</i>	8 (1)	1 (0)	14 (1)
<b>Musculoskeletal/connective tissue</b>	<b>125 (12)</b>	<b>56 (12)</b>	<b>95 (10)</b>
<i>Arthralgia</i>	17 (2)	9 (2)	17 (2)
<i>Back pain</i>	26 (2)	14 (3)	12 (1)
<i>Rheumatoid arthritis</i>	24 (2)	6 (1)	16 (2)
<b>Investigations</b>	<b>72 (7)</b>	<b>37 (8)</b>	<b>112 (11)</b>
<i>Creatine phosphokinase increase</i>	6 (1)	11 (2)	35 (4)
<i>Alanine aminotransferase increase</i>	10 (1)	5 (1)	15 (2)
<i>Aspartate aminotransferase increase</i>	5 (1)	2 (0)	14 (1)
<b>Nervous system</b>	<b>69 (6)</b>	<b>48 (10)</b>	<b>79 (8)</b>
<i>Headache</i>	32 (3)	30 (6)	38 (4)
<i>Dizziness</i>	8 (1)	7 (2)	14 (1)
<b>Metabolism and nutrition</b>	<b>57 (5)</b>	<b>28 (6)</b>	<b>80 (8)</b>
<i>Hypercholesterolemia</i>	14 (1)	7 (2)	28 (3)
<i>Hyperlipidemia</i>	8 (1)	6 (1)	20 (2)
<i>Dyslipidemia</i>	5 (1)	6 (1)	10 (1)
<b>Respiratory, thoracic, and mediastinal</b>	<b>47 (4)</b>	<b>97 (7)</b>	<b>36 (8)</b>
<i>Cough</i>	17 (2)	9 (2)	19 (2)
<i>Oropharyngeal pain</i>	5 (1)	10 (2)	12 (1)
<b>Skin and subcutaneous tissue</b>	<b>60 (6)</b>	<b>27 (6)</b>	<b>59 (6)</b>
<i>Rash</i>	8 (1)	7 (2)	9 (1)
<b>General and administration site conditions</b>	<b>62 (6)</b>	<b>31 (7)</b>	<b>48 (5)</b>
<i>Fatigue</i>	14 (1)	7 (2)	11 (1)

<i>Pyrexia</i>	9 (1)	6 (1)	10 (1)
Blood and lymphatic	43 (4)	21 (4)	47 (5)
<i>Anemia</i>	23 (2)	9 (2)	21 (2)
Injury, poisoning, procedural complications	39 (4)	19 (4)	49 (5)
Vascular	28 (3)	20 (4)	34 (3)
<i>Hypertension</i>	18 (2)	16 (3)	22 (2)
Eye	29 (3)	36 (2)	26 (3)
Psychiatric	29 (3)	12 (3)	23 (2)
Renal and urinary	17 (2)	9 (2)	20 (2)
Ear and labyrinth	12 (1)	5 (1)	17 (2)
Surgical and medical	13 (1)	22 (2)	15 (2)
Reproductive system and breast	10 (1)	9 (2)	12 (1)
Hepatobiliary	10 (1)	5 (1)	15 (2)
Cardiac	7 (1)	8 (2)	11 (1)
Neoplasms	5 (0)	4 (1)	8 (1)
Immune system	8 (1)	1 (0)	7 (1)
Endocrine	3 (0)	2 (0)	1 (0)
Congenital, familial, and genetic	0	1 (0)	0
Social	1 (0)	0	1 (0)

Abbreviations: BARI=baricitinib

Source: adapted from Applicant's response to information request dated November 14, 2016, p. 29-75

#### 8.4.6. Laboratory Findings

**Table 94** shows laboratory abnormalities that occurred during the phase 2 and phase 3 studies that used 2 mg and 4 mg doses of baricitinib up to week 16. In general, a higher number of patients had elevations in liver function tests in the baricitinib groups and the elevations appeared to be dose dependent. The creatinine was similar among groups but lower glomerular filtration rate was noted in the baricitinib groups (27% for baricitinib 2 mg daily, 28% for baricitinib 4 mg daily) versus placebo (16%). Elevated creatine phosphokinase (CPK) was noted in the baricitinib groups as compared to placebo. Increased lipids were also noted in the baricitinib groups versus placebo.

**Table 94. Integrated safety analyses: Chemistry abnormalities at week 16 for placebo, BARI 2, and BARI 4**

Analyte	Placebo N=551	BARI 2 mg N=479	BARI 4 mg N=479
	n (%)	n (%)	n (%)
ALT			
Low	6 (1.1)	6 (1.3)	1 (0.2)
High	50 (10.7)	61 (14.2)	92 (21.1)

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AST			
Low	18 (3.3)	5 (1.1)	4 (0.8)
High	40 (8)	49 (11)	83 (18.5)
Alkaline phosphatase			
Low	13 (2.4)	14 (3)	26 (5.6)
High	25 (5.7)	20 (5.2)	14 (3.9)
Total bilirubin			
Low	57 (11.8)	52 (11.9)	50 (12)
High	6 (1.1)	2 (0.4)	12 (2.5)
Albumin			
Low	7 (1.3)	2 (0.4)	3 (0.6)
High	5 (1)	33 (7.1)	34 (7.4)
Creatine phosphokinase			
Low	12 (2.2)	1 (0.2)	1 (0.2)
High	48 (9.7)	90 (20)	153 (34.9)
Creatinine			
Low	1 (0.2)	0	0
High	11 (2.3)	11 (2.5)	16 (3.6)
Estimated GFR			
Low	58 (15.9)	90 (26.5)	93 (28.3)
High	38 (8.8)	19 (4.8)	18 (4.6)
Sodium			
Low	8 (1.5)	4 (0.5)	8 (1.7)
High	42 (9.6)	33 (8.8)	39 (10.8)
Potassium			
Low	9 (1.7)	11 (2.3)	11 (2.4)
High	9 (1.7)	8 (1.7)	11 (2.4)
Calcium			
Low	9 (1.7)	8 (1.7)	6 (1.3)
High	14 (2.6)	15 (3.2)	14 (3)
Cholesterol			
Low	50 (13.5)	13 (4)	15 (14.7)
High	11 (2.3)	12 (2.8)	24 (5.6)
Triglycerides			
Low	15 (3.1)	5 (1.2)	9 (2.1)
High	22 (4.8)	26 (6.3)	28 (6.9)
LDL			
High	30 (13)	52 (19.6)	67 (27.2)
Total iron			
Low	34 (10.1)	9 (3.1)	10 (3.4)
High	7 (1.5)	21 (4.9)	35 (8.2)
Ferritin			
Low	11 (2.4)	16 (3.8)	7 (1.7)
High	5 (1.1)	3 (0.7)	18 (4.4)

Abbreviations: AST=aspartate aminotransferase, ALT=alanine transaminase, LDL=low density lipoprotein, GFR=glomerular filtration rate, BARI=baricitinib

Source: adapted from Applicant's summary of clinical safety appendix 1, p. 1751-1754

*Reviewer’s comments: The finding of elevated lipids was consistent with what is seen with other JAK inhibitors. Liver function tests were elevated in the baricitinib groups as compared to placebo and will be explained in more detail in the adverse events of special interest section. The finding of elevation in CPK is described further in adverse events of special interest. More patients appeared to have elevations in creatinine and decrease in glomerular filtration rate in the baricitinib groups as compared to placebo. Please see the adverse events of special interest for more details regarding the changes in renal function seen with baricitinib.*

**Table 95** shows hematologic lab abnormalities that occurred during the phase 2 and phase 3 studies that incorporated doses of 2 mg and 4 mg baricitinib to week 16. A slightly higher percentage of patients taking baricitinib versus placebo had abnormally low hemoglobin. In addition, patients who were taking baricitinib had abnormally low neutrophils as compared to placebo. Lymphocytes were abnormally high in more patients taking baricitinib versus placebo.

Additionally, a number of patients taking baricitinib developed thrombocytosis in the first few weeks of initiating baricitinib. The thrombocytosis moved closer to baseline as the patients continued to take baricitinib but never reached baseline values.

**Table 95. Integrated safety analyses: Hematologic abnormalities at week 16 for placebo, BARI 2, and BARI 4**

Analyte	Placebo N=551	BARI 2 mg N=479	BARI 4 mg N=479
	n (%)	n (%)	n (%)
Hemoglobin			
Low	95 (23.3)	86 (25.1)	95 (26.4)
High	2 (0.4)	0	0
Leukocytes			
Low	12 (2.2)	20 (4.3)	18 (3.9)
High	76 (17.9)	43 (11.7)	41 (11.6)
Neutrophils			
Low	15 (2.8)	31 (6.5)	35 (7.5)
High	96 (25.4)	62 (18.6)	55 (18)
Lymphocytes			
Low	48 (9.6)	29 (6.5)	38 (8.6)
High	11 (2.1)	43 (9.4)	45 (9.9)
Platelets			
Low	6 (1.1)	2 (0.4)	4 (0.9)
High	37 (7.7)	65 (15.5)	98 (23)

Abbreviations: BARI=baricitinib

Source: adapted from Applicant Summary of Clinical Safety Appendix 1, p. 2134-2135

*Reviewer’s comment: The finding of thrombocytosis was not consistent with the other JAK*

*inhibitors which typically cause thrombocytopenia. The reason for the thrombocytosis is unclear at this time. Of note, there were events of pulmonary embolism and deep venous thrombosis in the baricitinib groups that were imbalanced when compared to placebo. It is unclear whether the thrombocytosis might have been a risk factor for other clinical adverse events.*

#### 8.4.7. Vital Signs

Vital signs were assessed through the entire study period for all phase 2 and phase 3 studies. Table 96 shows the percent of patients who had treatment emergent changes in vital signs up to week 24. The patients are from the phase 2 and phase 3 studies in RA that used both baricitinib 2 mg daily and baricitinib 4 mg daily doses. For systolic blood pressure and diastolic blood pressure, a slightly numerically higher percentage of baricitinib patients had high treatment emergent abnormalities (7% in placebo versus 8% in baricitinib 2 mg and 9% in baricitinib 4 mg). Pulse rate was similar across groups (placebo, baricitinib 2 mg, and baricitinib 4mg). More patients had weight gain in the baricitinib groups (7% for both baricitinib 2 mg and baricitinib 4 mg) compared to placebo (3%).

**Table 96. Integrated Safety Analyses: Vital Sign measurements in placebo, BARI 2, and BARI 4**

	placebo		BARI 2 mg		BARI 4 mg	
	NAR	n (%)	NAR	n (%)	NAR	n (%)
Systolic blood pressure (mm Hg)						
Low	539	2 (0.4)	472	4 (0.8)	473	2 (0.4)
High	416	30 (7.2)	359	29 (8.1)	337	31 (9.2)
Diastolic blood pressure (mm Hg)						
Low	543	2 (0.4)	476	2 (0.4)	474	3 (0.6)
High	463	28 (6)	413	25 (6.1)	377	34 (9)
Pulse rate (beats per minute)						
Low	538	0	474	2 (0.4)	474	2 (0.4)
High	532	12 (2.3)	471	10 (2.1)	457	14 (3.1)
Weight (kg)						
Low	528	21 (4)	476	7 (1.5)	473	7 (1.5)
High	528	15 (2.8)	476	32 (6.7)	473	31 (6.6)

Abbreviations: NAR=number at risk, BARI=baricitinib  
Source: adapted from Applicant clinical safety summary appendix 1, p. 2455

#### 8.4.8. Electrocardiograms (ECGs)

A subset of patients in study JADX participated in an optional ECG Addendum. 27 patients in

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placebo, 28 patients receiving 2 mg of baricitinib daily, and 28 patients receiving 4 mg of baricitinib daily. ECG parameters were measured at Weeks 0, 1, 4, and 12 post-dose. Compared to placebo, a small statistically significant increase in QTcF was seen in the baricitinib groups compared to placebo at week 0 but at no other time points.

Of treatment emergent ECG abnormalities, one patient on 2mg daily of baricitinib had an abnormally high QTcF through week 12. No patients had a QT interval greater than 500 milliseconds. No meaningful correlations were seen in QTcF and plasma concentration of baricitinib from week 0-12 in the baricitinib groups.

#### 8.4.9. QT

The Applicant conducted study JADO, which was a two part placebo controlled study in healthy volunteers. Part A was a single dose, dose escalation study and Part B was a study on the effect of ECG QT interval after a single dose of baricitinib. 53 healthy subjects (43 males and 10 females) participated in Part B of the study. A suprathereapeutic dose of 40 mg was used for Part B of the study.

A single suprathereapeutic 40 mg dose of baricitinib did not prolong QTcP to a clinically significant degree. Similar results were noted when measuring QTcI and QTcF.  
Insert text here.

#### 8.4.10. Immunogenicity

No immunogenicity studies were performed for baricitinib. As a small molecule drug, assessment of immunogenicity was not anticipated.

### 8.5. Analysis of Submission-Specific Safety Issues

#### 8.5.1. Opportunistic infections

Opportunistic infections were an adverse event of special interest given that JAK inhibition would be anticipated to be immunosuppressive. Ten cases of potential opportunistic infections classified by MedDRA preferred term were originally reported by the Applicant. The opportunistic infections included esophageal candidiasis (5 cases), pneumocystis jiroveci pneumonia (3 events), wound infection with coccidioides species (1 event), and blood beta-D-glucan increased (1 case).

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.

While the Applicant provided arguments for why cases were not opportunistic, the events were counted in data tables. On October 14, 2016, an information request was sent to the Applicant to provide additional details on the number of opportunistic infections that occurred from 0-16 weeks in the placebo, baricitinib 2 mg, and baricitinib 4 mg treatment arms. The Applicant provided the data from studies JADA, JADC, JADN, JADV, JADW, and JADX. During this time period, one patient in the baricitinib group (0.34 events per 100 patient years) and one patient in the placebo group (0.32 events per 100 patient years) had an opportunistic infection. The incidence rate difference between baricitinib and placebo was 0.01 per 100 patient years. No patients had opportunistic infections in the 2 mg baricitinib treatment arm.

An information request was sent to the Applicant on June 24, 2016 to provide additional details on the opportunistic infections that occurred from week 0 through week 52. The data presented shows the potential opportunistic infections that occurred in JADA, JADC, JADN, JADV, JADX, and JADW as well as patients who continued from these studies into JADY. Events after switch or rescue were attributed to the medication that the patient was on at the time of event.

There were 6 opportunistic infections noted in the >52 week period for patients who took baricitinib 4 mg daily. The incidence rate of opportunistic infections was 0.36 per 100 patient years for patients who took 4 mg of baricitinib daily. There were no opportunistic infections in patients who took placebo or baricitinib 2 mg daily. The infections reported were 3 cases of

esophageal candidiasis, 1 disseminated tuberculosis, 1 pneumocystis jirovecii pneumonia, and 1 case of tuberculosis.

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.

*Reviewer’s comments: During internal review of the Applicant’s submitted NDA, in addition to the potential opportunistic infections reported by the Applicant, other potential opportunistic infections were seen on review of the narratives for serious adverse events. These included a cryptococcal pneumonia (baricitinib 2 mg) well as a case of acute histoplasmosis (baricitinib 2 mg). In response to an information request to identify all unusual infections that occurred in immunocompetent hosts, the Applicant agreed to include the additional potential opportunistic infections found during FDA review as well as look for other infections that would not be expected to occur in an immunocompetent host during the RA studies. The Applicant stated that no other infections other than what were noted by the Applicant and FDA occurred during the RA studies. In the submission, the Applicant minimized the identified opportunistic infections. However, review of the case details suggested that they were actual opportunistic infections.*

### 8.5.2. Serious infections

**Table 97** shows the number of serious infections that occurred in a 16 week period for studies JADA, JADC, JADW, JADV, and JADX. The data included was prior to patients were rescued or switched from treatment. The patients had slightly increased incidence rate of serious infection in the patients who were randomized to baricitinib therapy with a slightly higher incidence rate of serious infections in the baricitinib 4 mg group as compared to placebo or 2 mg of baricitinib. However, the number of patients with at least one serious infection was slightly higher in the baricitinib 2 mg group compared to the 4 mg group.

**Table 97. Integrated safety set: number of serious infections at week 0 to 16**

	Placebo PY=308	Baricitinib 2 mg PY=140	Baricitinib 4 mg PY=298
Number of serious infections	13	7	16
Incidence rate per 100 PY (95% CI)	4.2 (2.3, 7.2)	5 (2, 10.3)	5.4 (3, 8.7)
Number of patients with ≥1 serious infection	13	6	12
Incidence rate per 100 PY	4.2 (2.3, 7.3)	4.3 (1.6, 9.4)	4.1 (2.1, 7.1)

(95% CI)			
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Abbreviations: CI=confidence interval, PY=person years

Source: adapted from Applicant's response to information request dated 10/28/16, p. 12

**Table 98** shows the number of serious infections that occurred from week 0 to week 52 in studies JADA, JADC, JADN, JADV, JADX, and JADW and corresponding extension studies. The amount of exposure to baricitinib 4 mg is larger because of the number of studies that included the 4 mg dose and because patients who switched to baricitinib 4 mg from 2 mg or placebo is included in this dataset. Incidence rate was reported to help account for the increased exposure to the 4 mg dose of baricitinib; however, patients who switched or rescued from other therapies had continued active disease and were likely sicker and potentially more prone to adverse events.

**Table 98. Integrated safety set: number of serious infection from week 0 to 52**

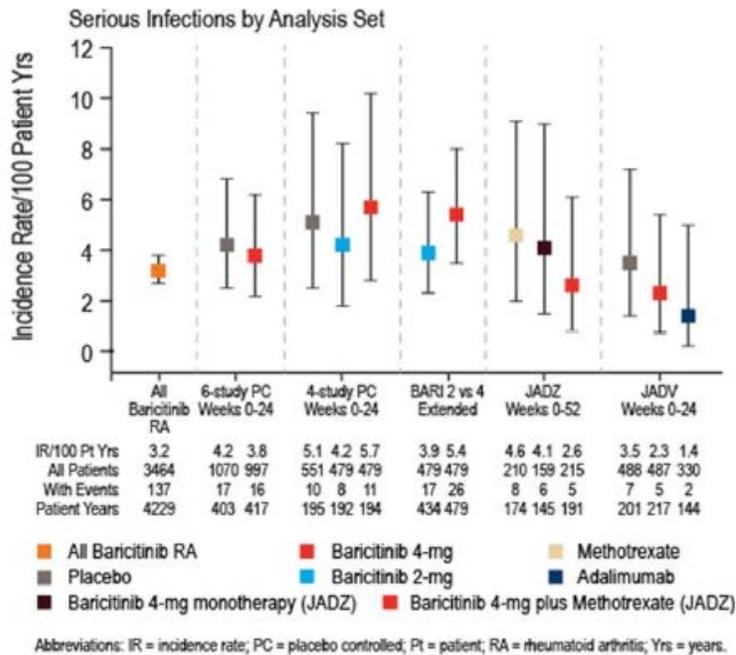
	Placebo N=1070 PY=406	BARI 2 mg N=479 PY=336	BARI 4 mg N=1833 PY=1671
Total number of serious infections	18	15	79
Incidence rate per 100 PY	4.4	4.5	4.7

Abbreviations: PY=person years, BARI=baricitinib

Source: adapted from Applicant's response to information request dated 7/21/16, p. 205

**Figure 16** shows the events of serious infection that occurred in the RA clinical studies by the Applicant's derived safety analysis datasets. The overall incidence rate of serious infections per 100 patient years for baricitinib in all RA studies was 3.2. In study JADV, the incidence rate was 2.3 per 100 patient years for baricitinib 4 mg, 3.5 per 100 patient years for placebo, and 1.4 per 100 patient years for adalimumab, a known immunosuppressant. Notably, incidence rates for serious infections in the placebo groups displayed ranged from 3.5 to 5.1 per 100 patient years and were at times higher than the study treatment arms using baricitinib or adalimumab.

**Figure 16. RA studies: serious infections in patients**



Source: Applicant summary of clinical safety, p. 153

*Reviewer’s comment: The Applicant initially concluded that baricitinib was not immunosuppressive due to the lack of significant imbalance in the incidence rates of infections in the baricitinib group versus placebo. However, there were some concerns regarding the reported findings. The background rate of serious infections was relatively high for all groups and larger than what was reported in many other rheumatoid arthritis study programs. Further, in study JADV, the rate of serious infections was lower for the adalimumab group as compared to baricitinib **and** placebo; however, adalimumab is a known immunosuppressant with a boxed warning for serious infections.*

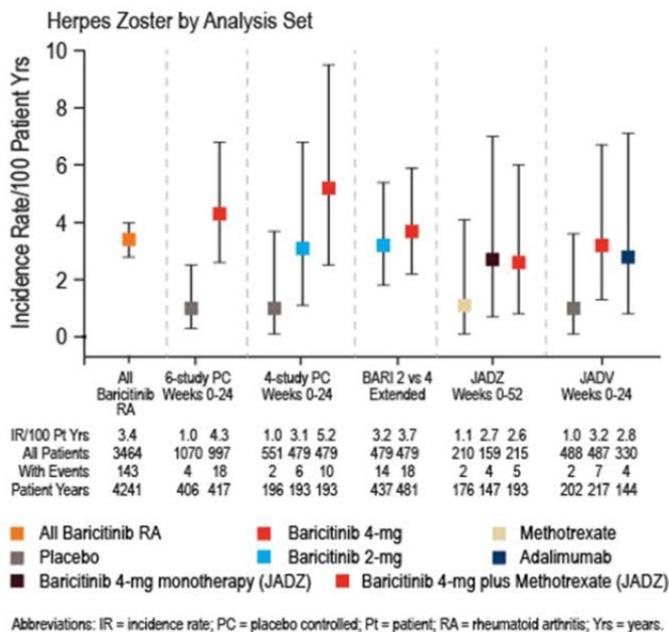
*These findings were discussed with the Applicant at the Late Cycle meeting. The Applicant did not have an explanation for the observation that adalimumab had a lower rate of serious infections than both placebo and baricitinib despite being an immunosuppressant. As there were several serious infections, infections, and opportunistic infections with exposure to baricitinib, the Division felt that the prescribing information should reflect that baricitinib was an immunosuppressant with adequate warnings. The Division provided recommendations to add infections, including serious infections and opportunistic infections, as warnings in the prescribing information which the Applicant agreed to.*

### 8.5.3. Herpes zoster

**Figure 17** shows the incidence rate of herpes zoster cases that occurred in the different safety analysis datasets provided by the Applicant. In the placebo controlled period to week 24 for

studies that had 2 mg and 4 mg baricitinib treatment arms, the incidence rate per 100 patient years was 1 in the placebo group, 3 in the 2 mg baricitinib group, and 5 in the 4 mg baricitinib group. A comparison of the 2 mg dose and 4 mg dose after the placebo controlled period is also shown in the figure. The incidence rate was closer with 3.2 events per 100 patient years occurring in the 2 mg baricitinib group and 3.7 events per 100 patient years in the 4 mg baricitinib group. Overall, patients who were exposed to baricitinib had an incidence rate of 3.4 herpes zoster infection per 100 patient years.

**Figure 17. Applicant integrated safety datasets: Herpes zoster**



Source: Applicant summary of clinical safety, p. 165

**Table 99** shows the number of herpes zoster infection that occurred during the placebo controlled period of the trials that included a 4 mg baricitinib treatment arm and the numbers of herpes zoster infections that occurred in all patients who were exposed to baricitinib in RA trials. Most patients who developed a herpes zoster infection had not had a prior herpes zoster infection. Most patients who developed an infection were between the ages of 50 and 65. There were a large number of cases that did occur in the Asian countries and Japan. 33% of herpes infections that occurred in all patients who received baricitinib were located within the United States.

**Table 99. Applicant BARI 4-mg RA PC and All BARI RA safety analysis datasets: herpes zoster infection**

	Placebo N=1070	BARI 4 mg N=997	All BARI RA
Patient with treatment emergent herpes zoster	4	18	141

cases			
n, (%)			
Age			
<50	1 (25)	3 (17)	31 (22)
≥50 and <65	2 (50)	9 (50)	73 (53)
≥65	1 (25)	6 (33)	35 (25)
Regions			
USA/Canada	1 (25)	8 (44)	47 (33)
Central America/ South America/Mexico	0	0	12 (9)
Asia (excludes Japan)	2 (50)	3 (17)	15 (11)
Japan	0	3 (17)	36 (26)
Europe	1 (25)	2 (11)	21 (15)
Rest of world	0	1 (6)	10 (7)
Prior herpes zoster	0	2 (11)	7 (5)
Prior herpes zoster vaccination	0	0	2 (2)
Serious by ICH	1 (25)	3 (17)	21 (15)

Abbreviations: ICH=International Conference on Harmonization, BARI=baricitinib  
Source: adapted from applicant summary of clinical safety, p. 166

*Reviewer's comments: A significant number of herpes zoster infections were noted in the baricitinib RA studies. The Applicant has included this risk in their proposed prescribing information.*

#### 8.5.4. Major cardiovascular events (MACE)

In the first 16 weeks of studies that contained 2 mg and 4 mg doses of baricitinib, there were two positively adjudicated MACE in the baricitinib 4 mg group (IR=1.7 per 100 patient years) and two in the placebo group (IR=1.7 per 100 patient years). No events were seen in the baricitinib 2 mg group.

**Table 100** shows the positively adjudicated MACE that occurred during JADV, JADX, and JADW as well as the extension study JADY. The phase 2 studies were not included as there was no adjudication of cardiovascular events in the phase 2 studies. The number of events over a 52 week period were small with comparable incidence rates reported in placebo (0.6 per 100 patient years), the 2 mg baricitinib treatment arm (0.3 per 100 patient years), and the 4 mg baricitinib treatment arm (0.5 per 100 patient years)

**Table 100. Integrated safety analyses to week 52: Major cardiovascular events**

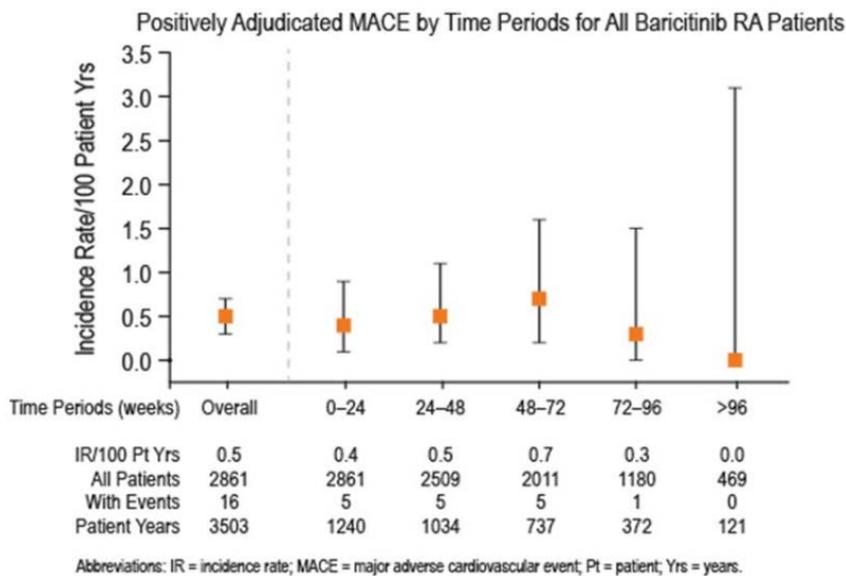
	Placebo N=892 PY=365	BARI 2 mg N=403 PY=305	BARI 4 mg N=1662 PY=1547
Total number of serious infections	2	1	8

Incidence rate per 100 PY	0.6	0.3	0.5
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Abbreviations: BARI=baricitinib, PY=person years  
Source: adapted from Applicant's response to information request dated 7/21/16, p. 205

**Figure 18** shows the overall MACE incidence rate per 100 patient years and incidence rate at 24 week intervals in the RA baricitinib studies. As shown in the figure, the incidence rate of MACE did not appear to increase over time, but the confidence intervals did widen. 16 events overall were reported in 3503 patient years which gave an incidence rate of 0.5 events per 100 patient years.

**Figure 18. RA studies: positively adjudicated MACE Events**



Source: Applicant clinical safety summary, p. 218

**Table 101** shows the positively adjudicated MACE that occurred during the phase 3 RA trials. 16 patients exposed to baricitinib in the phase 3 RA trials had positively adjudicated MACE (3 in the 2 mg baricitinib group and 13 exposed to 4 mg of baricitinib). 2 patients exposed to placebo, 2 patients exposed to methotrexate monotherapy, and 1 patient exposed to adalimumab had positively adjudicated MACE. The most common type of MACE was myocardial infarction with 8 of the 13 MACE attributed to myocardial infarction.

**Table 101. Positively adjudicated MACE in the Phase 3 rheumatoid arthritis trials**

N (person years exposure)	Placebo N=892 (354)	Methotrexate monotherapy N=210 (172)	Adalimumab N=330 (276)	Baricitinib 2 mg N=403 (604)	Baricitinib 4 mg N=1265 (1756)	Baricitinib after switch/rescue N=1194 (1102)
Total patients	2 (0.6)	2 (1.2)	1 (0.4)	3 (0.5)	8 (0.2)	5 (0.5)

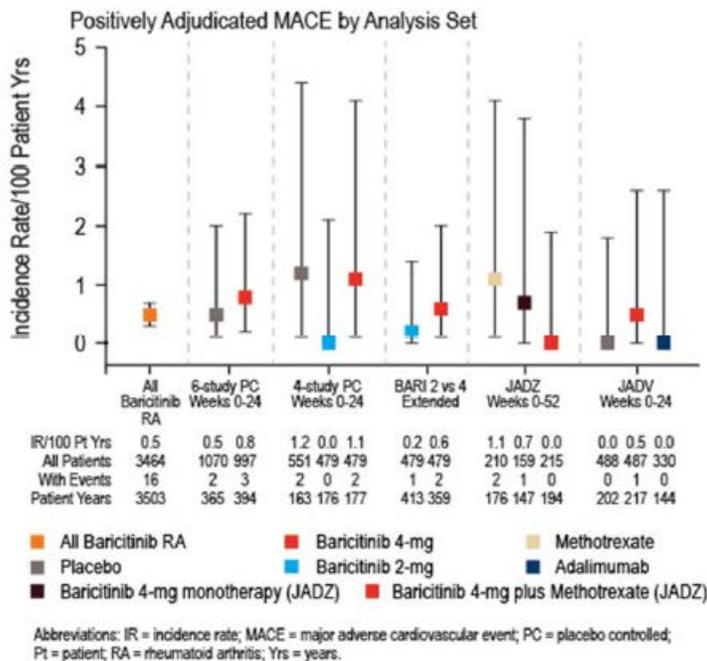
with at least one MACE						
Cardiovascular death	1	1	0	1	1	2
Myocardial infarction	1	0	1	1	5	3
Stroke	1	1	0	1	1	2

Abbreviations: MACE=major cardiovascular event  
Source: Applicant summary of clinical safety, p. 216

*Reviewer’s comments: While more cardiovascular events occurred in the baricitinib groups, the exposure adjusted rates were fairly balanced.*

**Table 102** shows the MACE that occurred in the baricitinib RA program by the different analyses submitted by the Applicant in their safety submission. Incidence rates are reported by treatment. The overall incidence rate of MACE in the all baricitinib RA studies was low (IR=0.5 per 100 patient years). MACE was numerically higher for the baricitinib 4 mg group (IR=0.5 per 100 patient years) as compared to adalimumab (0) in study JADV. MACE was numerically higher in the 4 mg baricitinib group (1.1 per 100 patient years) as compared to the 2 mg group (0); however the incidence rate for the baricitinib 4 mg group was comparable to placebo (1.2 per 100 patient years).

**Table 102. Applicant derived analyses: incidence rate per 100 patient years**



Source: Applicant clinical safety summary, p. 218

**Table 103** provides the conversion of mg/dL to mmol/L for interpretation of the LDL levels reported in **Table 104**. In **Table 104**, the listing of positively adjudicated events that occurred in studies JADV, JADX, JADW, JADZ, and the extension study JADY are reported. Overall, 268 events in 207 patients were sent to the Applicant. Of those the Applicant reported 26 events in 21 patients as having positively adjudicated major adverse cardiovascular events (MACE). Of these events, 8 were cardiovascular deaths, 12 myocardial infarctions occurred in 11 patients, and there were 6 strokes in 6 patients.

**Table 103. LDL cholesterol conversion: mg/dL to mmol/L**

LDL cholesterol (mg/dL)	LDL cholesterol (mmol/L)
Below 70	Below 1.8
Below 100	Below 2.6
100-129	2.6-3.3
130-159	3.4-4.1
160-189	4.1-4.9
190 and above	Above 4.9

Abbreviations: LDL=low density lipoprotein

Source: adapted from <http://www.mayoclinic.org/tests-procedures/cholesterol-test/details/results/rsc-20169555>

**Table 104. Positively adjudicated MACE events for JADV, JADX, JADW, JADZ, and JADY**

Study	Study drug, start date	CV Past medical history	LDL baseline, event (mmol/L)	Demographics	Event date	MedDRA PT	Fatal
(b) (6)	BARI 4 mg (b) (6)	Dyslipidemia, HTN	3.78, 3.6	68 year old white female	(b) (6)	Myocardial infarction	N
	BARI 4 mg (b) (6)	Dyslipidemia, HTN	Not provided	68 year old white female		Coronary revascularization	N
	BARI 4 mg (b) (6)	Dyslipidemia, HTN	Not provided	68 year old white female		Pneumonia	Y
	Adalimumab (b) (6)	Angina pectoris, cardiac failure chronic	2.82, 3.34	59 year old Asian male		Myocardial infarction	N
	Adalimumab (b) (6)	Angina pectoris, cardiac failure chronic	Not provided	59 year old Asian male		Thrombectomy	N
	Placebo (b) (6) rescued (b) (6) to 2 mg BARI (renally dosed)	DM, HTN, cardiac failure chronic	2.05, 2.1	59 year old American Indian		Acute myocardial infarction	Y
	Placebo (b) (6) rescued on (b) (6) to 4 mg BARI	None noted	2.51, 2.62	67 year old white female		Cerebrovascular accident	N
	BARI 4 mg (b) (6)	Type 2 DM, HTN, hypercholesterolemia	3.7, 2.1	69 year old white male		Coronary arterial stent insertion	N

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(b) (6)				(b) (6)	
BARI 4 mg (b) (6)	Type 2 DM, HTN, hypercholesterolemia	Not provided	69 year old white male	Myocardial infarction	N
BARI 4 mg (b) (6)	Type 2 DM, HTN, hypercholesterolemia	Not provided	69 year old white male	Catheterization cardiac	N
BARI 4 mg (b) (6)	Type 2 DM, HTN, hypercholesterolemia	Not provided	69 year old white male	Acute myocardial infarction	N
BARI 4 mg (b) (6)	Type 2 DM (steroid induced), bilateral interstitial pneumonitis, dyslipidemia	3.19, only baseline available	76 year old white female	Basilar artery thrombosis	Y
BARI 4 mg (b) (6)	Hypercholesterolemia	4.45, 6.79	54 year old white female	Acute myocardial infarction	N
BARI 4 mg (b) (6)	Hypercholesterolemia	Not provided	54 year old white female	Coronary revascularization	N
BARI 4 mg (b) (6)	DM, HTN	3.24, 2.77	45 year old white female	Myocardial infarction	N
BARI 4 mg (b) (6)	DM, HTN	Not provided	45 year old white female	Coronary revascularization	N
BARI 2 mg (b) (6)	None noted, + smoker	3.57, 4.2	54 year old white male	Acute myocardial infarction	N
BARI 2 mg (b) (6)	None noted, + smoker	Not provided	54 year old white male	Coronary angioplasty	N
BARI 2 mg (b) (6) until rescue to BARI 4 mg (b) (6)	HTN, hyperlipidemia, 40 year previous smoker	3.19, 3.19	72 year old white female	Ischemic stroke	N
Placebo (b) (6) switched to BARI 4 mg (b) (6)	+smoker, coronary artery disease, hyperlipidemia, HTN, Type 2 DM	2.72, 1.79	47 year old white male	Myocardial infarction	N
Placebo	+smoker, coronary	Not	47 year old white	Cardiac failure	N

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(b) (6)	(b) (6) switched to BARI 4 mg (b) (6)	artery disease, hyperlipidemia, HTN, Type 2 DM	provided	male	(b) (6)	congestive	
	Placebo (b) (6) switched to BARI 4 mg (b) (6)	+smoker, coronary artery disease, hyperlipidemia, HTN, Type 2 DM	Not provided	47 year old white male		Angina pectoris	N
	Placebo 9/16/2013	HTN	2.87, only baseline available	51 year old white female		Subarachnoid hemorrhage	Y
	BARI 4 mg (b) (6)	None noted	2.75, 3.24	57 year old white female		Acute coronary syndrome	N
	BARI 4 mg (b) (6)	None noted	Not provided	57 year old white female		Percutaneous coronary intervention	N
	Placebo (b) (6)	HTN, Type 2 DM, DVT	3.52, baseline	63 year old white female		Myocardial infarction	N
	Placebo (b) (6)	HTN, Type 2 DM, DVT	Not provided	63 year old white female		Coronary revascularization	N
	Methotrexate (b) (6) switched to BARI 4mg (b) (6)	HTN, + smoker	3.42, 2.64	70 year old white female		Hemorrhagic stroke	N
	Methotrexate (b) (6) switched to BARI 4mg (b) (6)	HTN, + smoker	Not provided	70 year old white female		Cardio-respiratory arrest	Y
	Methotrexate (b) (6)	None reported	2.85, 2.43	79 year old white female		Pulmonary embolism	Y
	BARI 4 mg (b) (6)	HTN, dyslipidemia	3.24, 2.82	74 year old white male		Myocardial infarction	N
	BARI 4 mg (b) (6)	HTN, dyslipidemia	Not provided	74 year old white male		Coronary revascularization	N
	BARI 4 mg (b) (6)	None reported	4.35, 3.65	48 year old white female		Acute myocardial infarction	N
	BARI 4 mg (b) (6)	None reported	Not provided	48 year old white female		Percutaneous coronary intervention following acute MI	N
	Methotrexate (b) (6)	None reported	1.32, 1.58	65 yo Asian female		Cerebral hemorrhage	N
	BARI 2 mg (b) (6) (rescued to BARI 4 mg on (b) (6)	Aortic valve incompetence, atrial fibrillation, HTN, mitral valve incompetence	2.67, 3.37	53 yo white male		Cardiac failure congestive	N

(b) (6) BARI 2 mg (b) (6) (rescued to BARI 4 mg on (b) (6))	Aortic valve incompetence, atrial fibrillation, HTN, mitral valve incompetence	Not provided	53 yo white male	(b) (6) Acute pulmonary edema	N
BARI 2 mg (b) (6) (rescued to BARI 4 mg on (b) (6))	Aortic valve incompetence, atrial fibrillation, HTN, mitral valve incompetence	Not provided	53 yo white male	Respiratory failure	Y
BARI 2 mg (4 mg group renal dosed) (b) (6)	Angina pectoris, cardiac failure congestive, hypertensive cardiomyopathy, vertebral artery stenosis	3.16, 3.68	65 yo white female	Pulmonary embolism	Y

Abbreviations: PT=preferred term, MedDRA=Medical Dictionary for Regulatory Activities, BARI=baricitinib  
Source: adapted from Applicant clinical safety summary appendix 2, p. 512

*Reviewer's comments: MACE occurred in the baricitinib studies with a higher number of events occurring in the 4 mg baricitinib group; however, this may have been a result of the increased exposure in the 4 mg baricitinib group. The overall incidence rate of MACE was low (0.5 per 100 patient years) and comparable to the placebo group. LDL did not seem to correlate with positively adjudicated MACE as often times the LDL decreased at or prior to the event. More events appeared to occur in the 4 mg baricitinib treatment arm as compared to the 2 mg baricitinib treatment arm. Overall, the incidence rate of MACE in the baricitinib treatment arms were comparable to the placebo group.*

### 8.5.5. Malignancies

In total, 32 cases of malignancies classified by standardized MedDRA query were reported in the 2862 RA patients who participated in the Phase 3 RA trials (3461 patient years of exposure). There were 7 basal cell carcinomas, 5 squamous cell carcinomas, 1 invasive ductal breast carcinoma, 2 keratocanthomas, 2 squamous cell carcinomas of the skin, 1 colon adenocarcinoma, 1 pancreatic adenocarcinoma, 1 adrenocortical carcinoma, 1 Bowen's disease, 1 breast cancer, 1 cervical carcinoma, 1 clear cell renal cell carcinoma, 1 diffuse large B-cell lymphoma, 1 gallbladder adenosquamous carcinoma, 1 gastric cancer, 1 malignant lung neoplasm, 1 lymphoma, 1 malignant fibrous histiocytoma, 1 malignant melanoma, 1 low malignant potential ovarian tumor, 1 prostate cancer, 1 renal cancer, and 1 squamous cell carcinoma of the lung.

**Table 105** shows the number of malignancies (non-melanoma skin cancers are excluded) that occurred in the integrated safety analyses from weeks 0-16. The patients were from the phase 2 studies JADA, JADC, and JADN and the phase 3 studies JADV, JADW, and JADX. In the first 16 weeks, no malignancies were seen in the placebo group and one malignancy was seen in the 2 mg baricitinib group and one malignancy was seen in the 4 mg baricitinib group. The overall

incidence rate of malignancy was 0.7 events per 100 patient years in the 2 mg baricitinib group and 0.3 events per 100 patient years in the 4 mg baricitinib group.

**Table 105. Integrated safety analyses: Incidence rate of malignancies excluding NMSC from week 0-16**

	placebo	BARI 2 mg	BARI 4 mg	BARI 2/4
Total # of patients	1070	479	997	1476
Total exposure, patient years	308	140	298	438
Total number of patients with events	0	1	1	2
Incidence rate, patients per 100 patient years	0	0.7	0.3	0.5

Abbreviations: BARI=baricitinib, PY=person years

Source: adapted from Applicant's response to information request dated October 14, 2016, p. 11

**Table 106** shows the number of malignancies (non-melanoma skin cancers are excluded) reported for placebo, baricitinib 2 mg, 4 mg, and both doses of baricitinib. The exposure adjusted incidence rates for the baricitinib groups were 0.72 per 100 patient years in the 4 mg baricitinib group and 0.6 per 100 patient years in the 2 mg baricitinib group. The placebo group had an incidence rate of 0.49 per 100 patient years.

**Table 106. Integrated safety analyses: Incidence rate of malignancies from week 0-52**

	placebo	BARI 2 mg	BARI 4 mg	BARI 2/4
Total # of patients	1070	479	1833	2312
Total exposure, patient years	405.8	335.6	1671.1	2085.6
Total number of patients with events	2	2	12	14
Incidence rate, patients per 100 patient years	0.49	0.6	0.72	0.67

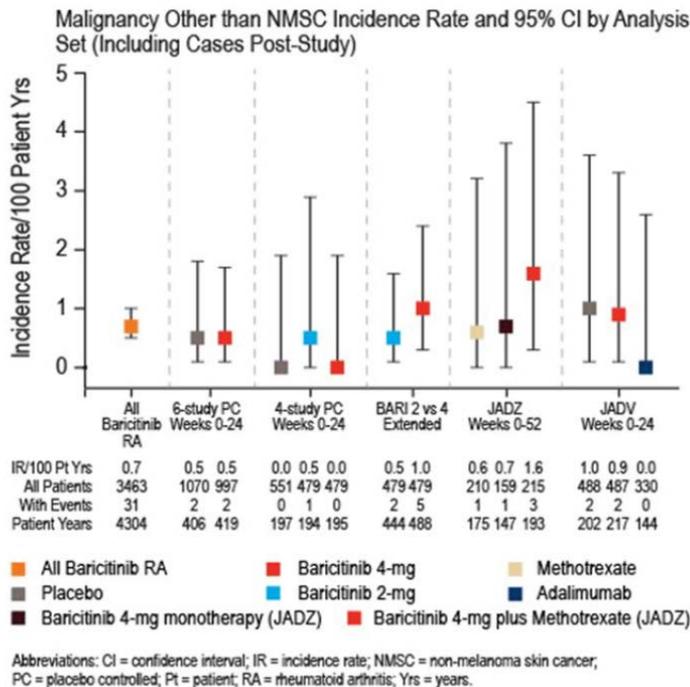
Abbreviations: BARI=baricitinib, PY=person years

Source: adapted from Applicant's response to information request dated July 21, 2016, p. 210

**Figure 19** shows the incidence rate of malignancies by Applicant derived safety analysis sets. Overall the incidence rate of malignancies in the all baricitinib set was 0.7 per 100 patient years. The incidence rate of malignancy was higher with the 4 mg baricitinib dose compared to the 2 mg baricitinib dose when looking at the extended data. The incidence rate of malignancies were similar in the placebo groups and the 4 mg baricitinib group. In study JADV, the number of malignancies in the adalimumab group was smaller than the placebo and baricitinib groups.

The highest incidence rate of malignancy (1.6 per 100 patient years) was seen in patients who took the combination of methotrexate and baricitinib 4 mg daily, but the confidence intervals were wide.

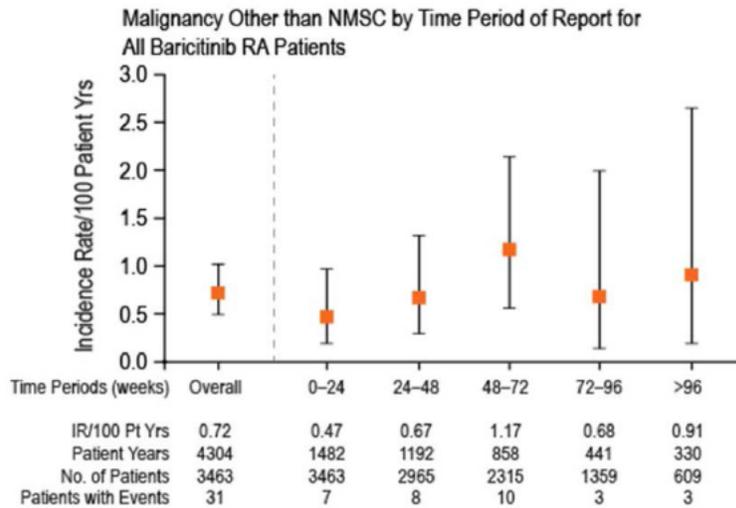
**Figure 19. Malignancy incidence rate by Applicant derived safety analysis sets**



Source: Applicant Summary of Clinical Safety, p. 178

**Figure 20** shows the incidence rate of reported malignancies by time period in all baricitinib patients who participated in a rheumatoid arthritis study. The peak incidence rate of malignancies (1.17 malignancies per 100 patient years) occurs at 48 to 72 weeks but then decreases with further exposure. Limited conclusions are possible as the confidence intervals overlap. The overall incidence rate of malignancies in the baricitinib groups is 0.72 per 100 patient years.

**Figure 20. Baricitinib rheumatoid arthritis patients: Malignancy by time period of report**



Source: Applicant's clinical safety summary, p. 179

*Reviewer's comment: The incidence rate of malignancies was increased for baricitinib compared to placebo and for baricitinib 4 mg compared to 2 mg. However, comparison of incidence rates between the doses is limited given the study design with patients crossing over from 2 mg to 4 mg and escaping to 4 mg for ongoing disease activity. In the RA programs, with the exception of non-melanoma skin cancers, there did not appear to be a predominance of any type of cancer and the types of cancers would be generally anticipated in the patient population. Three cases of diffuse B-cell lymphoma were reported beyond Week 52.*

### 8.5.6. 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 **Error! Not a valid bookmark self-reference..** 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 in the section on MACE. **Table 107: Triglyceride, LDL, and HDL Levels at Baseline and Change from Baseline**

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	PBO	BARI 2	BARI 4	BARI 2/4
<b>Triglycerides (mg/dL)</b>				
Baseline	127	128	125	126
Change from baseline at Week 12	-1	5	17	13
% change from baseline at Week 12	3.8%	8.9%	15.7%	13.6%
<b>LDL Cholesterol-Direct (mg/dL)</b>				

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Baseline	119	116	117	116
Change from baseline at Week 12	-1	8	14	12
% change from baseline at Week 12	0.4%	8.2%	14.4%	12.5%
<b>HDL Cholesterol-Direct (mg/dL)</b>				
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 baseline at Week 12	1.1%	11.3%	15.8%	14.4%

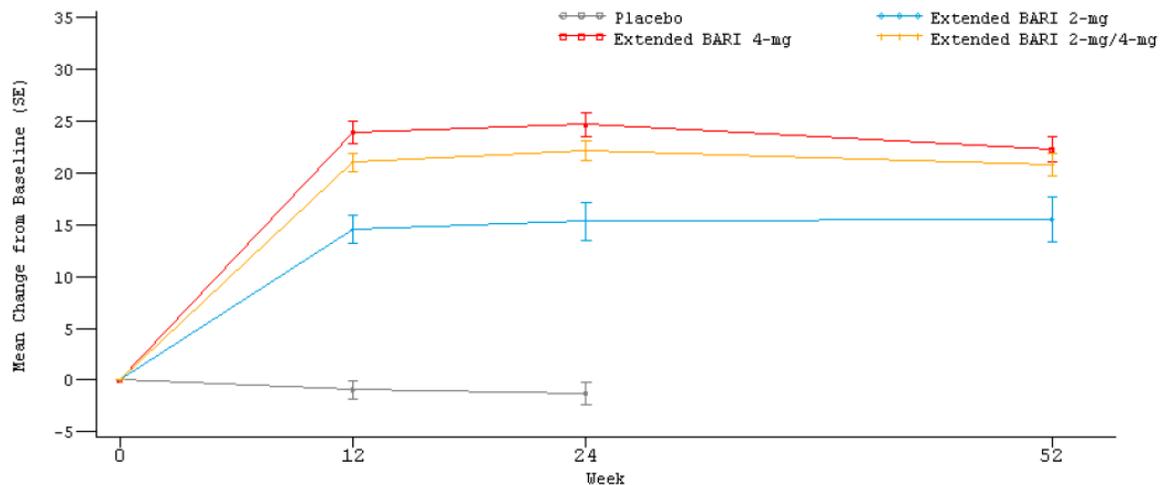
Abbreviations: PBO=placebo; BARI=baricitinib

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

Figure 21 shows changes in mean cholesterol level (mg/dL) from baseline in the phase 2 studies JADA, JADC, and JADN and the phase 3 studies JADX, JADW, and JADV as well as the extension study JADY. Both doses of baricitinib resulted in mean increases from baseline in lipid levels. The 4 mg dose showed approximately a 20 mg/dL change in cholesterol from baseline at week 12. The 2 mg dose showed approximately a 10 mg/dL change in cholesterol at week 12. These changes remained through week 52. There were no mean increases from baseline in the placebo group to week 24.

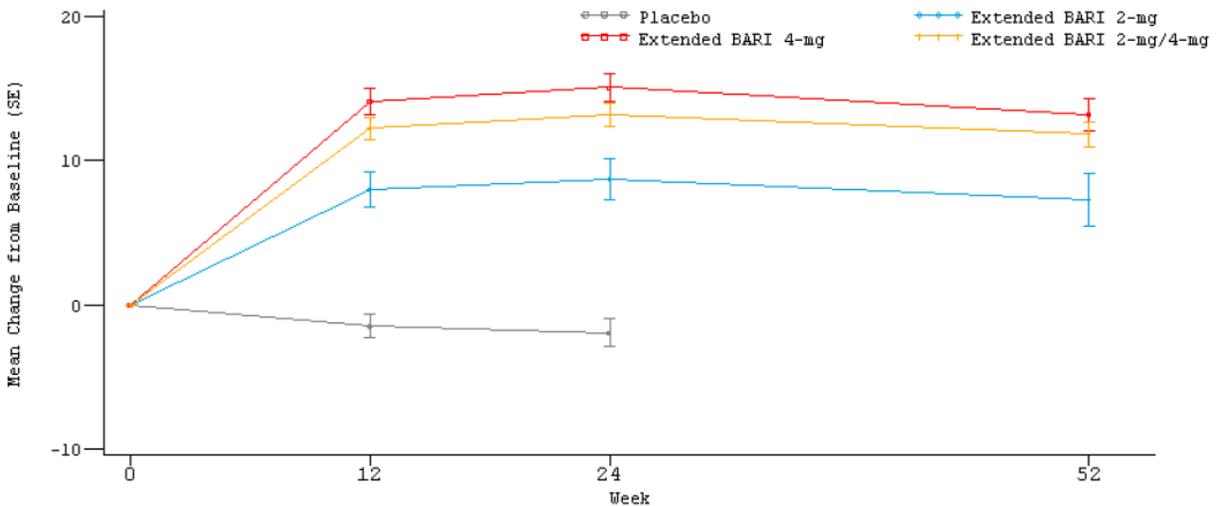
**Figure 21. Integrated Safety Summary: mean change in cholesterol from baseline through 52 weeks**



Source: Applicant's response to information request dated June 24, 2016, p. 100

**Figure 22** shows the mean change in LDL from baseline to Week 52. The LDL increases by more than 10 mg/dL in the 4 mg baricitinib group and by more than 5 mg/dL in the 2 mg baricitinib group. These increases remain stable to week 52. There were no mean increases from baseline in the placebo group to week 24.

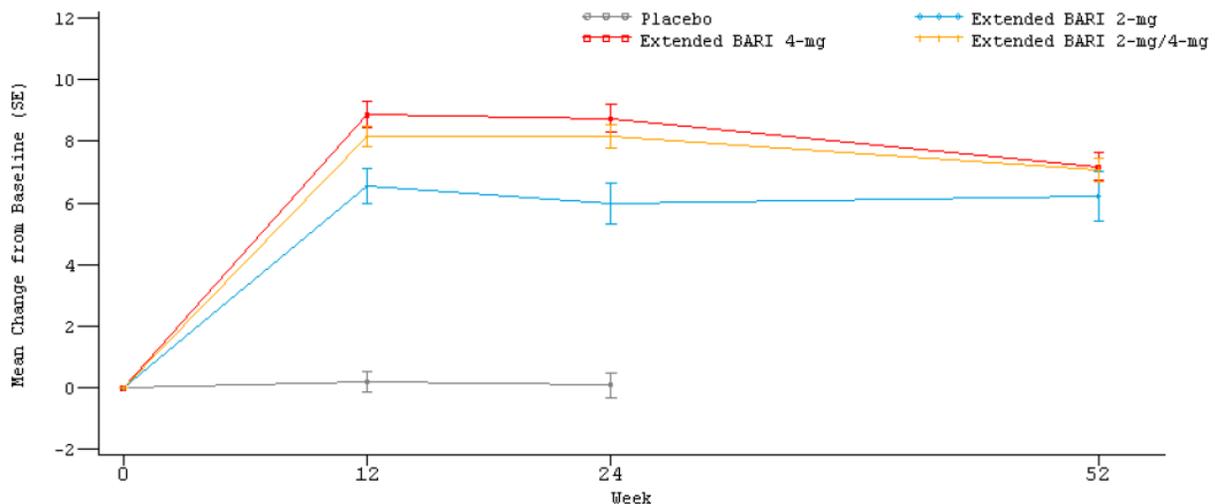
**Figure 22. Integrated Safety Summary: mean change in LDL from baseline through 52 weeks**



Source: Applicant's response to information request dated June 24, 2016, p. 102

**Figure 23** shows the mean change from baseline for HDL in patients included in the integrated safety summary. As with the other lipid parameters, the HDL increased to week 12 and remained elevated in patients who were exposed to baricitinib. As with the other lipid parameters, the 4 mg dose appeared to increase HDL higher than the 2 mg dose.

**Figure 23. Integrated Safety Summary: Mean change in HDL from baseline through 52 weeks**



Source: Applicant's response to information request dated June 24, 2016, p. 103

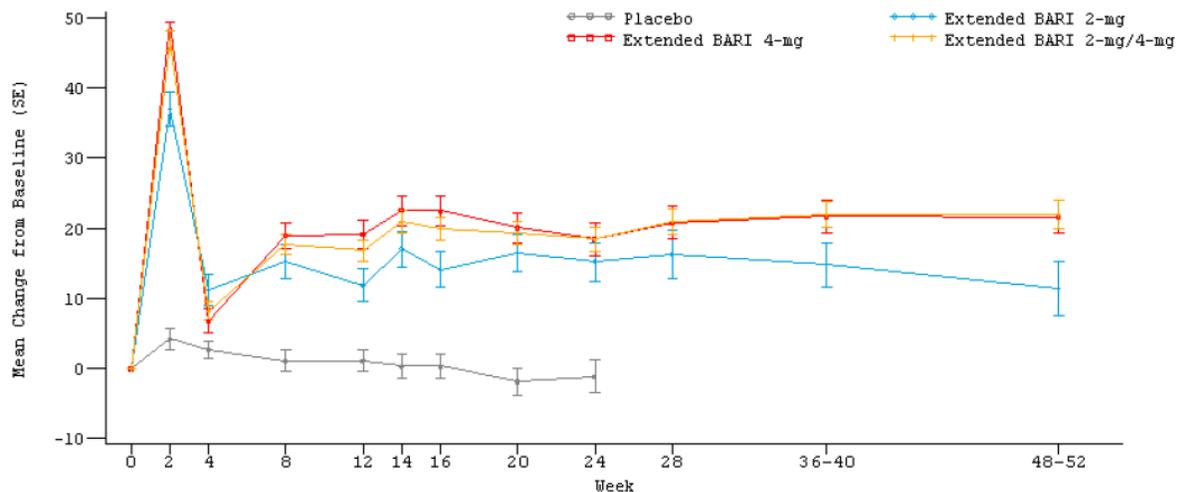
*Reviewer's comments: The lipid parameters increased from baseline to week 24 with exposure to baricitinib in a dose dependent fashion. Due to the increases in lipid parameters that were seen in the baricitinib groups as compared to placebo, the studies were scrutinized for increases*

in major cardiovascular events (MACE). During the phase 2 and phase 3 studies in RA there was no clear signal that increased MACE events occurred with baricitinib exposure.

### 8.5.7. Thrombocytosis

**Figure 24** shows the mean change in platelets over 52 weeks in the integrated safety study set. A spike in platelets is seen in the initial weeks of starting baricitinib. After the initial spike, platelet counts decrease, but remain elevated above baseline over the 52 week period. The mechanism of this increase in platelets is unknown at this time.

**Figure 24. Integrated safety analyses: Mean change from baseline over 52 weeks for platelets ( $10^9/L$ )**



Source: Applicant response to information request dated June 24, 2016, p. 105

The mean change in platelets is greatest at week 2 in the baricitinib groups with a change in platelet count (cells $\cdot 10^9$  per liter) of 37 in the 2 mg baricitinib group and 51 in the 4 mg baricitinib group compared to 4 in the placebo group. At week 16, the mean change in platelet count from baseline was 0 in the placebo group, 14 in the 2 mg baricitinib group, and 22 in the 4 mg baricitinib group. At weeks 48 through 52, the change from baseline in platelet count is 11 in the 2 mg baricitinib group and 22 in the 4 mg baricitinib group.

*Reviewer's comments: In the baricitinib RA studies, a dose dependent increase in platelets was noted with a maximal increase over the baseline platelet measure occurring at week 2. Platelet counts remained elevated about baseline to week 52 for patients who were on baricitinib. The mechanism for increase in platelets is not known at this time and whether the increase in platelets results in a clinical outcome is unclear. As there were additional events of venous*

*thrombotic events noted in the baricitinib studies, the change in platelet counts was evaluated for thrombotic events that occurred.*

### 8.5.8. Venous thrombotic events

**Table 108** shows the number of patients who had thrombotic events in the phase 2 studies JADA, JADC, and JADN, the phase 3 studies JADV, JADW, and JADX, and the extension study, JADY. Thrombotic events reported included arterial and venous thromboses. **Table 108** shows the number of events that occurred prior to week 52 and after the number of events that occurred after week 52. A numerical imbalance in thrombotic events was seen in the baricitinib groups as compared to placebo and numerically more thrombotic events occurred in the baricitinib 4 mg group when compared to the 2 mg group. The incidence rate as calculated per 100 patient years was similar between the 2 mg and 4 mg baricitinib groups for thrombotic events to Week 52.

**Table 108. Thrombotic events in baricitinib RA studies**

	Placebo	Bari 2 mg	Bari 4 mg
<b>Weeks 0-52</b>	N=1070 PY≈406	N=479 PY≈335	N=1833 PY≈1665
Patients with thrombotic events, n (rate per 100 PY)	2 (0.5)	5 (1.5)	20 (1.2)
Patients with venous thrombosis, n (rate per 100 PY)	0	2 (0.6)	11 (0.7)
Patients with arterial thrombosis (rate per 100 PY)	2 (0.5)	3 (0.9)	9 (0.5)
<b>Weeks&gt;52</b>	NA	N=177 PY≈155	N=1469 PY≈1020
Patients with thrombotic events, n (rate per 100 PY)	NA	1 (0.6)	15 (1.5)
Patients with venous thrombosis, n (rate per 100 PY)	NA	1 (0.6)	9 (0.9)
Patients with arterial thrombosis (rate per 100 PY)	NA	0	8 (0.78)

Abbreviations: BARI=baricitinib, PY=person years

Source: Applicant response to clinical information request received 10/28/16, p. 88, 92

*Reviewer's comment: The rate per 100 PY of thrombotic events and venous thromboses was higher with baricitinib than placebo. For venous thrombosis, the rate was higher for 4 mg compared to 2 mg. The cases reported by the Applicant were examined individually. The Applicant was requested to provide the incidence rates for the events that were occurring as shown in the tables above. A hematology consult was placed to determine whether the events*

*that were occurring were of clinical significance and to determine whether additional data needed to be requested from the Applicant.*

Six events of deep vein thrombosis or pulmonary embolism were reported within 180 days of starting baricitinib. The events are listed in **Table 109**. In most cases there was an increase in platelet count, but baricitinib was associated with platelet increases in patients without thromboses also. Of note, of the 6 cases, 2 patients had a traumatic fracture and 1 patient had a previous history of deep venous thrombosis.

**Table 109. DVT and PE events within 180 days of starting baricitinib in phase 3, RA trials**

Study number	Study drug exposure	Event	Baseline platelet count (*10 <sup>9</sup> L)	Comment
(b) (6)	Baricitinib 4 mg for 113 days	DVT	589	53 year old Asian smoker with BMI of 36; platelet count of 669 prior to event
	Baricitinib 4 mg for 140 days	DVT	282	66 year old white female who slipped, fell, and had comminuted fracture of right femur. DVT reported 2 days after fall. Platelet count 289 prior to DVT
	Baricitinib 4 mg for 37 days	PE	327	62 year old white female with BMI of 37, history of mild varicose veins; platelet count 431 prior to event
	Baricitinib 4 mg for approximately 150 days	DVT	249	58 year old white female who had history of DVT 17 months prior to enrolling in study; Platelet count 293 prior to event
	Baricitinib 4 mg for 50 days	PE	219	66 year old female with BMI of 45, bilateral peripheral edema, family history of PE developed dyspnea one week after discontinuing baricitinib; platelet count 274 prior to event
	Baricitinib 4 mg for 6 weeks	PE	234	65 year old female with history of rib fractures 8 months prior to study start and BMI of 52 developed dyspnea 6 weeks after starting baricitinib; platelet count 320 prior to event

Abbreviations: DVT=deep vein thrombosis, PE=pulmonary embolism  
Source: adapted from Applicant summary of clinical safety, p. 77-78

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**Table 110. Additional venous thrombosis cases from patients in phase 3 RA trials and extension**

Study number	Study drug exposure	Event	Baseline platelet count (*10 <sup>9</sup> L)	Comment
(b) (6)	Baricitinib 4 mg for 330 days	DVT	278	54 year old female with history of pancreatic adenocarcinoma; platelet count of 354 prior to event; patient died 8 days after DVT diagnosis (not due to PE per investigator)
	Baricitinib 4 mg for 523days	PE	219	66 year old white female with history of spine osteoarthritis and osteoporotic fracture. Platelet count 180 prior to PE
	Baricitinib 4 mg for 395 days	DVT	264	78 year old male with fracture of left femur 9 days prior to diagnosis of DVT. Platelet count 326 at time of diagnosis of DVT.
	Baricitinib for 169 days (received 2 mg and 4 mg doses)	PE	362	61 year old white female who complained of dyspnea and weakness during study visit; Platelet count 416 prior to event
	Baricitinib randomized to 2 mg and switched to 4 mg on baricitinib for total of 260 days	PE	260	51 year old white female with history of midsternal chest pain and shortness of breath; platelet count 332 prior to event
	Baricitinib 4 mg for 295 days	DVT/PE	200	49 year old white male with onset of dry cough and mild dyspnea; platelet count 223 prior to event
	Baricitinib 2 mg for 205 days	DVT	186	64 year old white female with history of previous blood clots and positive lupus anti-coagulant; platelet count 196 prior to event
	Baricitinib 2 mg for 298 days	DVT	315	Patient with history of meniscal tear; platelet count 293 prior to event
	Baricitinib 4 mg for 479 days	DVT/PE	275	64 year old white female with factor V mutation; platelet count 385 prior to event
	Baricitinib 4 mg for 466 days	PE	174	53 year old female with history of oral contraceptive use and left leg superficial

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(b) (6)				vein thrombosis; platelet count 255 prior to event
	Baricitinib 2 mg for 3 months rescued to 4 mg; total exposure 431 days	PE	233	70 year old male with history of left leg cellulitis developed dizziness, chest pain, and dyspnea; platelet count 292 prior to event
	Baricitinib 4 mg for 443 days	DVT	243	50 year old Asian female who had a previous history of DVT and reported non-serious rib fracture at time of DVT; platelet count 288 prior to event
	Methotrexate for 234 days	PE	204	79 year old female was diagnosed without imaging studies on clinical grounds; developed air edema from ruptured emphysematous bulla

Source: adapted from Applicant summary of clinical safety, p. 1137-1147

14 patients stopped baricitinib as a result of a thrombotic event. 7 patients resumed baricitinib and no events of thrombotic events have been reported in the patients who restarted baricitinib.

In study JADZ, one patient was reported to have a pulmonary embolism. The patient was receiving methotrexate monotherapy. No patients receiving baricitinib in study JADZ had an event of pulmonary embolism or deep vein thrombosis from week 0-52.

*Reviewer's comment: The number of thrombotic events that occurred in the RA baricitinib studies was not balanced between placebo and baricitinib groups. A hematology consult was placed to determine whether the imbalance of events warranted further labeling in the prescribing information and whether additional information to further investigate the imbalance was necessary. The consult noted that thrombotic events appeared to be higher in the baricitinib group as compared to placebo but the overall rate of events was low. The hematology consult stated that patients who received baricitinib would not need to be prophylactically anticoagulated. According to the hematology consult, the role of including thrombotic events in the prescribing information would be to raise awareness of the thrombotic events that occurred in the baricitinib trials. How the prescribing information would reflect the thrombotic events that occurred in baricitinib trials was a topic of ongoing discussion at the time of this review.*

### 8.5.9. Hematologic abnormalities

#### *Hematologic abnormalities*

Table 111 summarizes the mean changes in hematologic parameters. These parameters will be discussed in the sections below.

**Table 111: Hemoglobin, Platelets, Leukocyte Count, Neutrophils, and Lymphocytes at Baseline and Change from Baseline**

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

### 8.5.10. Anemia

**Table 112** show patients who had either treatment emergent abnormally low hemoglobin or had a CTCAE grade increase due to a decrease in hemoglobin while participating in a baricitinib RA trial. The placebo group and 4 mg baricitinib groups are derived from 6 studies (JADA, JADC, JADN, JADX, JADV, and JADW) while the 2 mg baricitinib group is derived from 4 studies (JADX, JADW, JADA, and JADN) as the 2 mg treatment arm was not available in some of the studies conducted by the Applicant. In the week 16 time period, similar percentage of patients had treatment emergent low abnormal hemoglobin regardless of whether they were in placebo (25%), baricitinib 2 mg (25%), or baricitinib 4 mg (27%) groups. Worsening of anemia defined by a worsening in CTCAE grade increase was numerically higher in the baricitinib 2 mg (26%) and baricitinib 4 mg group (27%) as compared to placebo (22%)

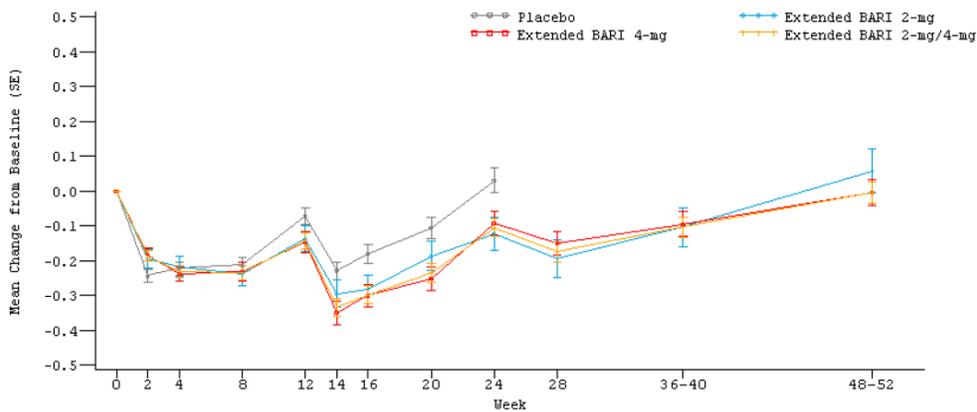
**Table 112. Integrated safety analyses to week 16: Low hemoglobin abnormalities**

n/NAR (%)	Placebo	BARI 2 mg	BARI 4 mg
Treatment emergent abnormal low	183/747 (25)	86/343 (25)	191/696 (27)
Any CTCAE grade increase	233/1059 (22)	125/477 (26)	262/988 (27)

Source: adapted from Applicant summary of clinical safety, p. 231

**Figure 25** shows the mean change from baseline in hemoglobin (mg/dL) to week 52 in patients who participated in the phase 2 studies JADA, JADC, and JADN and the phase 3 studies JADV, JADW, and JADX as well as extension study JADY. After an initial drop in hemoglobin, the hemoglobin appears to increase towards mean baseline by week 52.

**Figure 25. mean change from baseline to week 52: anemia**



Source: Applicant response to information request dated June 24, 2016, p. 104

**Table 113** shows patients who had discontinuations as a result of hematologic abnormalities. The data comes from patients who participated in studies JADA, JADC, JADN, JADV, JADW, and JADX. The patients who had discontinuations due to anemia were small. Overall, 3 patients who took baricitinib (0.2 events per 100 patient years) had a discontinuation from anemia compared to zero events in placebo in the first 16 weeks.

**Table 113. Integrated safety analyses to week 16: permanent discontinuation due to hematologic abnormalities**

	placebo	BARI 2 mg	BARI 4 mg	BARI 2/4
Total # of patients	1070	479	997	1476
Total exposure, patient years	308.1	140.3	297.7	438
Anemia, n	0	2	1	3
Incidence rate, patients per 100 patient years	0	0.4	0.1	0.2
Lymphopenia	0	1	0	1
Incidence rate, patients per 100 patient years	0	0.2	0	0.1
Lymphocytosis	0	0	1	1
Incidence rate, patients per 100 patient years	0	0	0.1	0.1

Abbreviations: BARI=baricitinib, PY=person years

Source: adapted from Applicant response to information request dated November 14, 2016, p. 24

Drawing from the studies that were used in **Table 113**, **Table 114** shows the number of patients who had permanent discontinuations due to a hematologic abnormality through week 52. 9 patients on baricitinib discontinued due to anemia. The incidence rate was 0.4 events per 100 patient years. The incidence rate was higher in the 2 mg baricitinib group (0.6 events per 100 patient years) compared to the 4 mg baricitinib group (0.3 events per 100 patient years).

**Table 114. Integrated safety analyses to week 52: permanent discontinuation due to hematologic abnormalities**

	placebo	BARI 2 mg	BARI 4 mg	BARI 2/4
Total # of patients	1070	479	1833	2312
Total exposure, patient years	405.8	335.6	1671.1	2085.6
Anemia, n	0	3	6	9
Incidence rate, patients per 100 patient years	0	0.6	0.3	0.4
Leukopenia	0	0	1	1
Incidence rate, patients per 100 patient years	0	0	0.1	0
Lymphopenia	0	1	1	2
Incidence rate, patients per 100 patient years	0	0.2	0.1	0.1
Neutropenia	0	0	2	2
Incidence rate, patients per 100 patient years	0	0	0.1	0.1
Thrombocytosis	0	1	2	3
Incidence rate, patients per 100 patient years	0	0.2	0.1	0.1

Abbreviations: BARI=baricitinib

Source: adapted from Applicant's response to information request date June 24, 2016, p. 189

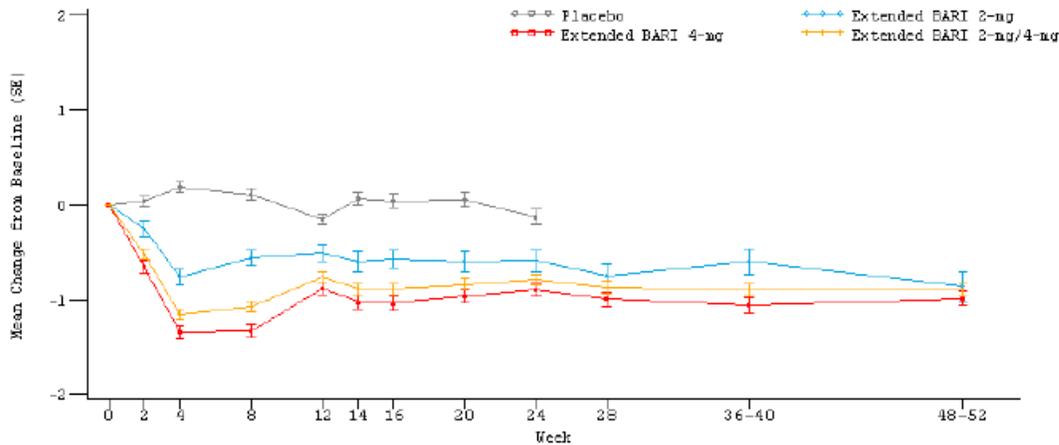
*Reviewer's comment: The percent of patients who had a decrease in hemoglobin was numerically higher in the baricitinib groups as compared to placebo. All discontinuations secondary to anemia were in the baricitinib group suggesting that baricitinib has an effect on hemoglobin. The overall incidence rate of anemia leading to permanent discontinuation was low at week 16 (0.2 per 100 patient years) and week 52 (0.4 events per 100 patient years). The discontinuations due to anemia did not appear to be dependent on dose.*

### 8.5.11. Neutropenia

**Figure 26** shows the mean change from baseline to week 52 in neutrophils (1000 cells per microliter). There was a mean decrease in neutrophils which was most evident at week 4. The decrease in neutrophils appeared to be dose dependent. At week 4, the mean change in neutrophil count from baseline was 0.19 in placebo, -0.77 in the 2 mg baricitinib group, and -1.34 in the 4 mg baricitinib group. At week 16, the mean change in lymphocyte count from baseline was 0.04 in the placebo group, -0.57 in the 2 mg baricitinib group, and -1.04 in the 4

mg baricitinib group. At weeks 48 through 52, the change from baseline in lymphocyte count is -0.86 in the 2 mg baricitinib group and -0.99 in the 4 mg baricitinib group. Discontinuations due to neutropenia were rare with 2 patients taking baricitinib 4 mg daily having a permanent discontinuation due to neutropenia as shown in **Table 114**.

**Figure 26. Mean change from baseline to week 52: neutrophils**

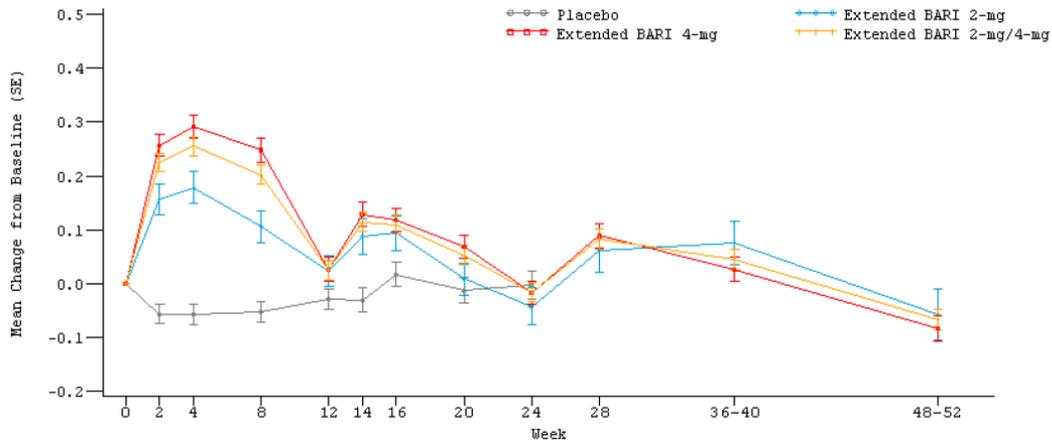


Source: Applicant response to information request dated June 24, 2016, p. 107

### 8.5.12. Lymphocytes

Figure 27 shows the mean change from baseline to week 52 in lymphocytes (1000 cells per microliter). There was an increase in lymphocytes initially that appeared to be sustained to approximately week 8 at which time the number lymphocyte appeared to steadily decrease. These findings appeared to be dose dependent. At week 8, the mean change in lymphocyte count from baseline was -0.05 in placebo, 0.11 in the 2 mg baricitinib group, and 0.25 in the 4 mg baricitinib group. At week 16, the mean change in lymphocyte count from baseline was 0.02 in the placebo group, 0.09 in the 2 mg baricitinib group, and 0.12 in the 4 mg baricitinib group. At weeks 48 through 52, the change from baseline in lymphocyte count is -0.06 in the 2 mg baricitinib group and -0.08 in the 4 mg baricitinib group.

**Figure 27. Mean change from baseline to week 52: lymphocytes**



Source: Applicant response to information request dated , p. 108

As shown in **Table 113**, the number of discontinuations to week 16 due to lymphocytosis or lymphopenia was low. At week 16, one patient on 2 mg baricitinib discontinued due to lymphopenia and one patient on 4 mg baricitinib discontinued due to lymphocytosis.

**Table 114** shows one discontinuation in the 2mg baricitinib group and one discontinuation in the 4 mg baricitinib group due to lymphopenia.

### 8.5.13. Liver function tests

On June 24, 2016, the Applicant was requested to provide information regarding the increased liver function tests that were seen with the 2 mg and 4 mg doses of baricitinib. The data was requested to be stratified by the severity of increase above the upper limit of normal for each liver function test. The Applicant provided the information which is summarized in **Table 115**. It did appear that baricitinib increased liver function tests in a dose dependent manner at 3 months and at 12 months. The increases in liver function tests were most commonly 1 to 2 times the upper limit of normal with rare cases of liver function tests increasing 5 to 10 times the upper limit of normal. At 3 months, 17% of patients receiving baricitinib 4 mg daily had an increase in AST and 10% in the baricitinib 2 mg dose group had an increase in AST. A similar pattern was seen in serum levels of ALT. At 12 months, 23% of patients taking 2 mg of baricitinib had an increase in AST and 31% of patients taking 4 mg of baricitinib had an increase in AST. A similar pattern was seen in measures of ALT. Increases above 2 times the upper limit of normal were uncommon in all groups but more events did appear to occur in the 4 mg baricitinib group.

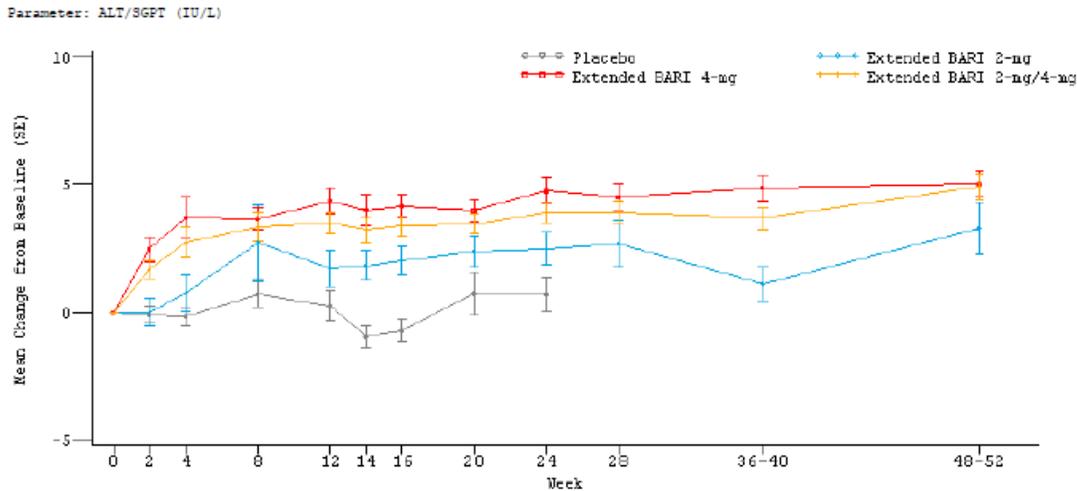
**Table 115. Integrated safety analyses: Liver transaminases**

	Placebo		BARI 2 mg		BARI 4 mg	
<b>0-3 months</b>						
<b>Total bilirubin</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>
≥1*ULN	1061	16 (1.5)	479	5 (1)	986	22 (2.2)
≥2*ULN	1065	0	479	0	991	0
≥3*ULN	1065	0	479	0	991	0
≥5*ULN	1065	0	479	0	991	0
≥10*ULN	1065	0	479	0	991	0
<b>Aspartate aminotransferase (AST)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>
≥1*ULN	1021	96 (9.4)	455	47 (10.3)	965	160 (16.6)
≥2*ULN	1061	20 (1.9)	474	9 (1.9)	989	21 (2.1)
≥3*ULN	1065	9 (0.8)	477	5 (1.0)	991	7 (0.7)
≥5*ULN	1065	3 (0.3)	478	0	991	3 (0.3)
≥10*ULN	1065	0	479	0	991	0
<b>Alanine aminotransferase (ALT)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>
≥1*ULN	992	130 (13.1)	443	50 (11.3)	935	185 (19.8)
≥2*ULN	1059	29 (2.7)	474	13 (2.7)	988	36 (3.6)
≥3*ULN	1065	9 (0.8)	477	5 (1)	991	13 (1.3)
≥5*ULN	1065	3 (0.3)	478	0	991	5 (0.5)
≥10*ULN	1065	0	479	0	991	1 (0.1)
<b>0-12 months</b>						
<b>Total bilirubin</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>
≥1*ULN	1064	23 (2.2)	479	12 (2.5)	986	41 (4.2)
≥2*ULN	1065	2 (0.2)	479	0	991	1 (0.1)
≥3*ULN	1065	1 (0.1)	479	0	991	0
≥5*ULN	1065	1 (0.1)	479	0	991	0
≥10*ULN	1065	0	479	0	991	0
<b>Aspartate aminotransferase (AST)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>
≥1*ULN	1041	136 (13.1)	455	104 (22.9)	965	300 (31.1)
≥2*ULN	1064	29 (2.7)	474	17 (3.6)	989	41 (4.1)
≥3*ULN	1065	14 (1.3)	477	9 (1.9)	991	14 (1.4)
≥5*ULN	1065	5 (0.5)	478	1 (0.2)	991	4 (0.4)
≥10*ULN	1065	0	479	0	991	0
<b>Alanine aminotransferase (ALT)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>	<b>NAR</b>	<b>n (%)</b>
≥1*ULN	1032	177 (17.2)	443	106 (23.9)	935	325 (34.8)
≥2*ULN	1063	40 (3.8)	474	33 (7)	988	75 (7.6)
≥3*ULN	1065	14 (1.3)	477	12 (2.5)	991	23 (2.3)
≥5*ULN	1065	5 (0.5)	479	5 (1)	991	8 (0.8)
≥10*ULN	1065	0	479	1 (0.2)	991	2 (0.2)

Abbreviations: ULN=upper limit of normal, NAR=number at risk, BARI= baricitinib  
Source: adapted from Applicant's June 24, 2016 response to FDA information request, p. 115-116

**Figure 28** shows the mean change from baseline in ALT for patients who were taking placebo, baricitinib 2 mg, or baricitinib 4 mg until week 52. Increases in ALT can be seen as early as week 2 and are consistently elevated as compared to baseline. The 4 mg baricitinib group had a slightly higher mean change from baseline as compared to the 2 mg baricitinib group.

**Figure 28. Integrated safety analyses: Mean change from baseline of serum ALT**

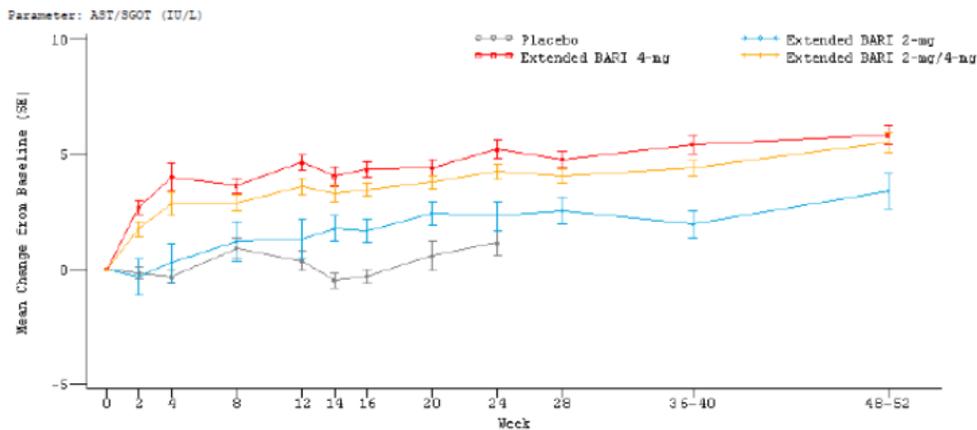


Data cut as of January 1, 2016.

Source: Applicant's response to information request dated June 24, 2016, p. 96

**Figure 29** shows the mean change from baseline of serum AST for the placebo and baricitinib exposed patients. Again, baricitinib appeared to mildly increase baseline serum AST in a dose dependent fashion.

**Figure 29. Integrated safety analyses: Mean change from baseline of serum AST**



Data cut as of January 1, 2016.

Source: Applicant's response to information request dated June 24, 2016, p. 97

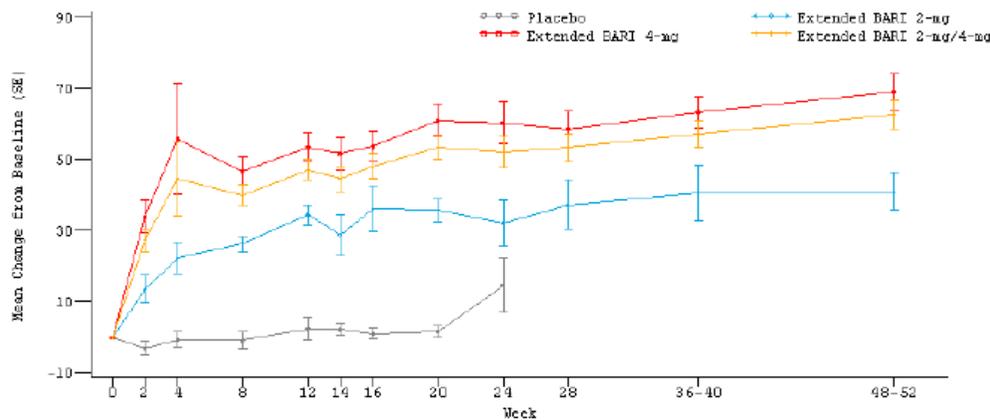
#### 8.5.14. Gastrointestinal perforations

5 cases of gastrointestinal perforations classified by broadly defined terms were reported in the 2862 RA patients who participated in the Phase 3 RA trials (3461 patient years of exposure). All patients were on baricitinib. The preferred terms for the 5 cases reported were abdominal abscess, anal abscess, perforated appendicitis, diverticular perforation, peritonitis, and rectal abscess.

#### 8.5.15. Creatine phosphokinase

Figure 30 shows the change from mean change from baseline in serum creatine phosphokinase (CPK) to week 52. The increase in CPK [international units per liter (IU/L)] appeared to spike at week 4 with the placebo group having a mean increase of -1 IU/L, the 2 mg baricitinib group having an increase of 22 IU per liter, and the 4 mg baricitinib group having an increase of 56 IU/per liter.

**Figure 30. Integrated safety analyses: mean change from baseline in serum CPK**



Data cut as of January 1, 2016.

Source: Applicant response to information request dated June 24, 2016, p. 99

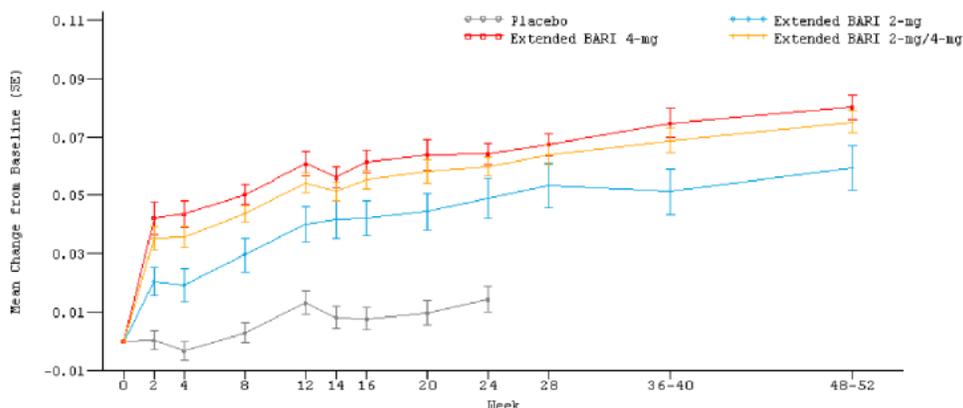
The increase in CPK was persistent throughout the time patients were exposed to baricitinib. At week 16, the mean change from baseline (IU/L) in the placebo group was 1 IU/L, 36 IU/L in the 2 mg baricitinib group, and 54 IU/L in the 4 mg baricitinib group. The mean change from baseline in the patients who were on baricitinib through weeks 48-52 was 41 IU/L in the 2 mg baricitinib group and 69 IU/L in the 4 mg baricitinib group.

*Reviewer's comments: Exposure to baricitinib resulted in an increase in CPK that was dose dependent and persisted while the patient was on medication. The reason for this increase is unknown at this time and has been seen with other JAK inhibitors. There did not appear to be a relationship between CPK elevations and myopathic events.*

### 8.5.16. Creatinine elevation

Figure 31 shows the mean change in creatinine (mg/dL) over time to week 52 that occurred in the phase 2 studies JADA, JADC, and JADN and the phase 3 studies JADV, JADX, and JADW. The mean change in baseline appeared to increase in a dose dependent fashion; however, the mean change from baseline was very small.

Figure 31. Integrated safety analyses to week 52: change in mean baseline creatinine



Source: Applicant response to information request sent October 14, 2016, p. 30

Table 116. Overview of changes in creatinine.

	Shift from Grade<1 to Grade≥1 n/NAR (%)	Shift from Grade<3 to Grade≥3 n/NAR (%)
Creatinine change to week 16		
Placebo (N=1070)	19/989 (1.9)	0/1010 (0)
BARI 2 mg (N=479)	11/444 (2.5)	0/453 (0)
BARI 4 mg (N=997)	23/951 (2.4)	2/964 (0.2)
Extended BARI exposure	n/PYE (EAIR per 100 PY)	
BARI 2 mg (N=479), PYE= 434.8	18/434.8 (4.1)	0/434.8 (0)
BARI 4 mg (N=479), PYE=477.7	30/477.7 (6.3)	4/477.7 (0.8)

Abbreviations: BARI=baricitinib, PYE=person year exposure, EAIR=exposure adjusted incidence rate, NAR=number at risk

Source: adapted from Applicant's clinical safety summary, p. 293

### 8.5.17. Alopecia

Alopecia was reported in the baricitinib RA studies with a numerically higher number of events occurring in the baricitinib arms versus placebo. Table 117 shows the number of events that occurred in 4 studies that included both a 2 mg and 4 mg dose of baricitinib (JADC, JADA, JADW, and JADX). There was a higher incidence rate of alopecia in the 4 mg baricitinib group as compared to placebo. There were fewer events in the 2 mg group. None of the alopecia

events were reported as severe. None of the alopecia events reported led to temporary or permanent discontinuation of study drug.

**Table 117. Integrated safety to week 24: alopecia events occurring in placebo, baricitinib 2 mg, and baricitinib 4 mg treatment arms**

	Alopecia, n (exposure adjusted incidence rate)
Placebo, N=551	5 (2.6)
BARI 2 mg, N=479	1 (0.5)
BARI 4 mg, N=479	9 (4.8)

Abbreviations: BARI=baricitinib

Source: adapted from Applicant summary of clinical safety, p. 930

*Reviewer's comments: While there was a numerical imbalance in alopecia events that occurred in the 4 mg baricitinib treatment arm as compared to placebo, the events did not lead to discontinuation of drug. None of the events were listed as severe. It appears that the alopecia that occurred in the studies were relatively mild in intensity.*

## 8.6. Safety Analyses by Demographic Subgroups

**Figure 32** was provided by the Applicant to address gender related differences that occurred during the first 16 week in studies that used 4 mg baricitinib daily and placebo. Six studies were included for analysis. Significant interactions were noted for the preferred terms nasopharyngitis and hypercholesterolemia. Analysis of labs showed significant interactions for high creatinine, low neutrophils, and low lymphocytes.

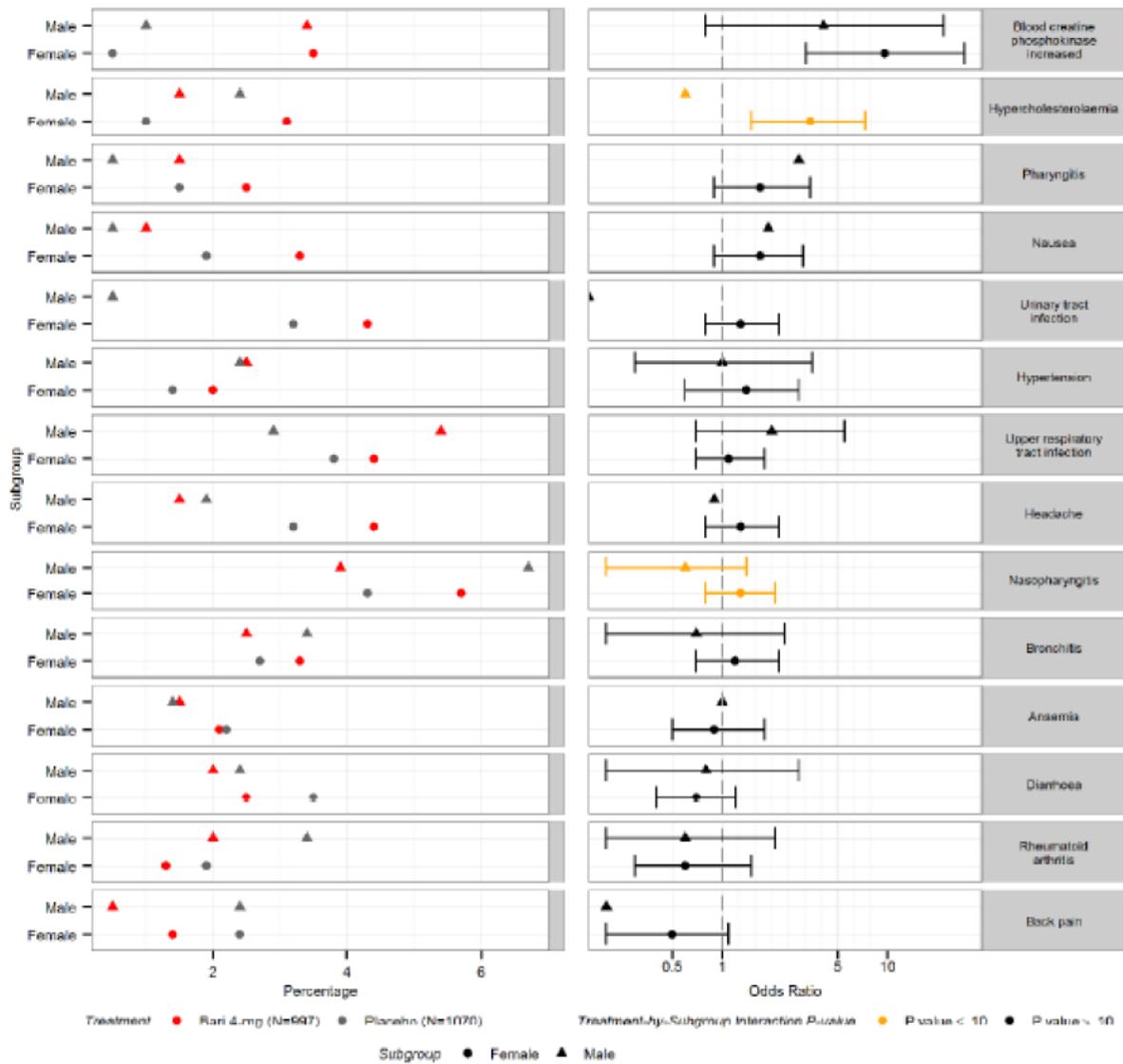
Most of the interactions that occurred were not statistically significant between the placebo groups and the 4 mg baricitinib groups. Only hypercholesterolemia and low neutrophils appeared to have significant differences between placebo and 4 mg baricitinib treatment arms. For low neutrophils, the odds ratio (OR) for males was 0.5 and for females it was 4.8. It did not appear that females with low neutrophils were at higher risk for infection than males.

For hypercholesterolemia, the OR for males was 0.6 and for females it was 3.4. There were increases in lipids for both males and females with a greater magnitude of lipid increase occurring in the females. In the baricitinib RA trials, there was no association between LDL and MACE.

**Figure 32. Integrated safety analysis: Gender related differences, placebo versus baricitinib 4 mg daily to week 16**

TEAEs Occurring in  $\geq 2\%$  in either BARI 4-mg or PBO by MedDRA Preferred Term based on Sex Acute, Placebo-Controlled Period up to Week 16  
 BARI 4-mg RA PC Analysis Sets (Studies JADA, JADC, JADN, JADV, JADW and JADX)

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Percentages are based on the number of patients by subgroup in each treatment group. The Mantel-Haenszel odds ratio is calculated with PBO as the denominator, so values  $> 1$  indicate increased risk with BARI 4-mg. CIs calculated if  $\geq 4$  events in treatment group and  $\geq 1$  in PBO. CIs in orange represent a significant treatment-by-subgroup interaction. Preferred terms are sorted by the Mantel-Haenszel odds ratio from subgroups combined.

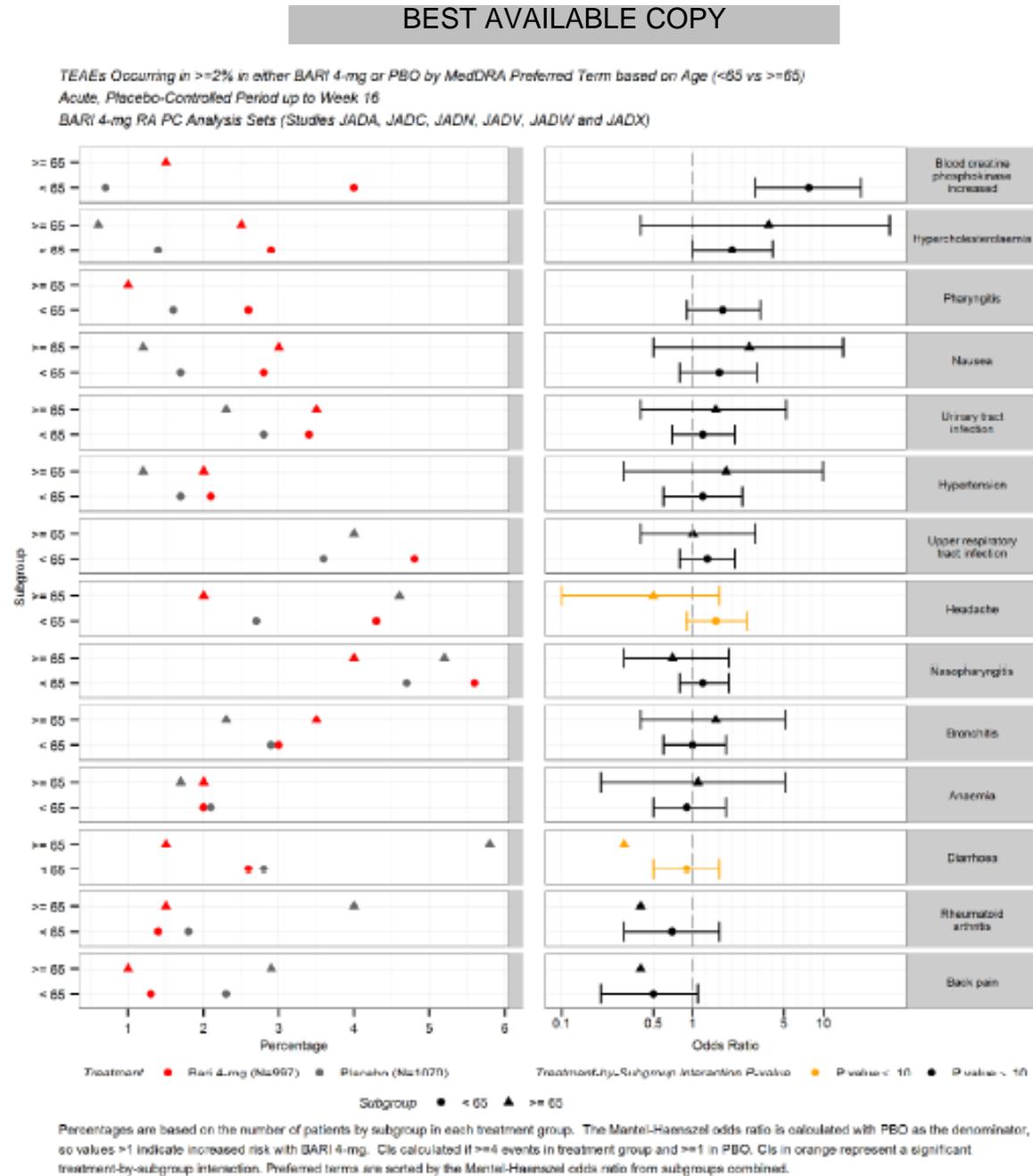
Source: Applicant summary of clinical safety Appendix 1, p. 2534

Age

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**Figure 33** was provided by the Applicant to evaluate differences between patients who were less than the age of 65 and patients who were greater than or equal to the age of 65. The odds ratio for higher platelets was 6.3 in patients who were greater than or equal to 65 years of age versus the odds ratio of 2.8 for patients who were less than 65 years of age. A similar finding was noted with high lymphocytes. Patients greater than or equal to 65 years of age had an odds ratio of 5.8 and patients less than 65 had an odds ratio of 2.5. For both findings, the patients greater than or equal to 65 had a higher risk of developing the laboratory finding but the significance of these findings is unknown.

**Figure 33. Integrated safety analysis: Age related differences, placebo versus baricitinib 4 mg daily to week 16**



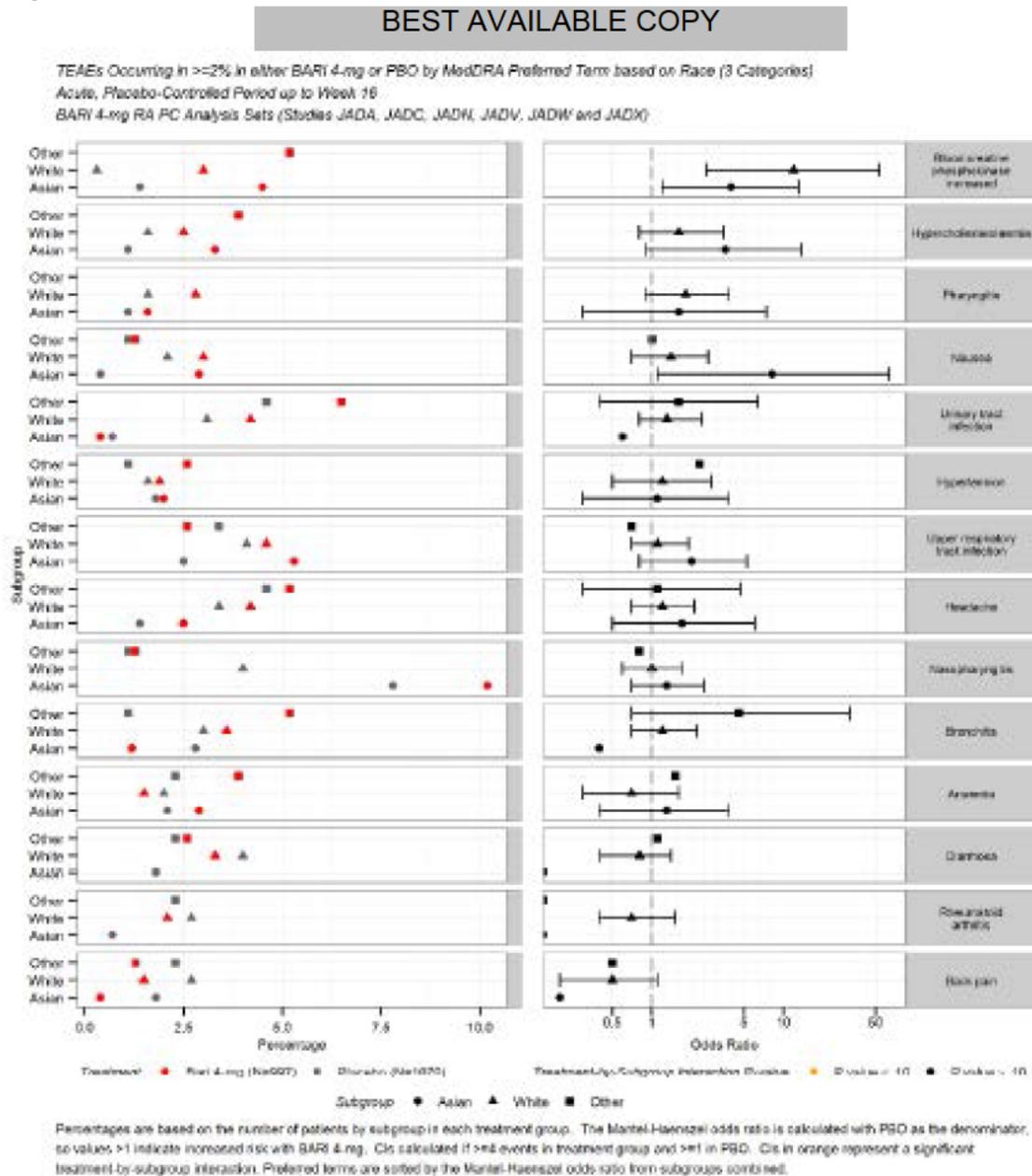
Source: Applicant summary of clinical safety Appendix 1, p. 2581

Race

**Figure 34** shows differences in race as other, White and Asian. In general there were no interactions between race and adverse events. There did appear to be a significant interaction

between race and high LDL. The odds ratio for high LDL was 4.8 for Asians, 4.0 for Whites and 1.0 for other race groups. The risk may not have been apparent in the other race group because proportionally, a very small number of patients in the other race group were enrolled compared to the White patients and Asian patients.

**Figure 34. Integrated safety analysis: Race related differences, placebo versus baricitinib 4 mg daily to week 16**



Source: Applicant summary of clinical safety Appendix 1, p. 2682

## 8.7. Specific Safety Studies/Clinical Trials

**Table 118** shows adverse events that occurred up to week 24 in the JADV safety population. Data is censored at the time of switch or rescue. The incidence rates shown in the table are exposure adjusted. The adverse events that occurred in the placebo, baricitinib, and adalimumab groups were relatively well balanced; however, a slightly greater number of patients experienced adverse events with baricitinib.

The serious adverse event rates were similar between placebo and baricitinib but the rates of serious adverse events were lower in the adalimumab group. Serious infections were also balanced between the baricitinib group and placebo with lower rates occurring in the adalimumab group. All deaths occurred in the baricitinib group. MACE was balanced between placebo and baricitinib. There were 3 events of deep vein thrombosis in the baricitinib group. No venous thromboses were seen in the adalimumab or placebo groups.

**Table 118. JADV: Key adverse events that occurred up to Week 24**

Adverse event, n (incidence rate per 100 patient years)	Placebo N=488 PYE=198	BARI 4 mg N=487 PYE=215	Adalimumab N=330 PYE=142
Patients with $\geq 1$ TEAE	295 (149.2)	347 (161.4)	224 (157.8)
SAE	22 (11.1)	23 (10.7)	6 (4.2)
Discontinuation	17 (8.6)	25 (11.6)	7 (4.9)
Serious infection	7 (3.5)	5 (2.3)	2 (1.4)
GI perforations	0	0	0
Malignancy	3 (1.5)	2 (0.9)	0
MACE (positively adjudicated)	0	1 (0.2)	0
Death	0	2 (0.9)	0
Deep venous thrombosis	0	3 (0.4)	0

Abbreviations: TEAE=treatment emergent adverse event, SAE=serious adverse event, PYE=person year exposure, BARI=baricitinib, GI=gastrointestinal, MACE=major cardiovascular event  
Source: derived from JADV clinical study report

*Reviewer's comments: One of the interesting findings in JADV was an increased number of serious infections in both the placebo and baricitinib group as compared to the active comparator adalimumab. This was unusual as adalimumab is a known immunosuppressant. Additional queries were made regarding the reporting of serious adverse events as a potential cause for this unexpected finding but did not appear to influence the outcome.*

**Table 119** shows key laboratory events that occurred up until week 24. The events that occurred were censored at the time of switch or rescue. The patients who received baricitinib had higher creatine phosphokinase levels as compared to placebo and adalimumab patients. Baricitinib patients also exhibited a higher percent of patients with cholesterol changes as seen

in the other baricitinib studies in RA. Baricitinib and adalimumab had numerically higher rates of elevations in liver enzymes as compared to placebo.

**Table 119. JADV: Key laboratory abnormalities that occurred up to week 24**

Any CTCAE grade increase, n (%)	Placebo N=488	BARI 4 mg N=487	Adalimumab N=330
ALT	80 (16)	121 (25)	77 (23)
AST	63 (13)	106 (22)	61 (19)
Total bilirubin	5 (1)	6 (1.2)	3 (0.9)
Creatinine	12 (2.5)	11 (2.3)	7 (2.1)
Creatine phosphokinase	40 (8)	179 (37)	41 (12)
Hemoglobin	117 (24)	127 (26)	56 (17)
Platelets	15 (3)	11 (2)	19 (6)
Neutrophils	17 (4)	55 (11)	42 (13)
Leukocytes	15 (3)	43 (9)	34 (10)
Lymphocytes	108 (22)	90 (19)	40 (12)
Cholesterol change*	28 (7)	124 (30)	43 (16)

Abbreviations: CTCAE=Common terminology criteria for adverse events, BARI=baricitinib, ALT= alanine aminotransferase, AST=aspartate aminotransferase, BARI=baricitinib

\*change from desirable or borderline high to high

Source: derived from JADV clinical study report

**Table 120** shows key adverse events that occurred in study JADZ up to week 24. The events were relatively balanced among groups. There was a slightly higher percentage of patients receiving combination baricitinib and methotrexate who had adverse events and a greater percentage of serious adverse events in patients who were treated with the combination of baricitinib and methotrexate; however, overall there were not any large discrepancies among treatment arms at week 24.

**Table 120. JADZ: Key adverse events that occurred up to Week 24**

Adverse event, n (%)	Methotrexate N=210 PYE=89	BARI 4 mg N=159 PYE=72	BARI 4 mg+MTX N=215 PYE=93
Patients with $\geq 1$ TEAE	136 (65)	103 (65)	146 (68)
SAE	12 (6)	9 (6)	21 (10)
Discontinuation	5 (2)	6 (4)	15 (7)
Serious infection	4 (2)	4 (3)	7 (3)
GI perforations	0	0	0
Malignancy	0	0	2 (1)
Cardiac disorders	0	1 (1)	0
Death	3	0	0
Deep venous thrombosis	0	0	0

Abbreviations: TEAE=treatment emergent adverse event, SAE=serious adverse event, PYE=person year exposure, BARI=baricitinib, GI=gastrointestinal, MACE=major cardiovascular event

Source: generated from JADZ clinical study report

**Table 121** shows any increase in CTCAE grade for clinical laboratory abnormalities that occurred during the first 24 weeks of JADZ. A higher percentage of patients who received the combination of methotrexate and baricitinib had an increase in liver transaminases as compared to baricitinib monotherapy. Increased CPK was noted in the baricitinib treatment arms as they were in the other phase 3 studies in RA. Neutropenia appeared to happen more frequently in the baricitinib treatment arms as well as hypercholesterolemia.

**Table 121. JADZ: Key laboratory abnormalities that occurred up to week 24**

Any CTCAE grade increase, n (%)	Methotrexate N=210	BARI 4 mg N=159	BARI 4 mg+MTX N=215
ALT	54 (26)	19 (12)	51 (24)
AST	35 (17)	14 (9)	44 (21)
Total bilirubin	4 (2)	1 (1)	3 (1)
Creatinine	3 (2)	8 (5)	6 (3)
Creatine phosphokinase	21 (10)	56 (35)	68 (32)
Hemoglobin	51 (25)	45 (28)	66 (31)
Platelets	5 (2)	2 (1)	5 (2)
Neutrophils	13 (6)	21 (13)	21 (10)
Leukocytes	17 (8)	15 (9)	17 (8)
Lymphocytes	45 (22)	15 (9)	38 (18)
Cholesterol change*	12 (7)	43 (30)	43 (23)

Abbreviations: CTCAE=Common terminology criteria for adverse events, BARI=baricitinib, ALT= alanine aminotransferase, AST=aspartate aminotransferase, BARI=baricitinib

\*change from desirable or borderline high to high

Source: derived from JADZ clinical study report

*Reviewer’s comments: The overall safety signals seen in JADZ were similar to what was noted in the other phase 3 clinical trials. There did appear to be a slightly increased frequency of adverse events and an increased frequency of laboratory abnormalities when using combination baricitinib and methotrexate versus methotrexate alone or baricitinib alone.*

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

No special human carcinogenicity or tumor development studies were performed. The malignancies that occurred in the baricitinib clinical program are reported in the safety discussion above.

### 8.8.2. Human Reproduction and Pregnancy

No special human reproduction and pregnancy studies were conducted.

The Applicant reported 16 women had become pregnant while exposed to baricitinib. 12 cases

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occurred during study participation and 4 additional cases occurred in the extension study JADY. Of the 12 cases that occurred during study participation, 5 pregnancies resulted in full-term or premature births with no evidence of fetal abnormalities, 4 pregnancies resulted in spontaneous abortions, and one elective abortion took place. The remainder of the pregnancies was ongoing.  
Insert text here.

### 8.8.3. Pediatrics and Assessment of Effects on Growth

Polyarticular juvenile idiopathic arthritis has been considered the juvenile equivalent of adult RA, and thus, a study in pJIA would be required by the Pediatric Research Equity Act (PREA) if this NDA in adult RA patients is approved. With this NDA, Eli Lilly and Company submitted a partial waiver of pediatric assessments for children with pJIA ages 0 to less than 2 years of age as the number of patients in this age group is so small that studies would be highly impractical to complete. A deferral was requested in children ages 2 to < 18 years of age until studies in adults are complete and ready for approval.

The Applicant proposes to perform the following pJIA studies to fulfill PREA requirements. These initial Pediatric Study Plan (iPSP) was submitted on July 14, 2014. The Applicant was asked to revise their submission to enroll patients with a minimum number of active joints to fulfill criteria of pJIA. The Applicant was also requested to revise their timeline for pediatric development of baricitinib. A revised iPSP was submitted on November 26, 2014. The Applicant provided the following studies and timeline for the agreed upon iPSP:



After submission of the NDA, the Applicant submitted some modifications to the BA study so that it is a BE study. The changes were reviewed by clinical pharmacology and felt to be reasonable. The studies will be performed as post-marketing requirements (PMRs). The baricitinib program was reviewed at the Pediatric Review Committee (PeRC) meeting on December 11, 2014. The PeRC agreed with the requested waiver, deferral, and proposed pJIA studies.

#### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant noted a few overdoses during the baricitinib clinical program. 3 patients had an overdose while taking baricitinib:

- (b) (6) (baricitinib 4 mg): overdose was over 15 days. The amount of overdose was unavailable to the Applicant; SAE of gastroenteritis was reported 4 months after the overdose
- (b) (6) (baricitinib 4 mg): mistakenly took 8 mg of baricitinib for 29 days. No additional treatment emergent effects
- (b) (6) (placebo rescued to baricitinib 4 mg): The overdose had duration of one day without a dose given. The patient reported mild anemia 2 months following the overdose.
- The daughter of patient (b) (6) ingested 32 mg of baricitinib to gain attention and was sent to the emergency department for gastric lavage and hydration. The daughter reported nausea and recovered in less than 24 hours.

The potential for misuse of baricitinib for illegal purposes is not considered a risk by the Applicant as other JAK inhibitors have not been reported to be associated with cases of abuse or dependence leading to addiction.

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The Applicant states there have been no safety findings with withdrawal of baricitinib. The Applicant assessed for rebound effects in studies JADV, JADW, JADX, and JADZ. Rebound effects were assessed at baseline, last treatment visit, and subsequent 28 day follow up. Change from baseline to follow up visit did not suggest meaningful rebound effect after cessation of baricitinib per the Applicant.

## 8.9. Safety in the Postmarket Setting

### 8.9.1. Safety Concerns Identified Through Postmarket Experience

Baricitinib is not marketed in any country at this time.

### 8.9.2. Expectations on Safety in the Postmarket Setting

No specific REMS for the purposes of evaluating safety are currently being recommended.

Study JADW and JADX provided safety data on the use of 2 mg and 4 mg daily baricitinib. However, most of the exposure to drug, especially at later time points in the study, was in the 4 mg dose group. Therefore, conclusions regarding the long term safety of the 2 mg dose of baricitinib versus the 4 mg dose of baricitinib were limited.

Study JADV provided safety data on the use of adalimumab 40 mg every other week and baricitinib 4 mg daily. Again, most of the longer term exposure was in the baricitinib group.

Due to the different exposure time of baricitinib 4 mg daily to other treatment arms and the study design with crossover to baricitinib 4 mg, only limited conclusions could be made regarding the rates of adverse events of special interest. The higher number of events in the baricitinib group could have been secondary to the higher exposure time on 4 mg baricitinib and the different patient characteristics compared to the other treatment arms.

Therefore, a post marketing requirement will be recommended in order to address these outstanding safety concerns. Specifically, it is recommended that the Applicant perform a long-term safety study powered to detect the events of malignancy, serious infections, and thrombotic events. The study should have more than one dose of baricitinib and an active comparator such as tofacitinib or adalimumab.

## 8.10. Additional Safety Issues From Other Disciplines

There are no additional safety issues from other disciplines that have not already been captured in other sections of this review.

## 8.11. Integrated Assessment of Safety

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Baricitinib is a JAK inhibitor. As such, there were many adverse events that were expected with treatment with baricitinib in the RA population.

In terms of safety, there were more of the following adverse events in the baricitinib group compared to the placebo groups: deaths, serious adverse events, adverse events leading to discontinuation, specific laboratory abnormalities (creatinine phosphokinase increase, thrombocytosis, elevated liver enzymes, elevation in lipids), overall infections, and venous thromboses. Some events occurred too infrequently to make a definitive conclusion regarding risk, namely, GI perforations, cardiovascular events, and malignancy.

#### Deaths

In the phase 2 and phase 3 RA studies, 22 deaths were reported up until November 2015. 13 deaths occurred in the baricitinib group versus 7 in the combined placebo, methotrexate, and adalimumab study arms.

#### Serious adverse events

In the integrated safety analyses conducted by the Applicant in response to the Division's information request, a similar number of serious adverse events were seen between the placebo groups, baricitinib 2 mg daily, and baricitinib 4 mg daily.

#### Discontinuations

There were a numerically greater number of patients who discontinued baricitinib (4.7%) as a result of an adverse event compared to placebo (3.3%). A majority of the adverse events that led to discontinuation in the baricitinib group were due to infections (2%)

#### Overall infections

Adverse events during the first 12 weeks on treatment were 20% for placebo, 25% for baricitinib 2 mg daily, and 28% for baricitinib 4 mg daily. The patients who received baricitinib had a numerically greater chance of experiencing an infection.

#### Venous thrombosis

DVTs and PEs were noted in the baricitinib groups and not the placebo group. The overall incidence rate of these events was small; however, no events were seen in the placebo groups. Also, several more events occurred in the 4 mg baricitinib group (11) versus the 2 mg baricitinib group (2) over a 52 week period. The incidence rates were similar with a rate of 0.7 events per 100 patient years in the 4 mg baricitinib group versus 0.6 events per 100 patient years in the 2 mg baricitinib group.

#### Creatine phosphokinase increases

Increases in creatine phosphokinase were seen with patients who took baricitinib versus placebo. The increases appeared early (around week 2) and were sustained. No association

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with cardiovascular events, myositis, or other clinical abnormalities seen with an increased creatine phosphokinase was noted with the creatine phosphokinase increases.

#### Thrombocytosis

A dose dependent increase in thrombocytosis was noted in the baricitinib RA studies. The increase in platelets was most dramatic at the beginning of starting therapy with increases in platelets spiking around week 2 after initiating baricitinib.

#### Malignancies

The number of malignancies in the baricitinib RA studies was relatively small, especially during the controlled period before cross overs. The incidence rate of malignancies from week 0 to 52 for patients on any dose of baricitinib was 0.7 per 100 patient years. The exposure adjusted incidence rate in placebo was 0.5 per 100 patient years.

#### Dyslipidemia

Patients on baricitinib had increases in total cholesterol, HDL, LDL, and triglycerides as compared to placebo. Examination of MACE in the RA baricitinib studies did not appear to show that baricitinib resulted in a higher risk of MACE. Therefore, it does not appear that the dyslipidemia seen with exposure to baricitinib results in increased cardiovascular risk, but the number of events were limited.

#### Other lab abnormalities

Dose dependent elevations in liver transaminases were seen in the baricitinib RA studies. The dose of baricitinib also appeared correlated with neutropenia and anemia.

In conclusion, based on the safety data from the pivotal trials, the risks associated with baricitinib were widely consistent with what is expected from a JAK inhibitor. However, there were other potential safety signals noted in the baricitinib RA studies including increased platelet counts, an imbalance in venous thrombosis with all events occurring in baricitinib versus placebo, and the occurrence of alopecia. The label should convey the safety risks that were seen in the RA clinical development program. Please see section 10 for details on labeling for safety associated with baricitinib.

A post marketing requirement is recommended at this time to address some of the safety signals seen with baricitinib. Some of the safety signals seen were not seen with other JAK inhibitors. As the studies required to evaluate the additional safety concerns will need to be of a longer duration, the study will need to use an active comparator. Additionally, the adverse events are potentially dose dependent, so the clinical trial will also need to evaluate the long term effects of both the 2 mg and 4 mg doses of baricitinib.

## 9 Advisory Committee Meeting and Other External Consultations

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An advisory committee was not recommended for baricitinib. The data from the pivotal trials support efficacy. The safety signals identified during review of the baricitinib RA studies were for rare events and will require a longer term study to better characterize the safety of baricitinib for longer term risks such as serious infections, malignancy, and venous thromboses. The PMR will also need to study two doses of baricitinib as the safety appeared to be different between the two doses of baricitinib that were studied in the phase 3 RA studies.

## 10 Labeling Recommendations

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### 10.1. 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.

## 10.2. Patient Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) identified deficiencies that could be improved to decrease medication errors. They provided the following recommendations to improve labeling:

- revising the font color of the established name to increase readability.

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- Revise the font color of the proprietary name (orange color) or revise [REDACTED] (b) (4) [REDACTED] so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths
- Relocate the net quantity and Rx only statements away from the product strength
- increase the prominence of important information, relocate the strength statement underneath the established name and dosage form statements, ensure that the first letter of the proprietary name, Olumiant is capitalized.
- To ensure there is an adequate amount of white space, consider removing the company name, website, or logo
- Revise dosage statement to “Usual dosage: See Prescribing Information” for consistency with other labels.

### 10.3. Nonprescription Labeling

Not applicable

## 11 Risk Evaluation and Mitigation Strategies (REMS)

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### 11.1. Safety Issue(s) that Warrant Consideration of a REMS

Based on the review of the data, there are no safety issues that warrant consideration of a REMS. See Section 11.3 below.

### 11.2. Conditions of Use to Address Safety Issue(s)

Not applicable

### 11.3. Recommendations on REMS

Eli Lilly and Company proposed product labeling to address the risks of the product. Based on the review of safety and efficacy data, Risk Evaluation and Management Strategies (REMS) are not recommended. Product labeling will be adequate to ensure that the product’s benefits outweigh its risks in the postmarketing setting. The review by the Division of Risk Management concurs with this approach.

## 12 Postmarketing Requirements and Commitments

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As previously discussed in this review, Eli Lilly and Company will have a PREA postmarketing requirement. The studies that will comprise this PMR are described in Section 8.3.3.

There has been additional discussion regarding rare events that were noted in the baricitinib groups including malignancies, major cardiovascular events, and venous thrombosis. Due to the design of the phase 3 program, it was difficult to determine whether there was an increased risk of rare events with baricitinib. It was also unclear whether there was a dose response for long term adverse events when comparing the 2 mg and 4 mg group.

A PMR is recommended to address concerns whether there is an increased risk for rare events such as venous thrombosis, MACE and malignancy with baricitinib. The study would evaluate two doses of baricitinib (b) (4) to address whether there is a dose response for any of these long term outcome events. Since the study will need to be a long-term study to capture these type of events, an active comparator will be a necessary treatment arm in this study along with the 2 baricitinib treatment arms.

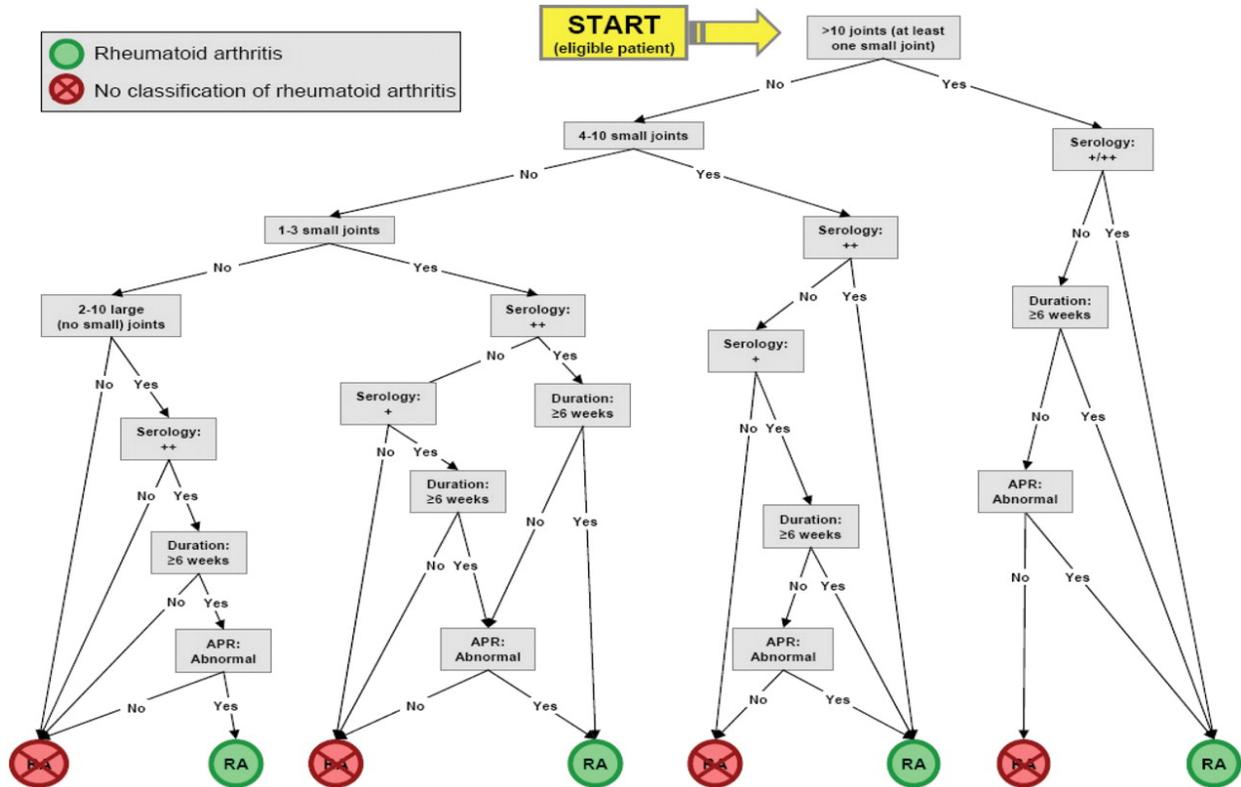
## 13 Appendices

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### 13.1. References

See included footnotes at end of page

### 13.2. ACR 2010 Classification Criteria



Source: <http://ard.bmj.com/content/69/9/1580/F1.large.jpg>

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### 13.3. Schedule of Visits for Phase 3 Studies

#### 13.3.1. JADX

Table JADX.9.4. Study Schedule

Visit	Screening		Blinded Treatment Part A										ET	Follow-Up Part B <sup>a</sup>
	1	1a	2	3	4	5	6	7	8	9	10	11		
Week of Treatment			Baseline 0	1	2	4	8	12	14	16	20	24	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	Any day	28 ± 5 days after last dose
Informed consent	X													
Clinical Assessments:														
History	X													
Physical examination	X													
Symptom-directed physical examination <sup>b</sup>			X	X	X	X	X	X	X	X	X	X	X	X
Previous therapy/previous RA therapy	X													
Patient demographics	X													
Height	X													
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X							X				X		
Vital signs (BP and pulse) <sup>f</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X
Habits <sup>c</sup>	X													
Electrocardiogram <sup>d</sup>	X													
Inclusion/exclusion review for entry	X													
Inclusion/exclusion review for enrollment			X											
Administer Tuberculosis test <sup>e</sup>	X													
Read PPD if used for tuberculosis testing <sup>e</sup>		X												

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Visit	Screening		Blinded Treatment Part A										ET	Follow-Up Part B <sup>a</sup>
	1	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	11		
Week of Treatment			Baseline 0	1	2	4	8	12	14	16	20	24	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	Any day	28 ± 5 days after last dose
Chest x-ray <sup>f</sup>	X													
Preexisting conditions	X		X											
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X											
Call IVRS	X		X	X	X	X	X	X	X	X	X	X	X	X
Investigational product dispensed <sup>g</sup>			X		X	X	X	X		X	X	X		
Investigational products returned and assess compliance				X <sup>h</sup>	X	X	X	X	X	X	X	X	X	
Tender/swollen joint count (68/66 joints)	X		X	X	X	X	X	X	X	X	X	X	X	X
Patient's assessment of pain visual analog scale			X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X
Physician global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X
Hand and foot x-rays	X <sup>i</sup>									X <sup>j</sup>		X <sup>*</sup>	X <sup>j</sup>	
HAQ-DI			X	X	X	X	X	X	X	X	X	X	X	X
FACIT-F			X			X	X	X		X	X	X	X	X
SF-36v2 Acute			X			X	X	X		X	X	X	X	X
EQ-5D-5L			X			X	X	X		X	X	X	X	X

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Visit	Screening		Blinded Treatment Part A											ET	Follow-Up Part B <sup>a</sup>
	1	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	11			
Week of Treatment			Baseline 0	1	2	4	8	12	14	16	20	24	Any week		
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	Any day	28 ± 5 days after last dose	
WPAI-RA			X		X	X	X	X		X	X	X	X	X	
QIDS-SR16			X					X				X	X	X	
Healthcare resource use			X			X	X	X		X	X	X	X	X	
Morning joint stiffness <sup>k,l</sup>			X												
Worst tiredness NRS <sup>l</sup>			X												
Worst Joint Pain NRS <sup>l</sup>			X												
Laboratory tests															
TSH	X														
HIV	X														
Hepatitis B testing (HBsAg, HBcAb, HBsAb)	X														
Hepatitis C antibody testing	X														
Serum pregnancy test <sup>m</sup>	X		X												
Urine pregnancy test <sup>m</sup>			X	X	X	X	X	X	X	X	X	X	X	X	
FSH <sup>n</sup>	X														
Clinical chemistry <sup>o</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	
Lipid panel <sup>p</sup>			X					X				X			
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X	
Iron studies (iron, TIBC, and ferritin)	X		X					X				X			
Urinalysis	X		X					X				X	X	X	
Rheumatoid factor	X		X					X				X	X		

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Visit	Screening		Blinded Treatment Part A										ET	Follow-Up Part B <sup>a</sup>
	1	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	11	ET	801
Week of Treatment			Baseline 0	1	2	4	8	12	14	16	20	24	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	Any day	28 ± 5 days after last dose
hsCRP	X		X	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate <sup>9</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X
Anti-CCP	X		X					X				X	X	
Immunoglobulin levels (IgG, IgA, IgM)	X		X			X		X				X	X	X
Lymphocyte subsets (T, B, NK, and T-cell subsets)	X		X			X		X				X	X	X
Exploratory storage samples (serum and plasma)			X	X	X	X		X				X		
Exploratory storage samples (RNA)			X	X	X	X		X				X		
Exploratory storage samples (urine)			X	X	X	X		X				X		
Baricitinib plasma concentration (PK sample) <sup>9</sup>			X			X	X	X			X	X	X	
Pharmacogenetic (DNA) collection			X									X		

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Abbreviations: BP = blood pressure; CCP = cyclic citrullinated peptide; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Level; ET = early termination visit; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire-Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IVRS = interactive voice-response system; NK = natural killer; NRS = numeric rating scale; PK = pharmacokinetic; PPD = purified protein derivative; QIDS-SR<sub>16</sub> = Quick Inventory of Depressive Symptomatology Self-Rated-16; RA = rheumatoid arthritis; RNA = ribonucleic acid; SF-36v2 Acute = Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Acute; TB = tuberculosis; TIBC = total iron binding capacity; TSH = thyroid-stimulating hormone; WPAI-RA = Work Productivity and Activity Impairment-Rheumatoid Arthritis.

- a Those patients who completed the study and did not enroll in long-term safety Study I4V-MC-JADY (JADY) returned for a safety follow-up visit 28 days after their last dose of study drug. Those patients who did enroll in Study JADY did not need to return for a follow-up visit.
- b Symptom-directed physical examinations may have been conducted at the investigator's discretion at any visit and any time a patient presents with physical complaints.
- c Included recording of habits such as caffeine, alcohol, and tobacco consumption.
- d Electrocardiograms were performed locally and were locally (machine) read.
- e If the PPD test results were positive and the patient had no medical history or chest x-ray findings consistent with active TB, the patient may have had a QuantiFERON-TB Gold or T-SPOT.TB test (if available). If the QuantiFERON-TB Gold or T-SPOT.TB test results were not negative, the patient was considered to have latent TB. If the QuantiFERON-TB Gold or T-SPOT.TB test was available and, in the judgment of the investigator, was preferred as an alternative to the PPD skin test for the evaluation of TB infection, it was used instead of the PPD TB test. If the QuantiFERON-TB Gold or T-SPOT.TB test was positive, the patient was considered to have latent TB. If the test was not negative, the test was repeated once within approximately 2 weeks of the initial value. If the repeat test results were again not negative, the patient was considered to have latent TB.
- f A chest x-ray was taken at screening unless one had been obtained within 6 months prior to the study (provided the x-ray and/or report were available for review).
- g At Visit 2 (Week 0), patients were asked to take their investigational product in the clinic, and PK samples were drawn at 30 and 90 minutes postdose. At Visit 5 (Week 4), patients were asked to take their investigational product at home prior to visiting the clinic. The clinic visit was scheduled so that the sample taken during this visit was 4 to 6 hours after the dose taken at home. At Visit 6 (Week 8), patients were asked to take their investigational product in the clinic, and PK samples were taken at 1 hour postdose. For Visits 7 (Week 12), 10 (Week 20), and 11 (Week 24), patients were asked to take their investigational product in the clinic, and a sample was taken at any time predose on the day of the clinic visits. If the patient had taken the dose before the visit, the sample was drawn any time postdose, and the inability to collect a predose sample was not considered a protocol violation. For the ET visit, a sample was drawn any time if the last dose of investigational drug was taken within the last 48 hours.
- h At Visit 3, patients should have brought their investigational product with them to the study visit, but no tablet counts were performed.
- i At screening, radiographic images of the hands and feet acquired within 4 weeks before screening were submitted to the central reader to confirm erosion status. If a patient underwent rescreening, radiographic images acquired as part of initial screening and within 10 weeks of randomization were used.
- j X-rays were only taken at Week 16 in patients who received rescue therapy. If rescue occurred at a time point other than Week 16 (including unscheduled visits), x-rays were taken at this time point of rescue instead. X-rays were only taken at ET if the most recent x-ray was more than 12 weeks earlier.
- k Morning joint stiffness assessment was collected using a battery of questions and an ePRO diary to assess duration and severity of morning joint stiffness and recurrence of stiffness during the day.
  - l Morning joint stiffness, Worst Tiredness, and Worst Joint Pain were collected using patient diaries through Week 12.
- m For all women of childbearing potential, a serum pregnancy test (central laboratory) was performed at Visits 1 and 2. Urine pregnancy tests (local laboratory) were also performed at Visit 2 and at all subsequent study visits.
- n To confirm postmenopausal status for women  $\geq 40$  and  $< 60$  years of age who have had a cessation of menses, FSH tests were performed. Nonchildbearing potential is defined as an FSH  $\geq 40$  mIU/mL and a cessation of menses for at least 12 months.
- o Clinical chemistry included the following values calculated from serum creatinine: calculated creatinine clearance (Cockcroft-Gault equation) and eGFR (calculated using the Modification of Diet in Renal Disease isotope dilution mass spectrometry traceable method).
- p Fasting lipid profile. Patients should not have eaten or had anything to drink except water for 12 hours prior to sample collection. If a patient attended these visits in a nonfasting state, this was not considered a protocol violation.
- q Erythrocyte sedimentation rate was performed locally using a kit provided by the sponsor.
- r At each time point, 3 replicate readings were made at approximately 30- to 60-second intervals. Blood pressure was recorded as the average of these three readings. A single pulse measurement was made simultaneously with at least one of the readings at each time point.
- s Week 24 x-rays were only taken if the most recent x-ray was at least 8 weeks earlier.

Source: JADX clinical study report, p. 97-105

13.3.2. JADW

Table JADW.9.3. Study Schedule

Visit	Screening		Blinded Treatment - Part A											Follow-up Part B <sup>a</sup>
	1	1a	2	3	4	5	6	7	8	9	10	11	ET	801
Week of Treatment			(Baseline) 0	1	2	4	8	12	14	16	20	24	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 5 days	Any day	28 ± 5 days after last dose
Informed consent	X													
Clinical assessments:														
History	X													
Physical examination	X													
Symptom-directed physical examination <sup>b</sup>			X	X	X	X	X	X	X	X	X	X	X	X
Previous therapy/previous RA therapy	X													
Patient demographics	X													
Height	X													
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X							X				X		
Vital signs (BP and pulse) <sup>c</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X
Habits <sup>c</sup>	X													
Electrocardiogram <sup>d</sup>	X													
Inclusion/exclusion review for entry	X													
Inclusion/exclusion review for enrollment			X											
Administer Tuberculosis test <sup>e</sup>	X													
Read PPD test if used for tuberculosis testing <sup>e</sup>		X												

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Visit	Screening		Blinded Treatment - Part A											Follow-up Part Ba
	1	1a	2	3	4	5	6	7	8	9	10	11	ET	801
Week of Treatment			(Baseline) 0	1	2	4	8	12	14	16	20	24	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 5 days	Any day	28 ± 5 days after last dose
Chest x-ray	X													
Preexisting conditions	X		X											
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X											
Call IVRS	X		X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed			X			X	X	X		X	X			
Study drugs returned and assess compliance				X <sup>h</sup>	X	X	X	X	X	X	X	X	X	
Tender/swollen joint count (68/66 joints)	X		X	X	X	X	X	X	X	X	X	X	X	X
Patient's assessment of pain VAS			X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X
Physician global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X
HAQ-DI			X	X	X	X	X	X	X	X	X	X	X	X
Morning joint stiffness			X	X	X	X	X	X		X	X	X	X	X
FACIT-F			X			X	X	X		X	X	X	X	X
SF-36 v.2 Acute			X			X	X	X		X	X	X	X	X
EQ-5D-5L			X			X	X	X		X	X	X	X	X
Worst tiredness NRS			X	X	X	X	X	X		X	X	X	X	X

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Visit	Screening		Blinded Treatment - Part A											Follow-up Part B <sup>a</sup>
	1	1a	2	3	4	5	6	7	8	9	10	11	ET	801
Week of Treatment			(Baseline) 0	1	2	4	8	12	14	16	20	24	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 5 days	Any day	28 ± 5 days after last dose
WPAI-RA			X		X	X	X	X		X	X	X	X	X
Worst pain NRS			X	X	X	X	X	X		X	X	X	X	X
QIDS-SR16			X					X				X	X	X
Healthcare resource use			X			X	X	X		X	X	X	X	X
Laboratory tests														
TSH	X													
HIV	X													
Hepatitis C antibody testing	X													
Hepatitis B testing (HBsAg, HBcAb, HBsAb)	X													
Serum pregnancy test <sup>f</sup>	X		X											
Urine pregnancy test <sup>f</sup>			X	X	X	X	X	X	X	X	X	X	X	X
FSH <sup>h</sup>	X													
Clinical chemistry <sup>k</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel <sup>l</sup>			X					X				X		
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X
Iron studies (iron, TIBC, and ferritin)	X		X					X				X		
Urinalysis	X		X					X				X	X	X
Rheumatoid factor	X		X					X				X	X	
hsCRP	X		X	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X

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Visit	Screening		Blinded Treatment - Part A											Follow-up Part B <sup>a</sup>
	1	1a	2	3	4	5	6	7	8	9	10	11	ET	801
Week of Treatment			(Baseline) 0	1	2	4	8	12	14	16	20	24	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 5 days	Any day	28 ± 5 days after last dose
Anti-CCP	X		X					X				X	X	
Immunoglobulin levels (IgG, IgA, IgM)	X		X			X		X				X	X	X
Lymphocyte subsets (T, B, NK, and T-cell subsets)	X		X			X		X				X	X	X
Exploratory storage samples (serum and plasma)			X	X	X	X		X				X		
Exploratory storage samples (urine)			X	X	X	X		X				X		
Exploratory storage samples (RNA)			X	X	X	X		X				X		
Baricitinib plasma concentration (PK sample) <sup>b</sup>			X			X	X	X				X	X	
Pharmacogenetic (DNA) collection			X									X		

Abbreviations: BP = blood pressure; CCP = cyclic citrullinated peptide antibody; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Level; ET = early termination visit; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire-Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IVRS = interactive voice-response system; NMR = nuclear magnetic resonance; NRS = numeric rating scale; PK = pharmacokinetic; PPD = purified protein derivative; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Rated (16 items); RA = rheumatoid arthritis; RNA = ribonucleic acid; SF-36v2 Acute = Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Acute; TB = tuberculosis; TIBC = total iron binding capacity; TSH = thyroid-stimulating hormone; VAS = visual analog scale; WPAI-RA = Work Productivity and Activity Impairment-Rheumatoid Arthritis.

- a Those patients who completed the study and did not enroll in long-term safety Study JADY returned for a safety follow-up visit 28 days after the last dose of study drug. Those patients who enrolled in Study JADY did not return for a follow-up visit.
- b Symptom-directed physical examinations were conducted at the investigator's discretion at any visit and any time a patient presented with physical complaints.

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- c Included recording of habits such as caffeine, alcohol, and tobacco consumption.
- d Electrocardiograms were performed locally and were locally (machine) read.
- e If the PPD test results were positive and the patient had no medical history or chest x-ray findings consistent with active TB, the patient may have had a QuantiFERON-TB Gold or T-SPOT.TB test (if available). If the QuantiFERON-TB Gold or T-SPOT.TB test results were not negative, the patient was considered to have latent TB. If the QuantiFERON-TB Gold or T-SPOT.TB test was available and, in the judgment of the investigator, was preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may have been used instead of the PPD TB test. If the QuantiFERON-TB Gold or T-SPOT.TB test was positive, the patient was considered to have latent TB. If the test was not negative, the test may have been repeated once within 2 weeks of the initial value. If the repeat test results were again not negative, the patient was considered to have latent TB.
- f A chest x-ray was taken at screening unless one had been obtained within 6 months prior to the study (provided the x-ray and/or report were available for review).
- g At Visit 2 (Week 0), patients were asked to take their study drug in the clinic, and PK samples were drawn at 15 minutes and 1 hour postdose. At Visit 5 (Week 4), patients were asked to take their study drug at home prior to visiting the clinic. The clinic visit was scheduled so that the sample taken during this visit was 2 to 4 hours after their dose taken at home. At Visit 6 (Week 8), patients were asked to take their study drug at home prior to visiting the clinic. The clinic visit was scheduled so that the sample taken during this visit was 4 to 6 hours after their dose taken at home. For Visit 7 (Week 12) and Visit 11 (Week 24), patients took their study drug in the clinic to allow for a predose PK sample to be taken during the study visit. If the patient took the dose before the visit, the sample was drawn any time postdose, and the inability to collect a predose sample was not considered a protocol violation. For the early termination visit, a sample was drawn any time if the last dose of investigational drug was taken within the last 48 hours.
- h At Visit 3, patients brought their study drug to the study visit, but no tablet counts were performed.
- i For all women of childbearing potential, a serum pregnancy test (central laboratory) was performed at Visits 1 and 2. Urine pregnancy tests (local laboratory) were also performed at Visit 2 and at all subsequent study visits.
- j To confirm postmenopausal status for women  $\geq 40$  and  $< 60$  years of age who had a cessation of menses, an FSH test was performed. Nonchildbearing potential was defined as an FSH  $\geq 40$  mIU/mL and a cessation of menses for at least 12 months.
- k Clinical chemistry included the following values calculated from serum creatinine: calculated creatinine clearance (Cockcroft-Gault equation) and eGFR (calculated using the Modification of Diet in Renal Disease isotope dilution mass spectrometry traceable method).
- l Fasting lipid profile. Patients did not eat or drink anything except water for 12 hours prior to sample collection. If a patient attended these visits in a nonfasting state, this was not considered a protocol violation.
- m Erythrocyte sedimentation rate was performed locally using a kit provided by the sponsor.
- n At each time point, 3 replicate readings were made at approximately 30- to 60-second intervals. Blood pressure was recorded as the average of these three readings. A single pulse measurement was made simultaneously with at least one of the readings at each time point.

Source: JADW clinical study report, p. 90-94

13.3.3. JADV

Table JADV.9.4. Schedule of Events

Visit	Screening		Blinded, Placebo- and Active-Controlled Treatment Part A									Blinded, Active-Controlled Part B				ETV	Follow-up Part C <sup>a</sup>	
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	14			15
Week of Treatment			Base-line 0	1	2	4	8	12	14	16	20	24	28	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	196 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Informed consent	X																	
Clinical assessments:																		
History	X																	
Physical examination	X																	
Symptom-directed physical examination <sup>b</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous therapy/previous RA therapy	X																	
Patient demographics	X																	
Height	X																	
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X							X				X				X		
Vital signs <sup>c</sup> (BP and pulse)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Habits <sup>c</sup>	X																	
Electrocardiogram <sup>d</sup>	X																	
Inclusion/exclusion review for entry	X																	
Inclusion/exclusion review for enrollment			X															

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Visit	Screening		Blinded, Placebo- and Active-Controlled Treatment Part A									Blinded, Active-Controlled Part B					ETV	Follow-up Part C <sup>a</sup>
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Week of Treatment			Base-line 0	1	2	4	8	12	14	16	20	24	28	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	196 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Administer tuberculosis tests	X																	
Read PPD test if PPD used for tuberculosis tests		X																
Chest x-ray <sup>f</sup>	X																	
Preexisting conditions	X		X															
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X															
Call IVRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational product dispensed			X <sup>g</sup>			X	X	X		X	X	X	X	X	X			
Investigational products returned and assess compliance				X <sup>h</sup>	X <sup>h</sup>	X	X	X	X <sup>h</sup>	X	X	X	X	X	X	X	X	
Tender/swollen joint count (68/66 joints)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's assessment of pain visual analog scale			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Visit	Screening		Blinded, Placebo- and Active-Controlled Treatment Part A									Blinded, Active-Controlled Treatment Part B				ETV	Follow-up Part C <sup>a</sup>	
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	14			15
Week of Treatment			Base-line 0	1	2	4	8	12	14	16	20	24	28	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	196 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Hand and foot x-rays	X <sup>i</sup>									X	X				X	X <sup>j</sup>		
HAQ-DI			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Morning joint stiffness - diary <sup>k</sup>			X															
Morning joint stiffness-tablet <sup>l</sup>			X	X	X	X	X	X		X	X	X	X	X	X	X	X	
FACIT-F			X			X	X	X		X	X	X	X	X	X	X	X	
SF-36v2 Acute			X			X	X	X		X	X	X	X	X	X	X	X	
EQ-5D-5L			X			X	X	X		X	X	X	X	X	X	X	X	
Worst tiredness NRS-diary <sup>k</sup>			X															
Worst tiredness NRS-tablet <sup>l</sup>			X	X	X	X	X	X		X	X	X	X	X	X	X	X	
WPAI-RA			X		X	X	X	X		X	X	X	X	X	X	X	X	
Worst joint pain NRS-diary <sup>k</sup>			X															
Worst tiredness NRS-tablet <sup>l</sup>			X	X	X	X	X	X		X	X	X	X	X	X	X	X	
QIDS-SR <sub>16</sub>			X					X				X				X	X	
Healthcare resource use			X			X	X	X		X	X	X	X	X	X	X	X	
Laboratory tests																		
TSH	X																	
HIV	X																	
Hepatitis C antibody testing	X																	
Hepatitis B testing (HBsAg, HBcAb, HBsAb)	X																	

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Visit	Screening		Blinded, Placebo- and Active-Controlled Treatment Part A									Blinded, Active-Controlled Part B				ETV	Follow-up Part C <sup>a</sup>	
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	14			15
Week of Treatment			Base-line 0	1	2	4	8	12	14	16	20	24	28	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	196 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Serum pregnancy test <sup>m</sup>	X		X															
Urine pregnancy test <sup>m</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH <sup>h</sup>	X																	
Clinical chemistry <sup>o</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel <sup>p</sup>			X					X				X				X		
Lipid NMRP			X					X										
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Iron studies (iron, TIBC, and ferritin)	X		X					X				X				X		
Urinalysis	X		X					X				X		X		X	X	X
Rheumatoid factor	X		X					X				X				X	X	X
hsCRP	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate <sup>q</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ACPA	X		X					X				X				X	X	
Immunoglobulin levels (IgG, IgA, IgM)	X		X			X		X				X				X	X	X
Lymphocyte subsets (T, B, NK, and T cell subsets)	X		X			X		X				X				X	X	X
Exploratory storage samples (serum and plasma)			X	X	X	X		X				X				X		

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Visit	Screening		Blinded, Placebo- and Active-Controlled Treatment Part A										Blinded, Active-Controlled Part B				ETV	801
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Week of Treatment			Base-line 0	1	2	4	8	12	14	16	20	24	28	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	98 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	196 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Exploratory storage samples (urine)			X	X	X	X		X				X				X		
Exploratory storage samples (RNA)			X	X	X	X		X				X				X		
Baricitinib plasma concentration (PK sample) <sup>c</sup>			X			X	X	X				X		X			X	
DNA collection			X									X						

Abbreviations: ACPA = anti-citrullinated peptide antibody; BP = blood pressure; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Levels; ETV = early termination visit; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue scale; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire-Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IVRS = interactive voice-response system; NK = natural killer; NMR = nuclear magnetic resonance; NRS = numeric rating scale; PK = pharmacokinetic; PPD = purified protein derivative; QIDS-SR<sub>16</sub> = Quick Inventory of Depressive Symptomatology Self-Rated-16; RA = rheumatoid arthritis; RNA = ribonucleic acid; SF-36v2 Acute = Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Acute; TB = tuberculosis; TIBC = total iron-binding capacity; TSH = thyroid-stimulating hormone; WPAI-RA = Work Productivity and Activity Impairment-Rheumatoid Arthritis.

<sup>a</sup> Those patients who completed the study and did not enroll in extension Study JADY returned for a safety follow-up visit 28 days after their last dose of study drug. Those patients who did enroll in Study JADY did not need to return for a follow-up visit.

<sup>b</sup> Symptom-directed physical examinations were conducted at the investigator's discretion at any visit and any time a patient presented with physical complaints.

<sup>c</sup> Included recording of habits such as caffeine, alcohol, and tobacco consumption.

<sup>d</sup> Electrocardiograms were performed locally and locally (machine) read.

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- e If the PPD test was positive and the patient had no medical history or chest x-ray findings consistent with active TB, the patient could have a QuantiFERON-TB Gold or T-SPOT.TB test (if available). If the QuantiFERON-TB Gold or T-SPOT.TB test results were not negative, the patient was considered to have latent TB. If the QuantiFERON-TB Gold or T-SPOT.TB test was available and, in the judgment of the investigator, preferred as an alternative to the PPD skin test for the evaluation of TB infection, it could be used instead of the PPD TB test. If the QuantiFERON-TB Gold or T-SPOT.TB test was positive, the patient was considered to have latent TB. If the test was not negative, the test could be repeated once within 2 approximately weeks of the initial value. If the repeat test results were again not negative, the patient was considered to have latent TB.
- f A chest x-ray was taken locally at screening unless one has been obtained within the past 6 months (provided the x-ray and/or report are available for review).
- g At Visit 2, the patient took his/her oral investigational product at the clinic under the supervision of study staff. Injectable investigational product was administered by the study staff with instructions given to the patient.
- h At Visits 3, 4, and 8, patients were to bring their investigational product with them to the study visit, but no tablet counts needed to be performed.
- i At screening, radiographic images of the hands and feet acquired within 4 weeks prior to study entry could be submitted to the central reader to confirm eligibility. If a patient underwent rescreening, radiographic images acquired as part of initial screening and within 10 weeks of randomization could be used.
- j X-rays were only taken at the ETV if the most recent x-ray was more than 12 weeks earlier.
- k Morning joint stiffness, Worst Tiredness, and Worst Joint Pain assessments were collected using a battery of questions and an electronic patient-reported outcomes [ePRO] diary to assess duration, severity of morning joint stiffness, recurrence of stiffness during the day, worst tiredness, and worst joint pain.
- l Morning joint stiffness duration, Worst Tiredness, and Worst Joint Pain assessments were collected using an ePRO tablet at each visit in a subset of patients.
- m For all women of childbearing potential, a serum pregnancy test (central laboratory) was performed at Visit 1 and Visit 2. Urine pregnancy tests (local laboratory) were also performed at Visit 2 and at all subsequent study visits.
- n To confirm postmenopausal status for women  $\geq 40$  and  $< 60$  years of age who had a cessation of menses, an FSH test was performed. Nonchildbearing potential was defined as an FSH  $\geq 40$  mIU/mL and a cessation of menses for at least 12 months.
- o Clinical chemistry included the following values calculated from serum creatinine: calculated creatinine clearance (Cockcroft-Gault equation) and eGFR (calculated using the Modification of Diet in Renal Disease isotope dilution mass spectrometry traceable method).
- p Fasting lipid profile. Patients were not to eat or drink anything except water for 12 hours prior to sample collection. If a patient attended these visits in a nonfasting state, this was not considered a protocol violation.
- q Erythrocyte sedimentation rate was performed locally using a kit provided by the sponsor.
- r At Visit 2 (Week 0), patients took their oral investigational product in the clinic, and PK samples were drawn at 15 minutes and 1 hour postdose. At Visit 5 (Week 4), patients were asked to take their oral investigational product at home prior to visiting the clinic. The clinic visit was scheduled so that the sample taken during this visit was 2 to 4 hours after the oral dose taken at home. At Visit 6 (Week 8), patients were asked to take their oral investigational product at home prior to visiting the clinic. The clinic visit was scheduled so that the sample taken during this visit was 4 to 6 hours after the oral dose taken at home. For Visits 7 (Week 12), 11 (Week 24), and 13 (Week 32), patients were asked not to take their oral investigational product prior to visiting the clinic, and a sample was taken at any time predose on the day of the clinic visits. If the patient had taken his/her oral dose prior to the visit, the sample could be drawn any time postdose, and the inability to collect a predose sample was not considered a protocol violation. For the ETV, a sample could be drawn any time if the last dose of oral investigational drug was taken within the last 48 hours.
- s At each time point, 3 replicate readings could be made at approximately 30- to 60-second intervals. Blood pressure was recorded as the average of these 3 readings. A single pulse measurement could be made simultaneously with at least 1 of the readings at each time point.

Source: JADV clinical study report, p. 128-133

13.3.4. JADZ

Table JADZ.9.4. Schedule of Events

Visit	Screening		Blinded Active-Controlled Part A													Follow-Up Part Ba
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	ET	801
Week of Treatment			Baseline 0	1	2	4	8	12	16	20	24	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Informed consent	X															
Clinical Assessments:																
History	X															
Physical examination	X															
Symptom-directed physical examination <sup>b</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous therapy/previous RA therapy	X															
Patient demographics	X															
Height	X															
Weight	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X							X			X			X		
Vital signs <sup>P</sup> (BP and pulse)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Habits <sup>c</sup>	X															
Electrocardiogram <sup>d</sup>	X															
Inclusion/exclusion review for entry	X															
Inclusion/exclusion review for enrollment			X													

Visit	Screening		Blinded Active-Controlled Part A													Follow-Up Part Ba
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	ET	801
Week of Treatment			Baseline 0	1	2	4	8	12	16	20	24	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Administered TB test <sup>e</sup>	X															
Read PPD test if used for TB testing <sup>e</sup>		X														
Chest x-ray <sup>f</sup>	X															
Preexisting conditions	X		X													
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X													
Called IVRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed <sup>g</sup>			X			X	X	X	X	X	X <sup>g</sup>	X	X			
Study drugs returned and assess compliance					x <sup>h</sup>	x <sup>h</sup>	X	X	X	X	X	X	X	X	X	
Tender/swollen joint count (68/66 joints)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's assessment of pain visual analog scale			X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Visit	Screening		Blinded Active-Controlled Part A													Follow-Up Part Ba
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	ET	801
Week of Treatment			Baseline 0	1	2	4	8	12	16	20	24	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Patient global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician global assessment of disease activity			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand and foot x-rays	X <sup>i</sup>							X			X			X	X <sup>i</sup>	
HAQ-DI			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Morning joint stiffness			X	X	X	X	X	X	X	X	X	X	X	X	X	X
FACIT-F			X	X		X	X	X	X	X	X	X	X	X	X	X
SF-36 v.2			X			X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L			X			X	X	X	X	X	X	X	X	X	X	X
Worst tiredness NRS			X	X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-RA			X			X	X	X	X	X	X	X	X	X	X	X
Worst joint pain NRS			X	X	X	X	X	X	X	X	X	X	X	X	X	X
QIDS-SR16			X					X			X		X	X	X	X
Healthcare resource use			X			X	X	X	X	X	X	X	X	X	X	X
Laboratory tests																
TSH	X															
HIV	X															

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Visit	Screening		Blinded Active-Controlled Part A													Follow-Up Part Ba
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	ET	801
Week of Treatment			Baseline 0	1	2	4	8	12	16	20	24	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Hepatitis B testing (HBsAg, HBcAb, HBsAb)	X															
Hep C antibody testing	X															
Serum pregnancy test <sup>k</sup>	X		X													
Urine pregnancy test <sup>k</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH <sup>l</sup>	X															
Clinical chemistry <sup>m,r</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel <sup>n</sup>			X					X			X			X		
Hematology <sup>r</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Iron studies (iron, TIBC, and ferritin)	X		X					X			X			X		
Urinalysis	X		X					X			X			X	X	X
Rheumatoid factor	X		X					X			X			X	X	
hsCRP	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation ratio	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-CCP (ACPA)	X		X					X			X			X	X	
Immunoglobulin levels (IgG, IgA, IgM)	X		X			X		X				X			X	X
Lymphocyte subsets (T, B, NK, and T-cell subsets)	X		X			X		X				X			X	X

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Visit	Screening		Blinded Active-Controlled Part A													Follow-Up Part Ba
	1	1a	2	3	4	5	6	7	8	9	10	11	12	13	ET	801
Week of Treatment			Baseline 0	1	2	4	8	12	16	20	24	32	40	52	Any week	
Days from Visit 2	-42 to -3 days		0	7 ± 2 days	14 ± 2 days	28 ± 2 days	56 ± 3 days	84 ± 3 days	112 ± 3 days	140 ± 3 days	168 ± 3 days	224 ± 5 days	280 ± 5 days	365 ± 5 days	Any day	28 ± 5 days after last dose
Exploratory storage samples (serum and plasma)			X	X	X	X		X			X			X		
Exploratory storage samples (urine)			X	X	X	X		X			X			X		
Exploratory storage samples (RNA)			X	X	X	X		X			X			X		
Baricitinib plasma concentration (PK sample)g			X			X		X			X	X			X	
Pharmacogenetic (DNA) collection			X								X					

Abbreviations: ACPA= anti-citrullinated protein antibody; BP = blood pressure; CCP = cyclic citrullinated peptide; DNA = deoxyribonucleic acid; ET = early termination visit; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Level; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire-Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; Hep C = hepatitis C; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IVRS = interactive voice-response system; NK = natural killer; NRS = numeric rating scale; PK = pharmacokinetic; PPD = purified protein derivative; QIDS-SR<sub>16</sub> = Quick Inventory of Depressive Symptomatology-Self Report (16 items); RA = rheumatoid arthritis; RNA = ribonucleic acid; SF-36v2 Acute = Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Acute; TB = tuberculosis; TIBC = total iron binding capacity; TSH = thyroid-stimulating hormone; VAS = visual analog scale; WPAI-RA = Work Productivity and Activity Impairment-Rheumatoid Arthritis.

- a Those patients who completed the study and did not enroll in long-term safety Study I4V-MC-JADY (JADY) should have returned for a safety follow-up visit 28 days after their last dose of study drug. Those patients who enrolled in Study JADY did not need to return for a follow-up visit.
- b Symptom-directed physical examinations were conducted at the investigator's discretion at any visit and any time a patient presented with physical complaints.
- c Included recording of habits such as caffeine, alcohol, and tobacco consumption.
- d ECGs were performed locally and were locally (machine) read.

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- e If the PPD test results were positive and the patient had no medical history or chest x-ray findings consistent with active TB, the patient may have had a QuantiFERON®-TB Gold or T-SPOT®.TB test (if available). If the QuantiFERON-TB Gold or T-SPOT.TB test results were not negative, the patient was considered to have latent TB. If the QuantiFERON-TB Gold or T-SPOT.TB test was available and, in the judgment of the investigator, was preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may have been used instead of the PPD TB test. If the QuantiFERON-TB Gold or T-SPOT.TB test was positive, the patient was considered to have latent TB. If the test was not negative, the test may have been repeated once within approximately 2 weeks of the initial value. If the repeat test results were again not negative, the patient was considered to have latent TB.
- f A chest x-ray was taken at screening unless one had been obtained within 6 months prior to the study (provided the x-ray and/or report were available for review).
- g At Visit 2 (Week 0), patients were asked to take their study drugs in the clinic, and PK samples were drawn at 30 and 90 minutes postdose. For Visit 5 (Week 4), patients were asked to take their study drugs prior to visiting the clinic. The clinic visit should have been scheduled so that the sample taken during this visit was 2 to 4 hours after their dose taken at home. For Visit 7 (Week 12), patients were asked to take their study drugs prior to visiting the clinic. The clinic visits should have been scheduled so that the sample taken during this visit was 4 to 6 hours after the dose taken at home. At Visit 10 (Week 24), patients did not take their study drugs before visiting the clinic, and a sample was taken any time predose on the day of the clinic visit. The patient was advised to take the investigation product at the clinic, and a PK sample was drawn at 1 hour postdose. For Visit 11 (Week 32), patients were advised not to take their study drugs before visiting the clinic, and a sample was taken from each patient at any time predose on the day of the clinic visit. If the patient had taken the dose before the visit, the sample may have been drawn any time postdose, and the inability to collect a predose sample was not considered a protocol violation. For the early termination visit, a sample may have been drawn any time if the last dose of investigational drug was taken within the previous 48 hours.
- h At Visits 3 and 4, patients should have brought their study drug with them to the study visit, but no tablet or capsule counts needed to be performed.
- i At screening, radiographic images of the hands and feet acquired within 4 weeks before screening may have been submitted to the central reader to confirm erosion status. If a patient underwent rescreening, radiographic images acquired as part of initial screening and within 10 weeks of randomization may have been used.
- j X-rays were only taken at early termination if the most recent x-ray was more than 12 weeks earlier.
- k For all women of childbearing potential, a serum pregnancy test (central laboratory) was performed at Visits 1 and 2. Urine pregnancy tests (local laboratory) were also performed at Visit 2 and at all subsequent study visits.
- l To confirm postmenopausal status for women ≥40 and <60 years of age who had a cessation of menses, FSH tests were performed. Nonchildbearing potential was defined as an FSH ≥40 mIU/mL and a cessation of menses for at least 12 months.
- m Clinical chemistry included the following values calculated from serum creatinine: calculated creatinine clearance (Cockcroft-Gault equation) and eGFR (calculated using the Modification of Diet in Renal Disease isotope dilution mass spectrometry traceable method).
- n Fasting lipid profile. Patients should not have eaten or drunken anything except water for 12 hours prior to sample collection. If a patient attended these visits in a nonfasting state, this was not considered a protocol violation.
- o Erythrocyte sedimentation rate was performed locally using a kit provided by the sponsor.
- p At each time point, 3 replicate readings were made at approximately 30- to 60-second intervals. Blood pressure was recorded as the average of these 3 readings. A single pulse measurement was made simultaneously with at least 1 of the readings at each time point.
- q Patients undergoing rescue therapy should have returned to the site approximately 4 weeks after rescue for chemistry and hematology testing (see Schedule of Events for Additional Laboratory Visits).
- r Patients with renal impairment should have returned to the site at approximately Weeks 28, 36, 44, and 48 for chemistry and hematology testing (see Schedule of Events for Additional Laboratory Visits).

Schedule of Events for Additional Laboratory Visits

Week of Treatment	Week 28	Week 36	Week 44	Week 48
Days from Visit 2	196 ± 3 days	252 ± 3 days	308 ± 3 days	336 ± 3 days
Patients that underwent rescue therapy <sup>a</sup>				
Chemistry	X			
Hematology	X			
Patients with renal impairment (eGFR <60 mL/min/1.73 m <sup>2</sup> )				
Chemistry	X	X	X	X
Hematology	X	X	X	X

Abbreviation: eGFR = estimated glomerular filtration rate.

<sup>a</sup> Patients had laboratory tests performed approximately 4 weeks after rescue; rescue could have occurred from Week 24 onwards. Week 28 was provided as an example of laboratory tests performed 4 weeks after rescue at Week 24.

Source: JADZ clinical study report, p. 115-121

### 13.4. Financial Disclosure

#### Covered Clinical Study (Name and/or Number): JADC

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from
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		Applicant)
Total number of investigators identified: <u>35</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S _____</p> <p>Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): JADA**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>76</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

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<u>3</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>3</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): JADN**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>25</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		

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Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): JADZ**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>197</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from

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of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): JADV**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>297</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>3</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation

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reason:		from Applicant)
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**Covered Clinical Study (Name and/or Number): JADX**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>184</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): JADW**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
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Total number of investigators identified: <u>140</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____  Significant payments of other sorts: _____  Proprietary interest in the product tested held by investigator: _____  Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): JADY**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>411</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the		

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 Olumiant (baricitinib)

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Clinical Review  
Raj Nair  
NDA 207924  
Olumiant (baricitinib)

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/s/  
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RAJ NAIR  
01/09/2017

JANET W MAYNARD  
01/09/2017

## Cross-Discipline Team Leader Review

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

### 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
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic symmetric inflammation of joints and is the most common type of autoimmune inflammatory arthritis.</li> <li>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.</li> </ul>	<p>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.</p>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>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-<math>\alpha</math>) 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-<math>\alpha</math> therapy. For these patients, additional anti-TNF-<math>\alpha</math> therapies or therapies that target different pathways</li> </ul>	<p>There are multiple current treatment options for patients with RA.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>can be used.</p> <ul style="list-style-type: none"> <li>• Tofacitinib is approved for the treatment of RA and is a Janus kinase inhibitor, similar to baricitinib.</li> </ul>	
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> <li>• 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).</li> <li>• 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).</li> <li>• The ACR20 response is calculated as a &gt;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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> </ul>	<p>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.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	<ul style="list-style-type: none"> <li>• A total of 3,464 patients with RA were exposed to baricitinib in RA studies. The drug exposure data are considered adequate.</li> <li>• Major safety concerns:</li> <li>• <u>Infections</u>: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving baricitinib.</li> <li>• <u>Laboratory abnormalities</u>: Baricitinib treatment is associated with neutropenia, lymphopenia, decreases in hemoglobin, and increases in liver enzymes and lipids.</li> <li>• <u>Malignancy</u>: Malignancies were observed in clinical studies with baricitinib.</li> <li>• <u>Gastrointestinal perforations</u>: Events of gastrointestinal perforation have been reported in clinical trials with baricitinib.</li> <li>• <u>Thrombosis</u>: Arterial and venous thromboses were observed in association with baricitinib.</li> </ul>	<p>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.</p>
<u>Risk Management</u>	<ul style="list-style-type: none"> <li>• The safety concerns with baricitinib are well-characterized. Healthcare providers are familiar with treatments for RA associated with immunosuppression and lipid elevations.</li> </ul>	<p>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.</p>

## 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<sup>®</sup>, 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<sup>™</sup>, 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.<sup>1,2</sup>

RA affects approximately 1% of the adult population in North America and Northern Europe.<sup>3</sup> 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 comorbidities. In contrast to clinical symptoms, structural damage is irreversible and cumulative.<sup>4</sup>

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.

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<sup>1</sup> Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.

<sup>2</sup> Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706-14.

<sup>3</sup> Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11(3):229.

<sup>4</sup> 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.<sup>5</sup> Treatment with a tumor necrosis factor-alpha (TNF- $\alpha$ ) antagonist is generally the next line of treatment for patients with ongoing disease activity. Currently approved TNF- $\alpha$  antagonists include etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab pegol (CIMZIA), golimumab IV (SIMPONI ARIA), infliximab-dyyb (INFLECTRA), etanercept-szsz (ERELZI) and adalimumab-atto (AMJEVITA). Between 30% and 40% of patients fail to respond or become intolerant to anti-TNF- $\alpha$  therapy.<sup>6</sup> For patients with ongoing disease activity, the therapeutic strategy usually involves trying another TNF- $\alpha$  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

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<sup>5</sup> 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.

<sup>6</sup> 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, (b) (4) 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<sub>50</sub> 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  $\geq 3$  mg/kg/day. The dog is the more sensitive nonclinical species, with an AUC<sub>0-24h</sub> of 1.21  $\mu\text{M}\cdot\text{hr}$  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: Chandras 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  $AUC_{0-inf}$  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  $AUC_{0-inf}$  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  $AUC_{0-inf}$  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, its 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  $AUC_{0-inf}$  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 CL<sub>r</sub>/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 (IC<sub>50</sub>=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
<b>Phase 2</b>						
<b>JADC</b> May 2009- July 2010 24 weeks	MTX/cDMAR D-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%)
<b>JADA</b> Nov 2010- March 2014 128 weeks	MTX/cDMAR D-IR (no previous biologics allowed)	MC, R, DB, PG study in 4 parts: <b>Part A (Wk 0 to 12):</b> DB, PC, R evaluation of baricitinib or PBO QD for 12 weeks <b>Part B (Wk 12 to 24):</b> DB, R evaluation of baricitinib BID or QD for 12 additional weeks <b>Part C (Wk 24 to 76):</b> 52 wk OLE <b>Part D (Wk 76 to 128):</b> 52 wk OLE	<b>Part A:</b> B1 B2 B4 B8 PBO <b>Part B:</b> B1→B2 BID or B4 QD B2 B4 B8 <b>Part C:</b> B2 QD or BID→B4 B4 (NR increase to B8 at wk 28 or 32) B8 <b>Part D:</b> B4	<b>Part A:</b> 49 52 52 50 98 Total: 301	ACR20 at 12 weeks	Europe (39%); USA (32%); Mexico (16%); India (14%)
<b>JADN</b> Nov 2011- Dec 2011 64 weeks	MTX/cDMAR D-IR (previous biologics allowed)	R, PC, dose-ranging study of baricitinib in Japanese patients <b>Part A:</b> 12-week DB <b>Part B:</b> 52-week SB	<b>Part A:</b> B1 B2 B4 B8 PBO <b>Part B:</b> B4	<b>Part A:</b> 24 24 24 24 49 Total: 145 <b>Part B:</b> 142	ACR20 at 12 weeks	Japan (100%)
Dose for renally (<60mL/min/1.73m <sup>2</sup> ) 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
<b>Phase 3</b>					
<b>JADV</b> (RA-BEAM; II) <i>Oct 2012-Sept 2015</i>  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%)
<b>JADX</b> (RA-BUILD; III) <i>Jan 2013-Dec 2014</i>  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%)
<b>JADW</b> (RA-BEACON; IV) <i>Jan 2013-Sept 2014</i>  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%)
<b>JADZ</b> (RA-BEGIN; I) <i>Jan 2013-Aug 2015</i>  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 <sup>2</sup> ) 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
<b>JADY</b> (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 $\leq$ 10 for $\geq$ 12 weeks in study JADY JADZ CDAI $\leq$ 2.8 for $\geq$ 12 weeks in study JADY	2539
Baricitinib dose for renally (<60mL/min/1.73m <sup>2</sup> ) 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.

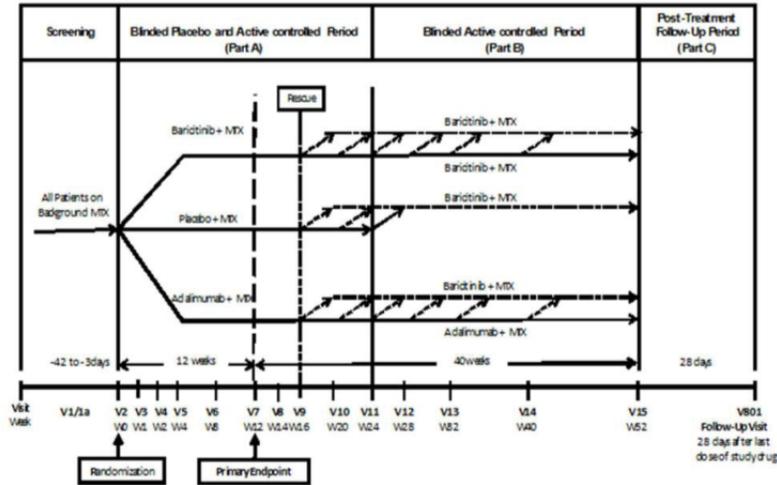
JADX (Figure 2) was a parallel group, double-blind, double-dummy, placebo controlled trial randomizing 660 patients to baricitinib 4 mg, baricitinib 2 mg, or placebo. All patients continued background cDMARDs. The placebo group was continued until Week 24, with the possibility of rescue to baricitinib 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 noninferiority 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  $CDAI \leq 10$  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

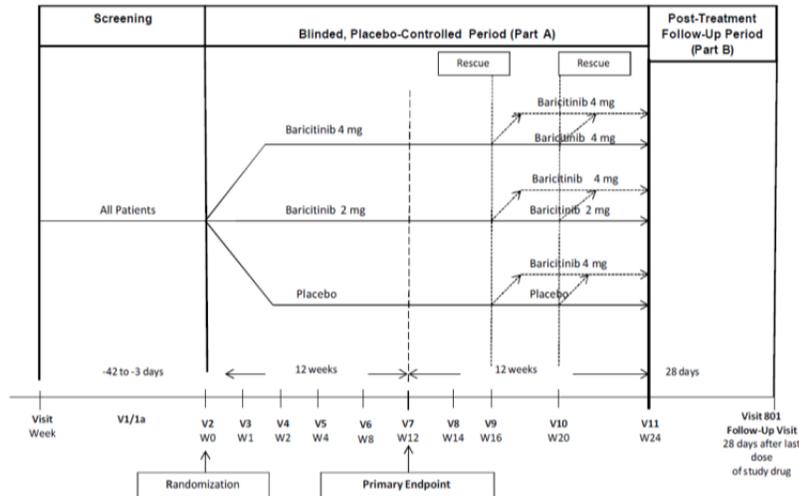


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Note: Diagonal dashed arrows indicate an option for rescue therapy. The diagonal solid arrow indicates a mandatory change to baricitinib treatment (at Week 24 for placebo-treated patients).  
 Abbreviations: V = visit; W = week.

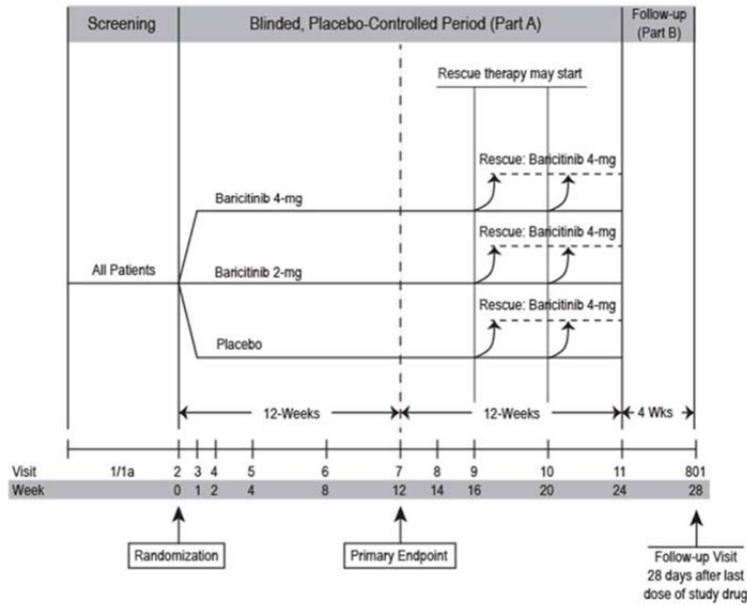
Source: JADV complete study report, page 112

Figure 2: JADX Study Design



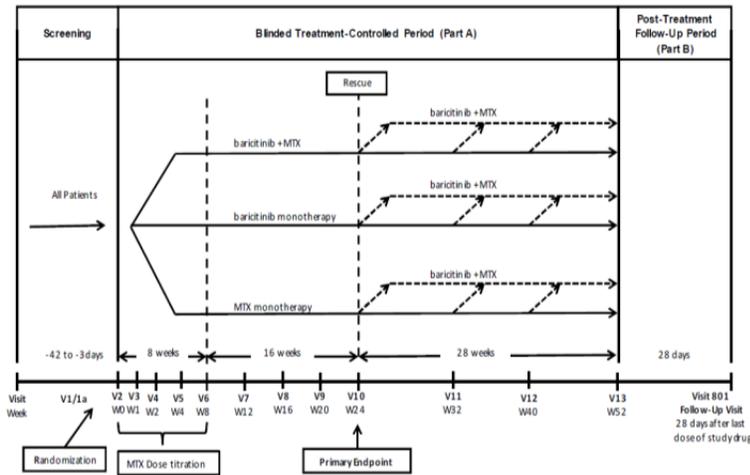
Abbreviations: V = study visit; W = study week. Diagonal dashed arrows indicate an option for rescue therapy.  
 Source: JADX complete study report, page 85

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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> An alternative equation

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<sup>7</sup> DT Felson, et al. *Arthritis Rheum* 1995. June, 38(6):727-735.

<sup>8</sup> B Bruce and JF Fries, “The Health Assessment Questionnaire (HAQ).” *Clin Exp Rheumatol* 2005; 23 (Suppl 39):S14-S18.

<sup>9</sup> 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.<sup>10</sup> 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)*

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<sup>10</sup> 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.<sup>11</sup> Disease remission has been defined as an SDAI score  $\leq 3.3$ <sup>12</sup> and low disease activity has been considered as an SDAI score  $\leq 11$ . 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  $\leq 2.8$  (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

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<sup>11</sup> 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.

<sup>12</sup> 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  $C_{avg,ss}$  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 <sup>1</sup>	7 mg <sup>1</sup>	10 mg <sup>1</sup>	
			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 <sup>2</sup>	2 mg <sup>2</sup>	4 mg <sup>2</sup>	8 mg <sup>2</sup>
			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 <sup>2</sup>	2 mg <sup>2</sup>	4 mg <sup>2</sup>	8 mg <sup>2</sup>
			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

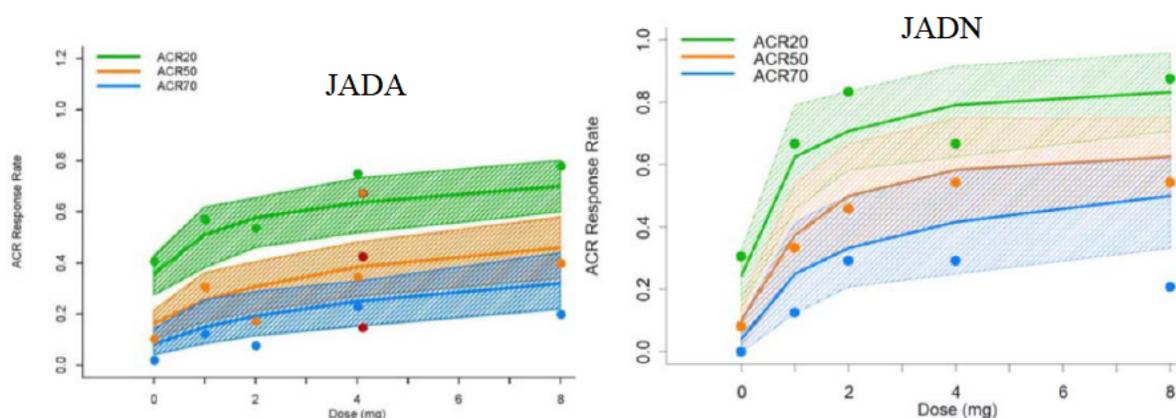
<sup>1</sup> as primary objective

<sup>2</sup> 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.<sup>13</sup> 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.

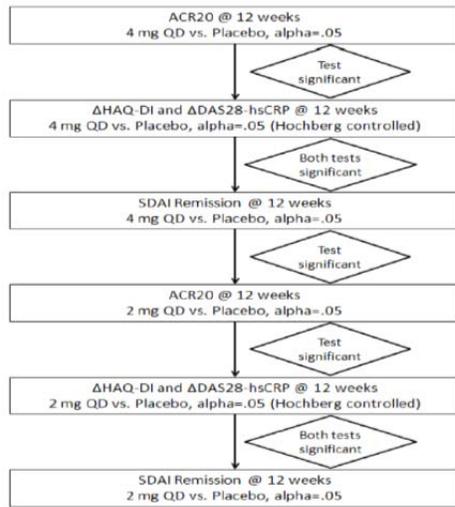
Non-response was recorded for binary response data missing or collected after permanent discontinuation or escape. Therefore, these variables were considered composite endpoints defined by remaining on randomized treatment through the time point of interest and meeting the binary response criteria at 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.

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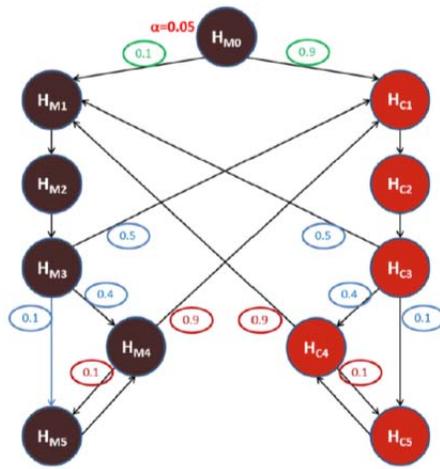
<sup>13</sup> Bretz, F. Maurer, W, Brannath, W, and Posch, M (2009). A graphical approach to sequentially rejective multiple test procedures. *Statistics in Medicine* 28 (4), 586-604.

Figure 6: Multiple Test Procedure, Study JADW



source: protocol Figure JADW.2

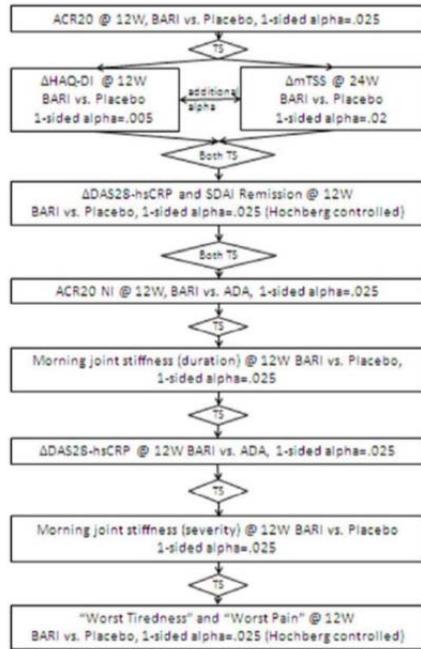
Figure 7: Multiple Test Procedure, Study JADZ



source: Figure JADZ.9.2 of CSR

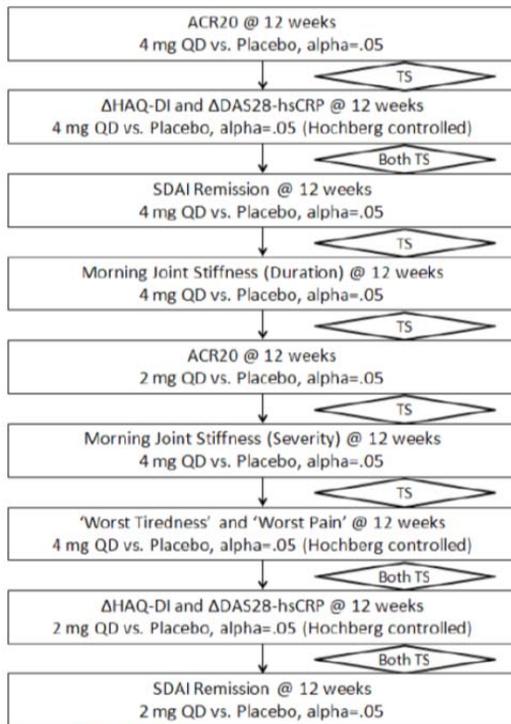
- **HM0**: Proportion of patients who achieved ACR20 at Week 24, noninferiority of baricitinib monotherapy to MTX monotherapy
- **HM1**: Proportion of patients who achieved ACR20 at Week 24, superiority of baricitinib monotherapy to MTX monotherapy
- **HM2**: Mean change from baseline in DAS28-hsCRP at Week 24, baricitinib monotherapy vs MTX monotherapy
- **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  $\leq 3.3$  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  $\leq 3.3$  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
<b>At week 12</b>						
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)
<b>At week 24</b>						
	<b>B4MTX</b>	<b>B4</b>	<b>MTX</b>	<b>B4MTX:MTX</b>	<b>B4:MTX</b>	<b>B4MTX:B4</b>
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
<b>ACR20</b>	70 (339/487)	61 (202/330)	40 (196/488)	3.6 (<0.001)	2.4 (<0.001)	1.5 (0.01)
<b>ACR50</b>	45 (219/487)	35 (115/330)	17 (82/488)	4.2 (<0.001)	2.7 (<0.001)	1.5 (0.005)
<b>ACR70</b>	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)		
	B4	A	Pbo	B4-Pbo	A-Pbo	B4-A
<b>At week 12</b>						
JADV	-0.66 (482)	-0.56 (327)	-0.34 (484)	-0.32 (<0.001)	-0.22 (<0.001)	-0.1 (0.004)
	<b>B4</b>	<b>B2</b>	<b>Pbo</b>	<b>B4-Pbo</b>	<b>B2-Pbo</b>	<b>B4-B2</b>
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)
<b>At week 24</b>						
	<b>B4MTX</b>	<b>B4</b>	<b>MTX</b>	<b>B4MTX:MTX</b>	<b>B4:MTX</b>	<b>B4MTX:B4</b>
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)		
	B4	A	Pbo	B4:Pbo	A:Pbo	B4:A
<b>At week 12</b>						
JADV	24 (119/487)	19 (63/330)	4 (21/488)	7.6 (<0.001)	5.5 (<0.001)	1.4 (0.077)
	<b>B4</b>	<b>B2</b>	<b>Pbo</b>	<b>B4:Pbo</b>	<b>B2:Pbo</b>	<b>B4:B2</b>
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)
<b>At week 24</b>						
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)
	<b>B4MTX</b>	<b>B4</b>	<b>MTX</b>	<b>B4MTX:MTX</b>	<b>B4:MTX</b>	<b>B4MTX:B4</b>
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**

At week 24	mTSS Mean Change from Baseline (N)			Difference (p-value)		
	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 ( $\Delta$ mean 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)**

At week 24	Proportion without radiographic progression			Odds ratio (p-value)		
	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)		
<b>Median change from baseline to week 12</b>						
<b>JADV</b>	<b>B4</b>	<b>A</b>	<b>Pbo</b>	<b>B4:Pbo</b>	<b>A:Pbo</b>	<b>B4:A</b>
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)
<b>JADX</b>	<b>B4</b>	<b>B2</b>	<b>Pbo</b>	<b>B4:Pbo</b>	<b>B2:Pbo</b>	<b>B4:B2</b>
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 <sup>a</sup>
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 <sup>b</sup> , JAGQ <sup>b</sup>	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.  
<sup>a</sup> 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.  
<sup>b</sup> 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  $\geq 52$  weeks and 467 patients were exposed for  $\geq 104$  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
<b>Number of patients, n</b>	1070	997	479	479	479	479	3464	3822
<b>Number of patients with ≥X weeks of exposure, n</b>								
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
<b>0-52 weeks</b>						
<b>Method 1</b>						
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)
<b>Method 2</b>						
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)
<b>&gt;52 weeks</b>						
<b>Method 1</b>						
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)<sup>14</sup>. Figure 10 provides a flow chart of the

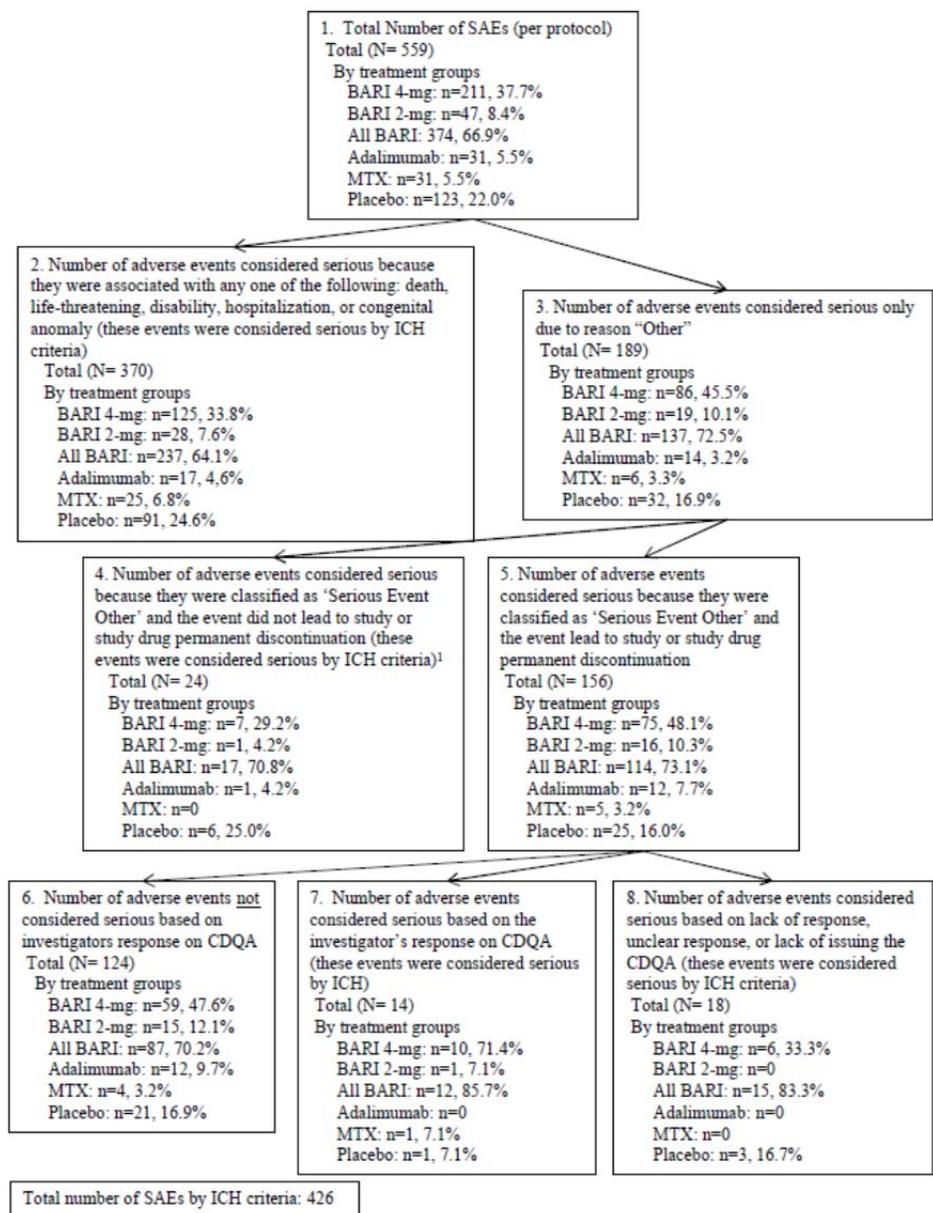
<sup>14</sup> An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent 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.

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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, JADW, and JADW)**



<sup>1</sup> An additional 9 CDQAs were inadvertently sent and received a response from the investigator that the event was not serious by ICH criteria. These were analyzed in the NDA as non-ICH events  
 Source: t\_sae\_4pc\_finald

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)**

# patients with ≥1	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
<b>0-16 weeks</b>						
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)
<b>Adjudication results</b>						
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)
<b>0-52 weeks</b>						
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)
<b>&gt;52 weeks</b>						
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
<b>0-16 weeks</b>						
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)
<b>0-52 weeks</b>						
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)
<b>&gt;52 weeks</b>						
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
<b>0-16 weeks</b>						
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)
<b>Most common SOC, n (%)</b>						
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)	--	--
<b>Ext BARI 2 mg vs 4 mg</b>						
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*

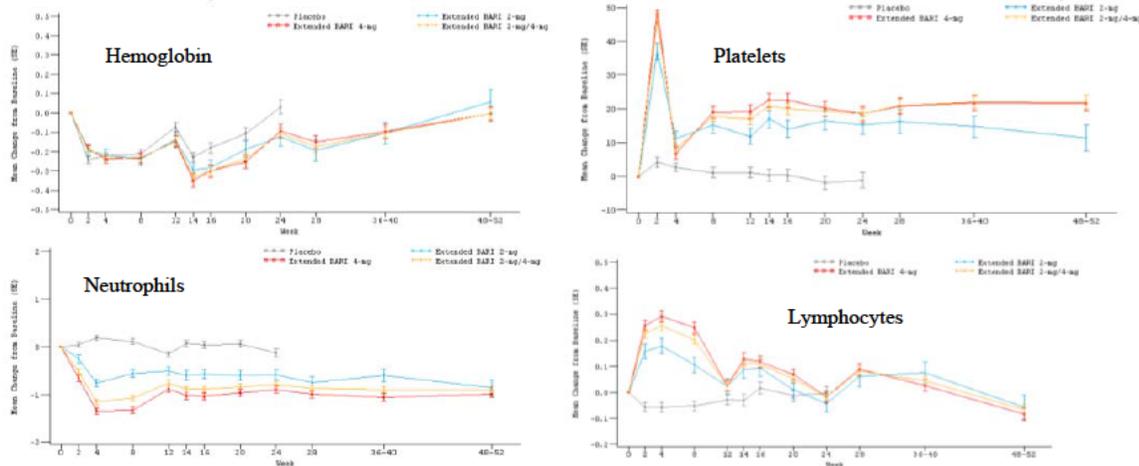
Table 18 and Figure 11 summarize the mean changes in hematologic parameters.

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

	PBO	BARI 2	BARI 4	BARI 2/4
<b>Hemoglobin (g/dL)</b>				
Baseline	12.66	12.58	12.68	12.65
Change from baseline at Week 12	-0.07	-0.14	-0.15	-0.14
<b>Platelets (10<sup>9</sup>/L)</b>				
Baseline	289	285	293	290
Change from baseline at Week 12	1	12	19	17
<b>Leukocyte count (thousand cells/uL)</b>				
Baseline	8.18	8.25	8.40	8.35
Change from baseline at Week 12	-0.15	-0.56	-0.89	-0.79
<b>Neutrophils (thousand cells/uL)</b>				
Baseline	5.82	5.76	6.01	5.93
Change from baseline at Week 12	-0.15	-0.51	-0.89	-0.76
<b>Lymphocytes (thousand cells/uL)</b>				
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  $\geq 3$  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  $50 \times 10^9/L$ ) and then returned towards baseline and remained stable and increased from baseline (mean increase approximately  $20 \times 10^9/L$ ). 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  $\leq 600$  to  $>600 \times 10^9/L$  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  $>700 \times 10^9$  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  $\leq 600 \times 10^9$  cells/L to  $>600 \times 10^9$  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  $\geq 1$  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  $\geq$ 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  $ALC \geq LLN$  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  $ALC < 500 \times 10^9/L$ .

#### *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  $\geq 1$  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  $< 1 \times 10^9/L$ . 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  $\geq 3x$  ULN,  $\geq 5x$  ULN or  $\geq 10x$  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  $\geq 10 \times$  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  $> 3x$ ULN, evidence of liver dysfunction by increase in bilirubin  $\geq 2x$ ULN and without evidence of cholestasis by ALP  $< 2x$ ULN, 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
<b>ALT (IU/L)</b>				
Baseline	21.1	21	20.3	20.5
Change from baseline at week 12	0.3	1.7	4.4	3.5
<b>AST (IU/L)</b>				
Baseline	20.7	21.8	20.4	20.8
Change from baseline at week 12	0.4	1.3	4.6	3.6
<b>Total bilirubin (mg/dL)</b>				
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
<b>Triglycerides (mg/dL)</b>				
Baseline	127	128	125	126
Change from baseline at Week 12	-1	5	17	13
% change from baseline at Week 12	3.8%	8.9%	15.7%	13.6%
<b>LDL Cholesterol-Direct (mg/dL)</b>				
Baseline	119	116	117	116
Change from baseline at Week 12	-1	8	14	12
% change from baseline at Week 12	0.4%	8.2%	14.4%	12.5%
<b>HDL Cholesterol-Direct (mg/dL)</b>				
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 baseline 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
<b>0-16 weeks</b>						
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)
<b>0-52 weeks</b>						
<b>Method 1</b>						
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)
<b>Method 2</b>						
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)
<b>&gt;52 weeks</b>						
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**

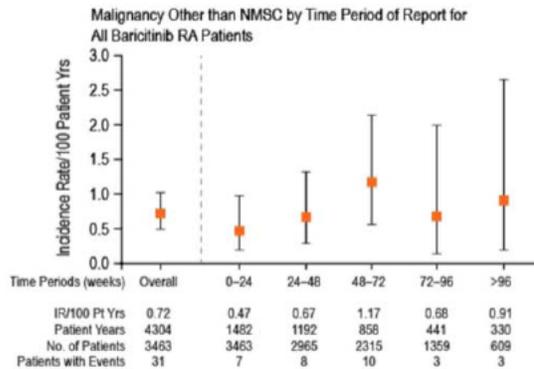


Figure 2.7.4.11. Malignancy excluding NMSC by time period of report in RA.

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  $\geq 4$  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
<b>0-16 weeks</b>						
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)
<b>Adjudication results</b>						
# 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)
<b>0-52 weeks</b>					<b>BARI 4 vs. PBO</b>	<b>BARI 4 vs. 2</b>
Total exposure, PY	405.8	1318	335.6	903.6		
# serious infections, n	18 (4.4)	59 (4.5)	15 (4.5)	39 (4.3)	--	--
Rate per 100 PY						
# 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)		
<b>&gt;52 weeks</b>						
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

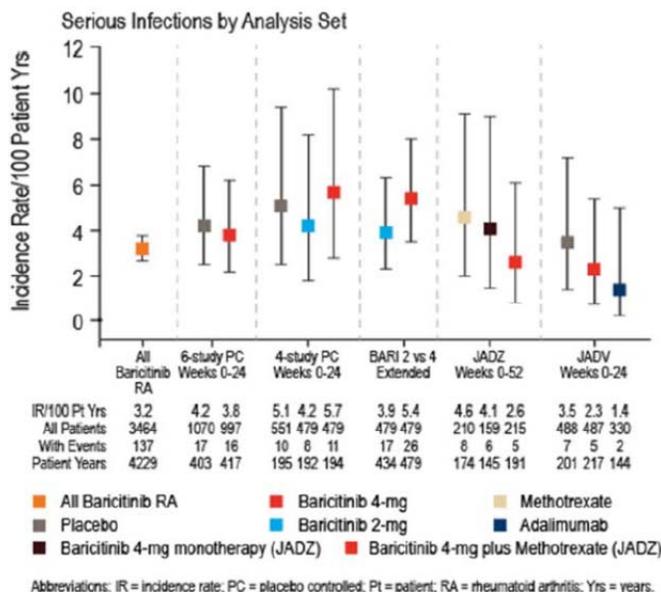
0-52 and > 52 weeks: Studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY

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 perforations 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
<b>0-16 weeks</b>						
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)
<b>0-52 weeks</b>						
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)
<b>&gt;52 weeks</b>						
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
<b>0-16 weeks</b>						
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)
<b>0-52 weeks</b>						
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)		
<b>&gt;52 weeks</b>						
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)**

	<b>Placebo N=488 PYE=197.7 n (%) [EAIR]</b>	<b>BARI 4 mg N=487 PYE=215 n (%)</b>	<b>Adalimumab N=330 PYE=141.9 n (%)</b>
<b>Pts with ≥1 AE</b>			
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)**

<b>Any CTCAE increase</b>	<b>Placebo N=488 n (%)</b>	<b>BARI 4 N=487 n (%)</b>	<b>Adalimumab N=330 n (%)</b>
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)
<b>Treatment-emergent abnormalities occurring at any time (Weeks 0 to 24)</b>			
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 baricitinib'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
<b>Week 2</b>						
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
<b>Week 4</b>						
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

Weeks 0 through 12

Modified Intent-to-Treat Population, Study JADA, JADN, JADX, and JADW Combined

Page 2 of 4

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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
<b>Week 8</b>						
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
<b>Week 12</b>						
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

Cross Discipline Team Leader Review  
Janet Maynard, MD, MHS  
DHHS/FDA/CDER/ODE2/DPARP

NDA 207924: Baricitinib for RA  
Eli Lilly and Company

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANET W MAYNARD  
01/05/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service

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**Memorandum**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
10903 New Hampshire Ave.  
Silver Spring, MD 20903

**Memorandum to File**

**Date:** October 19, 2016

**From:** Lori Ehrlich, M.D., Ph.D.  
Medical Officer, Division of Hematology Products

**Through:** R. Angelo de Claro, M.D.  
Clinical Team Leader, Division of Hematology Products  
Edvardas Kaminskas, M.D.  
Deputy Division Director, Division of Hematology Products

**To:** Division of Pulmonary, Allergy, and Rheumatology Products

**Subject:** Incidence of thromboembolic events with baricitinib treatment  
NDA 207924 from Eli Lilly and Co.

**Reference:** none

**Background:**

*Non-clinical*

Baricitinib is a JAK1/2 inhibitor that is being developed for the treatment of rheumatoid arthritis (RA). Specificity for JAK1 and JAK2 was reported in Fridman et al, J Immunol, 2010. The IC<sub>50</sub> results are shown in the following table.

Table 1. Enzyme potency of INCB028050 (nM ± SD)

JAK1	JAK2	JAK3	Tyk2	cMET	CHK2
5.9 ± 0.9	5.7 ± 1.7	>400	53	>10,000 <sup>a</sup>	>1,000 <sup>a</sup>
n = 4	n = 6	n = 2	n = 2	n = 1	n = 1

<sup>a</sup>Highest concentration tested.

From: Fridman et al, J Immunol, 2010

Moderate inhibition was also seen with Tyk2, which is also in the Jak family. Other kinases that were evaluated were Abl, Akt1, AurA, AurB, CDC2, CDK2, CDK4, CHK2, c-kit, EGFR, EphB4, ERK1, ERK2, FLT-1, HER2, IGF1R, IKK $\alpha$ , IKK $\beta$ , JNK1, Lck, MEK1, p38 $\alpha$ , p70S6K, PKA, PKC $\alpha$ , Src, and ZAP70. The results were not reported in the publication, but the authors stated that no significant inhibition was observed.

Per the DPARP pharmacology/toxicology reviewer:

- (1) The in vitro pharmacology data for baricitinib is generally summarized by the following points:
  - In cell free, isolated enzyme assays: baricitinib is selective for JAK1 and JAK2 over JAK3 (~70 fold) and Tyk2 (~10 fold)
  - In cell based assays in human immune cells: baricitinib inhibited all JAK enzymes with comparable potencies (i.e. no clear selectivity)
- (2) Off-target kinase inhibition: Study T07-07-11 examined the effects of baricitinib on 30 separate isolated recombinant human kinases. There were no significant inhibitory effects of baricitinib observed on the kinases tested
- (3) The sponsor conducted another secondary pharmacology study (Study QSB30) in cell lysates derived from human PBMCs and monocyte cell lines (THP1 cells). Baricitinib was found to inhibit Calcium/calmodulin kinase enzymes 2d and 2g. The potency at these enzymes was 3 – 7x lower than inhibition of JAK1 or JAK2. It is not clear at this time whether inhibition of these enzymes could contribute to thrombocytosis.

*Clinical*

In the development of baricitinib in RA, several dose finding studies (JADA, JADC, and JADN) were performed with doses ranging from 1-10 mg daily. Phase 3 studies (JADV, JADW, JADX, JADZ, and JADY; JAGS is ongoing) evaluated doses of 2 mg or 4 mg daily or placebo. An imbalance was seen in the incidence in thromboembolic events in the treatment arm. The incidence of events in the first 52 weeks of treatment is shown in the following table.

**Table 1: Thromboembolic events with baricitinib treatment in RA**

	< 52 weeks			
	placebo	2 mg	4 mg	2 or 4 mg
Total number of patients	1070	479	1833	2312
Patient years	405.8	335.6	1671.1	2085.6
DVT	0	2	7	9
PE	0	0	5	6
Total patients with events	0	2	11	14

\*Note: The numbers in the above table were provided by the Applicant, and it is unclear why the combined 2 or 4 mg counts do not equal the sum of the 2 mg and 4 mg counts.

Per the DPARP reviewer, a total of 20 patients had a VTE event during treatment with baricitinib when the long term exposure and follow up was included, with a total of 15 serious cases. (Note that in the midcycle response from the Applicant, only 18 patients were including in the listing of patients who had a VTE.)

A statistical evaluation of incidence rates performed by the Applicant is shown below. Compared to placebo, the rate of VTE events is significantly higher in the 4 mg treatment group, but not in the 2 mg treatment group. In addition, there was not a significant difference between the 2 mg and 4 mg treatment groups.

**Table 4.15. Summary of Incidence Rate Differences for Thrombotic Events through Weeks 0-52 and after Week 52**

	PBO vs BARI 2-mg Weeks 0-52	PBO vs BARI 4-mg Weeks 0-52	BARI 2-mg vs BARI 4-mg Weeks 0-52	BARI 2-mg vs BARI 4-mg > 52 Weeks
	IRD (95% CI)	IRD (95% CI)	IRD (95% CI)	IRD (95% CI)
FDA Method 1	0.59 (-0.23,1.41)	0.67 (0.13,1.22)*	0.01 (-1.12,1.13)	0.85 (-1.02,2.73)
FDA Method 2	0.59 (-0.23,1.41)	0.65 (0.27,1.03)*	0.11 (-0.92,1.14)	0.86 (-0.78,2.51)
Balanced Method 1	0.59 (-0.23,1.41)	0.73 (0.14,1.31)*	0.10 (-1.07,1.27)	1.12 (-1.56,3.80)
Balanced Method 2	0.59 (-0.23,1.41)	0.65 (0.25,1.06)*	0.11 (-0.93,1.15)	0.88 (-1.22,2.97)

Abbreviations: BARI = baricitinib; CI = confidence interval; FDA = Food and Drug Administration; IRD = incidence rate difference; PBO = placebo; vs = versus.

\* The 95% CI excludes 0 and is considered statistically significant.

Per the Applicant, all the patients who experienced a VTE had risk factors including MTX use, steroids, obesity, recent surgery, history of thrombotic events, or recent trauma.

Major Adverse Cardiovascular Events (MACE) were summarized by the Applicant in the midcycle response communication. Based on the Applicant's evaluation, there did not seem to be a statistically significant increase in MACE, though there was a numerical increase in events in the 4 mg treatment arm compared to placebo. In this evaluation, MACE included cardiovascular death, myocardial infarction, stroke, and transient ischemic attack.

### Consult Questions from DPARP to DHP:

Baricitinib is a JAK inhibitor with particular specificity for JAK1 and JAK2 being developed for treatment in rheumatoid arthritis. In the RA clinical development program, there is a numerical imbalance between the number of deep venous thrombosis and pulmonary emboli in the baricitinib group as compared to placebo. In the combined baricitinib trials for RA, by week 52, there were 9 DVTs and 6 PEs noted in the baricitinib study arms (person years 2085.6) and zero in the placebo group (person years 405.8). More events occurred in the baricitinib 4 mg daily group when compared to the baricitinib 2 mg daily group. For all 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. There were no events in the placebo group and 1 event in the methotrexate monotherapy group.

Another notable finding is that baricitinib is associated with elevations in platelet counts. This seems to peak during the first 4 weeks of treatment, but platelet counts remain elevated by approximately 20,000 on baricitinib compared to placebo.

1. What is your impression of the data provided by the Applicant regarding thrombotic events and is your opinion that this is a significant safety risk?

We note a statistically significant increase in the rate of VTEs in the 4 mg treatment group compared to placebo. With no VTEs in the placebo group and increasing rates in the 2 mg and 4 mg treatment groups, the risk of VTE events appears to be dose dependent.

From a hematology perspective, the clinical meaningfulness of these findings are uncertain. Despite the apparent dose-dependent increase in VTE, the absolute incidence rate of VTEs in the RA trials was low, 0.6% in the 4 mg treatment group. Whether this is a significant safety risk for patients with RA would be more appropriately determined by DPARP, rather than DHP.

We could not find any evidence that the increase in VTEs was a class effect of JAK1/2 inhibitor drugs. Neither of the approved JAK1/2 inhibitors, ruxolitinib or tofacitinib, have VTEs listed as AEs in the prescribing information. Additionally, an Empirica Signal search for post-marketing events of VTEs (search of HLT=Peripheral embolism and thrombosis, Pulmonary embolism and thrombosis) revealed only 36 DVT events for ruxolitinib and 22 DVT events for tofacitinib with EB05 values of 0.54 and 0.26, respectively. An EB05 value of <2 is generally considered to signify the risk of the event is unlikely related to the drug. (For comparison, lenalidomide which has a known risk of VTE had 2122 events of DVT with an EB05 of 4.3).

The evidence provided suggests that baricitinib is an inhibitor with specificity for JAK1/2 and some Tyk2 inhibition, but little known off-target kinase inhibition. Therefore, the mechanism of increase in VTE with baricitinib is unclear. A mild increase in platelet count of 20,000/uL will not result in an increase in risk of thromboembolic events.

2. The Division is currently considering a Warning and Precaution related to thrombosis and thromboembolic events. Do you have recommendations regarding the labeling of this safety information?

The clinical meaningfulness of a <1% risk of VTE for patients with RA should be determined by DPARP.

Taking into consideration malignant and non-malignant indications within DHP, an increase in <1% is unlikely to warrant a W&P. For example, oncology drugs that include a W&P for VTE have an increased incidence of 3-5% (i.e. lenalidomide and ponatinib). However, the risk/benefit analysis changes with the underlying disease, expected baseline incidence of VTE, expected survival, duration of treatment, and other factors.

The rate of VTEs does not appear high enough that a hematologist would recommend routine prophylaxis. VTE prophylaxis for a population with <1% VTE risk would be

expected to result in an unfavorable risk:benefit assessment due to the known hemorrhagic risks of VTE prophylaxis.

Therefore, the goal of a potential W&P would be for increased awareness and to discontinue the drug, if needed.

3. Do you believe there is a potential mechanism of action that would suggest baricitinib confers a higher risk of thromboembolic events? Do you have recommendations on any additional testing or analyses that should be requested?

See answer to Question 1 regarding possible mechanism. We are unable to determine a potential mechanism for thromboembolic events.

DHP recommends the following to further assess the risk/benefit of baricitinib treatment:

- Evaluation of the arterial thrombotic events including stroke and myocardial infarction.
- Determination if any venous or arterial thrombotic or thromboembolic events occurred at higher doses of baricitinib used in the dose ranging studies.

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Lori A. Ehrlich, MD, PhD  
Medical Officer, Division of Hematology Products

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R. Angelo de Claro, MD  
Clinical Team Leader, Division of Hematology Products

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Edvardas Kaminskas, MD  
Deputy Division Director, Division of Hematology Products

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LORI A EHRLICH  
10/18/2016

ROMEO A DE CLARO  
10/18/2016

EDVARDAS KAMINSKAS  
10/19/2016

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**CONSULTATION**

**DATE:** September 8, 2016

**FROM:** Mary Roberts, M.D.  
Division of Metabolism and Endocrinology Products  
(DMEP)

**THROUGH:** Jim Smith, M.D., M.S. Deputy Director  
Division of Metabolism and Endocrinology Products

**TO:** Jessica Lee, RPM  
Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)

**SUBJECT:** NDA 207924  
Potential cardiovascular risk associated with lipid  
parameter changes seen with baricitinib (JAK Inhibitor)

**I. Basis for Consult Request**

Baricitinib, an orally administered, small molecule, JAK inhibitor, is currently under review for the treatment of patients with rheumatoid arthritis (RA). By inhibiting the intracellular tyrosine kinase called Janus kinase (JAK), baricitinib disrupts cytokine signaling through the JAK-STAT pathway which facilitates favorable changes in measures of RA disease activity. However in clinical testing, treatment with baricitinib resulted in increases in lipid parameters (LDL-C, HDL-C, TG).

Of note, tofacitinib (XELJANZ), an FDA approved JAK inhibitor, exhibited similar changes in lipid parameters. As a condition of its approval in 2012, a cardiovascular outcome trial was required in the post-marketing setting. This CVOT is ongoing (<https://clinicaltrials.gov/ct2/show/NCT02092467>). XELJANZ labeling has a Warning & Precaution for Laboratory Parameters which includes lipid abnormalities and states:

**Lipids**

Treatment with XELJANZ was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4–8 weeks following initiation of XELJANZ therapy.

Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

The Division of Metabolism and Endocrinology Products has been consulted to opine and provide recommendations regarding the potential implications of the lipid changes observed with baricitinib treatment on cardiovascular risk.

## **II. Background**

Baricitinib, an orally administered, selective JAK inhibitor, is currently under review for the treatment of moderately-to-severely active RA. The sponsor, Eli Lilly, has developed orally administered tablets of 2 and 4 mg. The proposed dose is 4 mg once daily, however for some patients, a dose of 2 mg once daily may be appropriate.

The clinical development program for baricitinib included studies using the 2 mg and 4 mg dose, baricitinib monotherapy, and baricitinib use in combination with methotrexate (MTX) or other stable disease modifying anti-rheumatic drugs (DMARDs). Four randomized, double-blind, controlled phase 3 pivotal trials, JADZ, JADV, JADX, and JADW, were submitted to establish baricitinib's efficacy and safety. JADZ was designed with an active-control (MTX), baricitinib monotherapy, and baricitinib in combination with MTX for 52 weeks. JADX and JADW evaluated the efficacy of baricitinib in placebo-controlled periods up to 24 weeks. JADV evaluated the efficacy of baricitinib versus placebo and an active comparator, adalimumab (Humira) a TNF-inhibitor, through 52 weeks. The primary endpoints were the proportion of American College of Rheumatology 20 responders at Week 12 (JADV, JADX, JADW) or Week 24 (JADZ). Subjects who completed the parent studies had the option of participating in a long-term extension study (JADY). Please note, after Week 16 for JADV, JADX, and JADW and Week 24 JADZ patients with an inadequate response were "rescued" with baricitinib 4 mg.

Safety analyses were conducted using a pooled study strategy using mostly phase 2 and phase 3 studies (Table 1).

The primary safety analysis pool compared the safety profile of the 4 mg dose of baricitinib to placebo (BARI 4 mg RA PC) from 6 studies (3 phase 2 studies of 12 weeks duration and 3 phase 3 studies of either 24 or 52 weeks duration). Some of the studies had both a placebo-controlled and open-label period. In these cases, only data from the placebo-controlled portion of each study were included.

Secondary safety analysis pools included phase 2 and phase 3 studies to evaluate (among other comparisons) the 2 mg dose of baricitinib to placebo (BARI 2 mg RA PC) and 4 mg baricitinib compared to 2 mg baricitinib (BARI 2 mg vs 4 mg RA).

This consult reviewed the lipid changes for the individual phase 3 trials - baricitinib versus placebo or active comparator to Week 12 and baricitinib with or without MTX versus MTX at Week 24 as well as in the primary (up to week 16) and some secondary pools.

There were no exclusion criteria for abnormal lipid levels at screening or baseline or for patients with new treatment or dose adjustment of lipid-modifying therapy within 6 weeks prior to randomization. Management of lipid levels and reporting of associated adverse events was left to Investigator discretion, with advice to follow local lipid treatment guidelines. A fasting lipid panel was obtained at baseline, Week 12, Week 24, and Week 52, depending on duration of study. Lipid NMR was conducted on samples at Week 12 in study JADV. An assessment of apolipoproteins was conducted on a phase 2 study, JADA.

**Table 1. Safety pools for Baricitinib**

**Table 2.7.4.4. Treatments by Study Contributing Data to the Integrated Analysis Sets from the Integrated Baricitinib Phase 1/2/3 Safety Database**

Population	Analysis Set	Study Alias	Phase	Treatment Groups Included in the Analysis Set <sup>a</sup>		
6 Study <sup>b</sup>	BARI 4-mg RA PC	JADA	2	PBO, BARI 4-mg		
		JADC	2	PBO, BARI 4-mg		
		JADN	2	PBO, BARI 4-mg		
		JADV	3	PBO, BARI 4-mg		
		JADW	3	PBO, BARI 4-mg		
		JADX	3	PBO, BARI 4-mg		
	BARI 2-mg/4-mg RA PC	JADA	2	PBO, BARI 2-mg, BARI 4-mg		
		JADC	2	PBO, BARI 4-mg		
		JADN	2	PBO, BARI 2-mg, BARI 4-mg		
		JADV	3	PBO, BARI 4-mg		
		JADW	3	PBO, BARI 2-mg, BARI 4-mg		
		JADX	3	PBO, BARI 2-mg, BARI 4-mg		
	4 Study <sup>b</sup>	BARI 2-mg vs 4-mg RA	JADA	2	BARI 2-mg, BARI 4-mg	
			JADN	2	BARI 2-mg, BARI 4-mg	
JADW			3	BARI 2-mg, BARI 4-mg		
JADX			3	BARI 2-mg, BARI 4-mg		
BARI 2-mg RA PC		JADA	2	PBO, BARI 2-mg		
		JADN	2	PBO, BARI 2-mg		
Ext BARI 2- mg vs 4-mg RA	Ext BARI 2-mg vs 4-mg RA	JADA/JADY	2	BARI 2-mg, BARI 4-mg		
		JADN	2	BARI 2-mg, BARI 4-mg		
		JADW/JADY	3	BARI 2-mg, BARI 4-mg		
		JADX/JADY	3	BARI 2-mg, BARI 4-mg		
All BARI RA	All BARI RA	JADA/JADY	2	BARI 1-mg, BARI 2-mg, BARI 2-mg BID, BARI 4- mg, BARI 8-mg		
		JADB	1	BARI 10-mg, BARI 5-mg BID, BARI 15-mg		
		JADC	2	BARI 4-mg, BARI 7-mg, BARI 10-mg		
		JADN	2	BARI 1-mg, BARI 2-mg, BARI 4-mg, BARI 8-mg		
		JADV/JADY	3	BARI 4-mg		
		JADW/JADY	3	BARI 2-mg, BARI 4-mg		
		JADX/JADY	3	BARI 2-mg, BARI 4-mg		
		JADZ/JADY	3	BARI 4-mg		
		All BARI	All BARI	All BARI RA		All BARI RA and
				JADP <sup>c</sup> JAGQ <sup>c</sup>	2 2	BARI 2-mg, BARI 4-mg, BARI 8-mg, BARI 10-mg BARI 0.75-mg, BARI 0.75-mg BID, BARI 1.5-mg, BARI 4-mg

Source: SCS Table 2.7.4.4

### III. Effect on Lipid levels

#### *Individual phase 3 studies*

#### JADV

Study JADV was a 52-week, Phase 3, multicenter, randomized, double-blind, double-dummy, placebo and active controlled, study comparing the efficacy of 4 mg of

baricitinib, placebo, and adalimumab in patients with RA who had an inadequate response to MTX and who had never been treated with a biologic DMARD. From baseline to Week 24 patients were randomized to placebo, baricitinib 4 mg or adalimumab. All patients were eligible for rescue therapy at Week 16 (nonresponders on placebo and adalimumab were rescued with baricitinib and those already on baricitinib continued to receive baricitinib, with ongoing assessment of response and use of concomitant medications as needed). After Week 24, all patients assigned to placebo were switched to baricitinib 4 mg and those originally assigned to baricitinib or adalimumab continued treatment until Week 52.

At Baseline the mean values of LDL-C and HDL-C were approximately 116 mg/dL (3.0 mmol/L) and 59 mg/dL (1.5 mmol/L), respectively; mean TG level was approximately 115 mg/dL (1.3 mmol/L) (median not provided). Concomitant statin therapy (not further defined) was reported for 8.5% of patients. No patients had a pre-existing condition of ischemic heart disease or cerebrovascular disease. Approximately 13.3% had “hyperlipidemia” not further defined.

The number of patients that initiated statin use during the study through Week 24 was 2.3% in the placebo group, 3.3% for baricitinib 4 mg, and 1.2% for adalimumab.

#### JADW

Study JADW was a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, outpatient study comparing the efficacy of 4 mg and 2 mg daily oral doses of baricitinib versus placebo on signs and symptoms of RA. Eligible patients had moderately to severely active RA, an insufficient response to or intolerance to at least 1 biologic TNF inhibitor therapy (TNF-IR patients), and were taking background conventional DMARD therapy (with or without MTX). Rescue to baricitinib 4 mg was allowed at Week 16. Lipids were obtained at Baseline, Week 12, and Week 24.

At Baseline the mean values of LDL-C and HDL-C were approximately 118 mg/dL (3.05 mmol/L) and 59 mg/dL (1.5 mmol/L), respectively; mean TG level was approximately 141 mg/dL (1.6 mmol/L) (median not provided). Concomitant statin therapy (not further defined) was reported for 18.2% of patients. No patients had a pre-existing condition of ischemic heart disease or cerebrovascular disease. Approximately 25.8% had “hyperlipidemia” not further defined.

The number of patients that initiated statin use during the study through Week 24 was 2.8% in the placebo group, 4.0% for baricitinib 2 mg, and 3.4% for baricitinib 4 mg.

#### JADX

Study JADX was a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, outpatient study comparing the efficacy of 4 mg and 2 mg daily doses of oral baricitinib with placebo, in combination with a cDMARD (including MTX) on signs, symptoms, and function during a 24-week treatment period. Eligible patients had moderately to severely active RA, had an insufficient response to cDMARDs, and had

not previously been treated with a bDMARD. Rescue to baricitinib 4 mg was allowed at Week 16. Lipids were obtained at Baseline, Week 12, and Week 24

At Baseline the mean values of LDL-C and HDL-C were approximately 118 mg/dL (3.04 mmol/L) and 60 mg/dL (1.56 mmol/L), respectively; mean TG level was approximately 133 mg/dL (1.5 mmol/L) (median not provided). Concomitant statin therapy (not further defined) was reported for 9.9% of patients. No patients had a pre-existing condition of ischemic heart disease or cerebrovascular disease. Approximately 17.1% had “hyperlipidemia” not further defined.

The number of patients that initiated statin use during the study through Week 24 was 3.5% in the placebo group, 2.6% for baricitinib 2 mg, and 2.6% for baricitinib 4 mg.

### JADZ

Study JADZ was a Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group, study that compared the efficacy of baricitinib monotherapy or baricitinib plus MTX to MTX monotherapy on signs and symptoms, physical function, remission, and structural progression during a 52-week treatment period in patients with moderately to severely active RA who had previously had limited or no treatment with MTX and were naive to other cDMARDs or bDMARDs. Rescue to baricitinib 4 mg was allowed at Week 24. Lipids were obtained at Baseline, Week 12, Week 24, Week 52.

At Baseline the mean values of LDL-C and HDL-C were approximately 112 mg/dL (2.91 mmol/L) and 56 mg/dL (1.46 mmol/L), respectively; mean TG level was approximately 120 mg/dL (1.35 mmol/L) (median not provided). Concomitant statin therapy (not further defined) was reported for 7.2% of patients. No patients had a pre-existing condition or history of ischemic heart disease or cerebrovascular disease. Approximately 12.5% had “hyperlipidemia” not further defined.

The number of patients that initiated statin use during the study through Week 52 was 2.4% (n=5) in the MTX group, 2.5% (n=4) for baricitinib 4 mg, and 5.6% (n=12) for baricitinib 4 mg+MTX.

*Reviewer comment: It is not unexpected to note normal levels of lipids in patients with RA as reflected in the baseline values in the patients.<sup>1</sup> However, these values may be misleading for use in assessing cardiovascular risk as evidence suggests a non-linear relationship between total cholesterol and LDL-C and degree of cardiovascular risk, known as the lipid paradox.<sup>2</sup> In a retrospective cohort study of 651 patients with RA, there was a U-shaped relationship observed, where patients with lower total cholesterol*

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<sup>1</sup> Liao KP et al. Lipid and lipoprotein levels and trends in rheumatoid arthritis compared with the general population. *Arthritis Care Res.* 2013;65:2046-50.

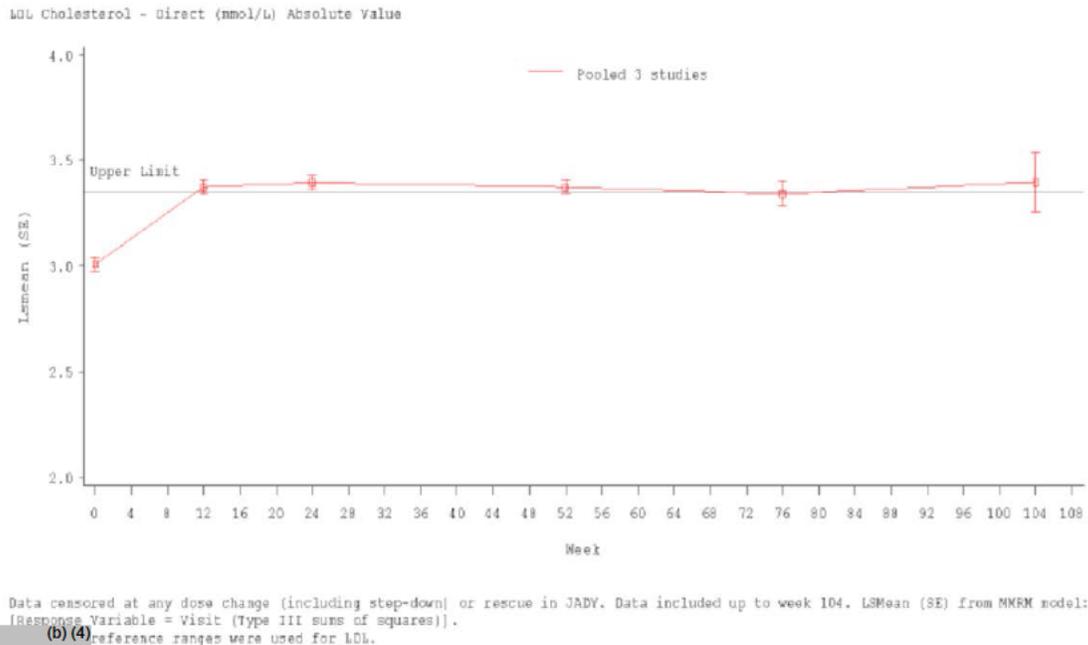
<sup>2</sup> Myasoedova E et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis* 2011;70:482-7.

and LDL-C levels had higher CV risk. Inflammation is thought to be underlying these altered lipid profiles, although the exact mechanism(s) is unknown.<sup>3</sup>

### Effects on Lipids for Individual and Pooled studies

Serum lipids, LDL-C, triglycerides, and HDL-C increased more in patients treated with 2 mg and 4 mg of baricitinib compared with patients treated with placebo or active comparator in the phase 3 studies (Table 2-Table 4). The individual study results for the phase 3 studies are presented below and generally were consistent with the pooled results of phase 2 and phase 3 studies. Study JADX had a slightly smaller difference in LDL-C compared to the individual and overall pooled studies.

In the individual phase 3 studies (JADV, JADW, JADX), the increase in lipids with baricitinib compared to placebo was evident at Week 12 (the first time lipid levels checked post-dose). At Week 12, the absolute LS mean difference in LDL-C between 4 mg baricitinib and placebo ranged from 0.20 to 0.47 mmol/L (approximately 7 to 18 mg/dL) and was statistically significant  $p=0.001$ . In the pooled analysis the absolute mean LS difference was 0.40 mmol/L (approximately 15 mg/dL). LDL-C values remained elevated throughout the treatment duration on average as seen in the figure below for the phase 3 pooled studies with data through the long-term study JADY (Figure 1).



**Figure 1. LDL-C (mmol/L) absolute value for patients randomized to a treatment regimen including baricitinib 4 mg in phase 3 studies and long-term extension (JADV, JADW, JADX, JADY)**

Source: SCS Figure 2.7.4.16

<sup>3</sup> Robertson J et al. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. Nat. Rev. Rheumatol. 2013;9:513-23.

A statistically significant difference between 2 mg baricitinib and placebo was also observed with an LS mean absolute difference of 0.17 to 0.21 mmol/L (approximately 6.5 to 8.1 mg/dL) at Week 12. These values in general remained elevated throughout the treatment period when evaluated up to Week 24.

A comparison of 2 mg versus 4 mg in the pooled safety analysis (BARI 2 mg vs. 4 mg RA), demonstrated a slightly higher and nominally statistically significant difference in LDL-C up to Week 16 (LS mean difference 0.11 mmol/L or 4 mg/dL; p=0.02). The clinical relevance of 4 mg/dL difference in LDL-C between the two doses is likely small.

A higher excursion in lipids was also observed with baricitinib treatment compared to the active comparators of adalimumab at Week 12 [LSM difference 0.22 mmol/L (8.5 mg/dL) p=0.001] or MTX at Week 24 [LSM difference 0.33 mmol/L (9 mg/dL)].

**Table 2 Absolute Change from Baseline in LDL-C (mmol/L) in Phase 3 trials at Week 12 (Week 24 for JADZ) at Week 16 for pooled analysis**

	Change from baseline LS means (SE)		Difference in change from baseline LSMD (95% CI) Baricitinib – Control	p-value	Number of patients	
	Control	Baricitinib			Control	Baricitinib
<b>LDL-C (mmol/L)</b>						
<b>BARI 4 mg vs placebo</b>						
JADV	-0.06	0.41	0.47 (0.40, 0.55)	0.001	443	458
JADW	-0.02	0.43	0.42 (0.27, 0.57)	0.001	146	156
JADX	0.02	0.22	0.20 (0.09, 0.32)	0.001	199	206
<i>Pool BARI 4 mg RA PC<sup>1</sup></i>	<i>-0.07</i>	<i>0.33</i>	<i>0.40 (0.34, 0.46)</i>	<i>0.001</i>	<i>788</i>	<i>820</i>
<b>BARI 2 mg vs placebo</b>						
JADW	-0.02	0.22	0.21 (0.06, 0.36)	0.006	146	153
JADX	0.02	0.19	0.17 (0.05, 0.29)	0.005	199	210
<i>Pool BARI 2 mg RA PC<sup>2</sup></i>	<i>0.02</i>	<i>0.21</i>	<i>0.19 (0.10, 0.28)</i>	<i>0.001</i>	<i>347</i>	<i>364</i>
<b>BARI 4 mg vs BARI 2 mg</b>						
<i>Pool BARI 2 mg vs. 4 mg RA<sup>3</sup></i>	<i>0.31</i>	<i>0.42</i>	<i>0.11 (0.02, 0.21)</i>	<i>0.016</i>	<i>364</i>	<i>362</i>
<b>BARI 4 mg vs Adalimumab</b>						
JADV	0.19	0.41	0.22 (0.14, 0.31)	0.001	302	458
<b>BARI 4 mg vs MTX (Wk 24)</b>						
JADZ	0.10	0.41	0.31 (0.17, 0.45)	0.001	190	154
<b>BARI 4 mg+MTX vs MTX (Wk 24)</b>						
JADZ	0.10	0.32	0.23 (0.10, 0.36)	0.001	190	200

Source: JADV CSR Table JADV.12.35, JADW CSR Table JADW.12.34, JADX CSR Table JADX.12.34, JADZ CSR Table JADZ.12.35, Summary of Clinical Safety Appendix 1 Table APP1.2.4.4.144, 145

<sup>1</sup> Pool BARI 4mg PC RA consists of 6 studies (3 phase 2 JADA, JADC, JADN and 3 phase 3 JADV, JADW, JADX)

<sup>2</sup> Pool BARI 2 mg PC RA consists of 4 studies (2 phase 2 JADA, JADC and 2 phase 3 JADW, JADX)

<sup>3</sup> Pool BARI 2 mg vs. 4 mg RA consists of 4 studies (2 phase 2 JADA, JADN and 2 phase 3 JADW, JADX)

Conversion from mmol/L (SI units) to mg/dL (US units) multiply by 38.7.

**Table 3 Absolute Change from Baseline in TG (mmol/L) in Phase 3 trials at Week 12 (Week 24 for JADZ) at Week 16 for pooled analysis**

	Change from baseline LS means (SE)		Difference in change from baseline LSMD (95% CI) Baricitinib – Control	p-value	Number of observations	
	Control	Baricitinib			Control	Baricitinib
<b>TG (mmol/L)</b>						
<b>BARI 4 mg vs placebo</b>						
JADV	-0.04	0.18	0.21 (0.14, 0.28)	0.001	451	463
JADW	-0.06	0.11	0.18 (0.04, 0.31)	0.01	148	161
JADX	0.04	0.19	0.15 (-0.02, 0.32)	0.089	199	206
<i>Pool BARI 4 mg PC<sup>1</sup></i>	<i>-0.00</i>	<i>0.18</i>	<i>0.18 (0.12, 0.25)</i>	<i>0.001</i>	<i>973</i>	<i>929</i>
<b>BARI 2 mg vs placebo</b>						
JADW	-0.06	0.10	0.16 (0.03, 0.30)	0.017	148	156
JADX	0.04	0.05	0.00 (0.17, 0.17)	0.959	199	210
<i>Pool BARI 2 mg PC<sup>2</sup></i>	<i>-0.01</i>	<i>0.06</i>	<i>0.07 (-0.01, 0.15)</i>	<i>0.078</i>	<i>494</i>	<i>439</i>
<b>BARI 4 mg vs Adalimumab</b>						
JADV	0.08	0.18	0.10 (0.02, 0.18)	0.016	304	463
<b>BARI 4 mg vs MTX (Wk 24)</b>						
JADZ	-0.01	0.16	0.17 (0.05, 0.30)	0.008	190	154
<b>BARI 4 mg+MTX vs MTX (Wk 24)</b>						
JADZ	-0.01	0.18	0.19 (0.07, 0.31)	0.002	190	201

Source: JADV CSR Table JADV.12.35, JADW CSR Table JADW.12.34, JADX CSR Table JADX.12.34, JADZ CSR Table JADZ.12.35

<sup>1</sup> Pool BARI 4mg PC consists of 6 studies (3 phase 2 JADA, JADC, JADN and 3 phase 3 JADV, JADW, JADX)

<sup>2</sup> Pool BARI 2 mg PC consists of 4 studies (2 phase 2 JADA, JADC and 2 phase 3 JADW, JADX)

Conversion from mmol/L (SI units) to mg/dL (US units) multiply by 88.6.

**Table 4. Absolute Change from Baseline in HDL-C (mmol/L) in Phase 3 trials at Week 12 (Week 24 for JADZ) at Week 16 for pooled analysis**

	Change from baseline LS means		Difference in change from baseline LSMD (95% CI) Baricitinib – Control	p-value	Number of observations	
	Control	Baricitinib			Control	Baricitinib
<b>HDL-C (mmol/L)</b>						
<b>BARI 4 mg vs placebo</b>						
JADV	0.003	0.245	0.242 (0.205, 0.279)	0.001	451	462
JADW	0.009	0.207	0.197 (0.132, 0.263)	0.001	148	161
JADX	0.015	0.208	0.192 (0.141, 0.244)	0.001	199	206
<i>Pool BARI 4 mg PC<sup>1</sup></i>	<i>0.001</i>	<i>0.228</i>	<i>0.227 (0.20, 0.25)</i>	<i>0.001</i>	<i>796</i>	<i>824</i>
<b>BARI 2 mg vs placebo</b>						
JADW	0.009	0.154	0.145 (0.079, 0.211)	0.001	148	156
JADX	0.015	0.156	0.141 (0.090, 0.192)	0.001	199	210

	Change from baseline LS means		Difference in change from baseline LSMD (95% CI) Baricitinib – Control	p-value	Number of observations	
<i>Pool BARI 2 mg PC<sup>2</sup></i>	<i>0.010</i>	<i>0.169</i>	<i>0.159 (0.123, 0.196)</i>	<i>0.001</i>	<i>347</i>	<i>363</i>
<b>BARI 4 mg vs Adalimumab</b>						
JADV	0.095	0.245	0.149 (0.101, 0.190)	0.001	304	462
<b>BARI 4 mg vs MTX (Wk 24)</b>						
JADZ	0.071	0.301	0.230 (0.160, 0.254)	0.001	190	154
<b>BARI 4 mg+MTX vs MTX (Wk 24)</b>						
JADZ	0.071	0.207	0.135 (0.068, 0.203)	0.001	190	201

Source: JADV CSR Table JADV 12.35, JADW CSR Table JADW.12.34, JADX CSR Table JADX.12.34, JADZ CSR Table JADZ 12.35

<sup>1</sup> Pool BARI 4mg PC consists of 6 studies (3 phase 2 JADA, JADC, JADN and 3 phase 3 JADV, JADW, JADX)

<sup>2</sup> Pool BARI 2 mg PC consists of 4 studies (2 phase 2 JADA, JADC and 2 phase 3 JADW, JADX)

Conversion from mmol/L (SI units) to mg/dL (US units) multiply by 38.7.

## NCEP shifts

Shift analyses of categorical changes in lipids used the following NCEP ATP III categories of LDL-C and triglyceride values. The applicant conducted shift analyses for cholesterol and HDL-C, however, this consult reviews only the LDL-C and TG as they are deemed most relevant to this discussion as primary risk factors for MACE and pancreatitis, respectively.

**Table 5. NCEP ATP III Categories**

Laboratory Test	Category	Criteria in SI Units	Criteria in Conventional Units
LDL Cholesterol	Optimal	< 2.59 mmol/L	< 100 mg/dL
	Near optimal	≥ 2.59 mmol/L and < 3.36 mmol/L	≥ 100 mg/dL and < 130 mg/dL
	Borderline high	≥ 3.36 mmol/L and < 4.14 mmol/L	≥ 130 mg/dL and < 160 mg/dL
	High	≥ 4.14 mmol/L and < 4.91 mmol/L	≥ 160 mg/dL and < 190 mg/dL
	Very high	≥ 4.91 mmol/L	≥ 190 mg/dL
Triglycerides	Normal	< 1.69 mmol/L	< 150 mg/dL
	Borderline high	≥ 1.69 mmol/L and < 2.26 mmol/L	≥ 150 mg/dL and < 200 mg/dL
	High	≥ 2.26 mmol/L and < 5.65 mmol/L	≥ 200 mg/dL and < 500 mg/dL
	Very high	≥ 5.65 mmol/L	≥ 500 mg/dL

Source: SCS Table APP2.2.7.4.54

## LDL-C

The applicant analyzed shifts in lipid values by NCEP ATP III LDL classification categories using baseline and maximum post-baseline LDL values. Consistent with the mean changes, a higher proportion of baricitinib-treated patients experienced a shift to a higher LDL-C category compared to placebo-treated patients in each baseline LDL-C category. For instance in the BARI 4 mg pool of Phase 3 studies JADV, JADW, JADX, of those with baseline LDL-C less than 130 mg/dL ('optimal' or 'near optimal'), 10% of patients treated with placebo had a maximum post-baseline LDL-C value which fell into a higher category, versus 34% of patients in treated with 4 mg baricitinib. This shift

toward a higher LDL-C with baricitinib treatment versus active or placebo control was observed in all the phase 3 studies.

**Table 6. Incidence of Treatment-Emergent High LDL-C by NCEP Category (Phase 3 studies)**

	'Optimal' or 'Near optimal' TO 'Borderline high', 'High' or 'Very high' n/NAR (%)	'Optimal' or 'Near optimal' or 'Borderline high' TO 'High' or 'Very high' n/NAR (%)	'Optimal' or 'Near optimal' or 'Borderline high' or 'High' TO 'Very high' n/NAR (%)
<b>BARI 4 mg RA PC and BARI 2 mg/4 mg RA PC Weeks 0-12 (JADV, JADW, JADX)</b>			
Placebo (N=892)	52/513 (10.1)	38/700 (5.4)	17/767 (2.2)
BARI 4 mg (N=891)	192/569 (33.7)	112/735 (15.2)	42/799 (5.3)
BARI 2/4 mg (N=1294)	245/830 (29.5)	150/1069 (14.0)	52/1155 (4.5)
<b>BARI 2 mg RA PC and BARI 2 mg vs. 4 mg RA Weeks 0-12 (JADW, JADX)</b>			
Placebo (N=404)	25/221 (11.3)	24/303 (7.9)	10/334 (3.0)
BARI 2 mg (N=403)	53/261 (20.3)	38/334 (11.4)	10/356 (2.8)
BARI 4 mg (N=404)	70/243 (28.8)	44/320 (13.8)	17/350 (4.9)
<b>Study JADZ Week 0-24</b>			
MTX (N=210)	Not provided	12/169 (7.1)	Not provided
BARI 4 mg (N=159)	51/117 (43.6)	32/143 (22.4)	8/149 (5.4)
BARI 4 mg +MTX (N=215)	54/148 (36.5)	34/187 (18.2)	13/195 (6.7)
<b>Study JADZ Weeks 0-52</b>			
MTX (n=210)	Not provided	20/169 (11.8)	Not provided
BARI 4 mg (N=159)	54/117 (46.2)	36/143 (25.2)	13/149 (8.7)
BARI 4 mg + MTX (N=215)	68/148 (45.9)	41/187 (21.9)	13/195 (6.7)

Source: SCS App2 Table APP2.2.7.4.80; SCS App2 Table APP2.2.7.4.69; SCS App2 Table APP2.2.7.4.70JADZ CSR Table JADZ.12.36, 38,

### *Triglycerides*

In the BARI 4 mg PC pool (JADA, JADC, JADN, JADV, JADW, and JADX), up to Week 12 a numerically higher proportion of 4 mg baricitinib treated patients increased to a higher NCEP TG category (19.0%) versus placebo (13.0%). Of those, a small proportion of patients exceeded TG $\geq$ 500 mg/dL and the proportion between treatment groups was similar (0.5% placebo versus 0.4% baricitinib 4 mg). This pattern was also similar to what was observed in the longer term study JADZ up to 52 weeks of MTX versus baricitinib.

Due to the association of elevated TG (usually greater than 500 mg/dL) and pancreatitis and the increase in TG observed with baricitinib treatment, the applicant provided narratives of all patients with a report of pancreatitis. Four patients in the clinical program reported a SAE of either acute or chronic pancreatitis. Of the 4 patients, 3 received treatment with baricitinib and 1 had elevated triglycerides.

*Reviewer comment: Review of the case narratives do not suggest these events were the result of severe hypertriglyceridemia.*

## Analyses with Statins

### Statin initiation

The following table shows the number and percentage of patients who initiated statin during the study as well as the number and percentage of patients using statins at baseline that increased the dose of statin in the completed phase 3 studies. Initiation of statin was left to Investigator discretion. Overall, the number of patients who started statins was low (<6%). There was not a consistent pattern observed, for example in study JADV a numerically higher proportion of baricitinib treated patients started statin therapy versus placebo and adalimumab patients; however in placebo controlled study, JADX, a higher percentage of placebo-treated versus baricitinib-treated patients started statin therapy.

**Table 7. Overview of Statin Initiation or Increase in Completed Phase 3 studies**

	Initiated during study, n (%)	Used at baseline ± increased dose during study	
		Used at baseline, n	Increased dose during study n (% of pts on statin at baseline)
<b>Study JADZ Wk 0-52</b>			
MTX (N=210)	5 (2.4)	16	1 (6.3)
Bari 4-mg (N=159)	4 (2.5)	14	2 (14.3)
Bari 4-mg + MTX (N=215)	12 (5.6)	12	0
<b>Study JADV Wk 0-24</b>			
Placebo (N=488)	11 (2.3)	41	0
Bari 4-mg (N=487)	16 (3.3)	42	1 (2.4)
Adalimumab (N=330)	4 (1.2)	28	0
<b>Study JADX Wk 0-24</b>			
Placebo (N=228)	8 (3.5)	26	1 (3.8)
Bari 2-mg (N=229)	6 (2.6)	22	0
Bari 4-mg (N=227)	6 (2.6)	20	0
<b>Study JADW Wk 0-24</b>			
Placebo (N=176)	5 (2.8)	28	0
Bari 2-mg (N=174)	7 (4.0)	28	1 (3.6)
Bari 4-mg (N=177)	6 (3.4)	40	0

Abbreviations: EAIR = exposure adjusted incidence rate; N = number of patients in the safety analysis set; n = number of patients in the specified category; pts = patients.

Data are n (%) patients as indicated (EAIR was not derived for rates of laboratory abnormalities).

Sources: t\_statin for each Study

Source: SCS APP 2, Table APP2.2.7.4.92

According to the applicant, there were 99 patients in the entire baricitinib RA Phase 3 program who initiated statin therapy after starting baricitinib 4 mg. The mean change of LDL-C from baseline to initiation of statin therapy was 38.7 mg/dL (1 mmol/L) or a 33% increase. LDL-C percent changes from initiation of statin therapy to end of statin therapy and from baseline to end of statin therapy were -28.3% and -5.5%, respectively.

### Change in lipids based on statin use at baseline

In the phase 3 studies with applicable data, regardless of statin use at baseline, LDL-C increased with baricitinib 4 mg treatment versus placebo and was statistically significant. Although there was a numerically smaller placebo-subtracted LDL-C change from

baseline among statin users compared non-statin users, the treatment interaction was not statistically significant.

**Table 8. Change in LDL (mg/dL) based on statin use at baseline (phase 3 studies JADV, JADW, JADX)**

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Variable	PBO (N=892)			BARI 4-mg (N=891)			BARI 2-mg/4-mg (N=1294)			BARI 4-mg vs. PBO			BARI 2-mg/4-mg vs. PBO			
	N-obs	LSM	SE	N-obs	LSM	SE	N-obs	LSM	SE	LSMD	95% CI	p-value	LSMD	95% CI	p-value	
LDL Cholesterol (mg/dL), change from baseline to Week 24, last observation																
Statin use at baseline																
No	696	-1.16	(0.90)	730	15.31	(0.88)				16.47	(14.2, 18.8)	0.001				0.439 (a)
Yes	84	7.92	(3.70)	92	20.70	(3.59)				12.79	(2.7, 22.8)	0.013				
No	696	-1.61	(0.90)				1049	13.63	(0.71)				15.24	(13.0, 17.4)	0.001	0.110 (a)
Yes	84	7.70	(3.58)				137	15.75	(2.81)				8.05	(-0.9, 17.0)	0.080	

Abbreviations: LSMD = least squares mean difference; N = number of patients in the specified category; N-obs = number of patients in the analysis.

Note: for statin users, data censored at statin dose change; for non statin users, data censored at statin use initiation.

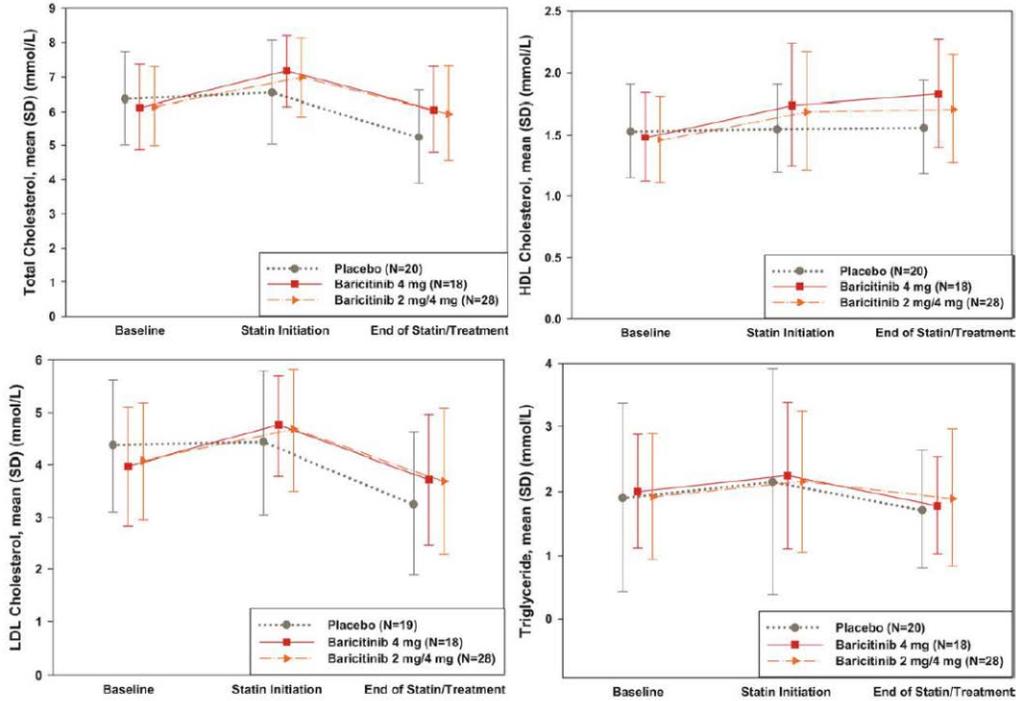
(a) P-value from the interaction of treatment by subgroup (baseline statin use status) in the ANCOVA model: change=treatment+study+baseline+subgroup+treatment by subgroup interaction. LSM, LSMD, SE, 95% CI and p-values within subgroup obtained from the same ANCOVA model with interaction and subgroup terms removed.

Source: SCS App2 Table APP2.2.7.4.93

### *Lipid changes after initiation of statin therapy*

The following figure shows the changes in lipids from baseline to initiation of statin therapy and end of statin use up to Week 24 for the BARI 4 mg RA PC and 2/4 mg RA PC analysis set that includes 3 phase 3 studies. Only patients who initiated statins after randomization were included in these analyses, so these figures should not be interpreted as randomized comparisons between study arms.

*Reviewer comment: Among baricitinib-treated patients, who initiate statin therapy, LDL-C levels fall to or slightly below baseline values appearing to mitigate the baricitinib induced increase. (Table 9)*



**Figure 2. Change in lipids with statin initiation up to Week 24 for the BARI 4 mg RA PC and the BARI 2/4 mg RA PC analysis sets**  
Source: SCS Figure 2.7.4.18

**Table 9. Change in LDL-C in Patients who Initiated Statins up to Week 24**

Change in Lipids in Patients who Initiated Statins after First Dose of Study Drug - CN Units  
Acute, Placebo-Controlled Period up to Week 24 with data up to rescue  
BARI 4-mg and BARI 2-mg/4-mg RA PC Analysis Sets (Studies with applicable data: JADV, JADW and JADX)

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	PBO (N=21)	BARI 4-mg (N=27)	BARI 2-mg/4-mg (N=40)	BARI 4-mg vs. PBO	BARI 2-mg/4-mg vs. PBO
<b>LDL Cholesterol (mg/dL)</b>					
Change from Baseline to Initiation of Statin Therapy					
LSM, LSMD (SE)	3.0 (5.52)	31.3 (5.88)		28.3 (7.79)	
95% CI	( -8.3, 14.2 )	( 19.3, 43.3 )		( 12.5, 44.2 )	
P-value	0.593	0.001		0.001	
LSM, LSMD (SE)	1.8 (6.64)		20.5 (4.58)		18.6 (8.02)
95% CI	( -11.9, 16.5 )		( 11.3, 33.9 )		( 2.3, 38.3 )
P-value	0.783		0.001		0.025
Change from Initiation of Statin Therapy to End of Statin Therapy					
LSM, LSMD (SE)	-46.1 (11.85)	-38.0 (12.62)		8.1 (16.72)	
95% CI	( -68.6, -26.7 )	( -58.1, -17.3 )		( -17.7, 37.7 )	
P-value	0.001	0.005		0.632	
LSM, LSMD (SE)	-45.6 (12.01)		-37.1 (9.54)		8.5 (15.20)
95% CI	( -69.8, -21.4 )		( -56.3, -17.9 )		( -22.2, 39.2 )
P-value	0.001		0.001		0.395
Change from Baseline to End of Statin Therapy					
LSM, LSMD (SE)	-43.1 (11.45)	-6.7 (12.19)		36.4 (16.16)	
95% CI	( -66.4, -19.8 )	( -31.5, 18.1 )		( 3.6, 69.3 )	
P-value	0.001	0.588		0.031	
LSM, LSMD (SE)	-43.9 (11.58)		-15.3 (8.62)		28.6 (14.12)
95% CI	( -66.7, -19.9 )		( -33.1, 4.1 )		( -0.8, 58.4 )
P-value	0.001		0.082		0.049

Abbreviations: LSM = least squares mean difference; N = number of patients in the specified category; N-obs = number of patients in the analysis.

Source: SCS App2, Table APP2.2.7.4.94

## Lipid Nuclear Magnetic Resonance

NMR was used to evaluate changes from baseline to Week 12 in study JADV in lipoprotein subfractions and particle sizes.

The following table shows an overview of lipid NMR findings during the study.

*Reviewer comment: Small dense LDL-C particles are purportedly more atherogenic, as an association between small dense LDL and cardiovascular risk has been shown in studies.<sup>4</sup> However, this association is attenuated when other risk factors for atherosclerotic CV disease are considered, and according to the National Lipid Association thus far, routine testing for clinical management is not recommended.<sup>5,6</sup> Although compared to placebo, treatment with baricitinib resulted in a decrease in the concentrations of small LDL particles, it is unknown what impact this observation on cardiovascular risk with baricitinib treatment would be in this patient population.*

**Table 10 Overview of Lipid Subfraction Changes as Measured using NMR (Study JADV Week 12)**

	Change from Baseline to Week 12		
	Placebo	Baricitinib	Adalimumab
<b>Subfraction concentrations</b>			
LDL particles (total)	↓	*↑ (~)	~ (*↓)
Large LDL	(~)	*↑ (*↑)	*↑ (*↑)
Small LDL (total)	(~)	*↓ (*↓)	*↓ (*↓)
Medium small LDL	(~)	*↓ (*↓)	*↓ (*↓)
Very small LDL	(~)	*↓ (*↓)	*↓ (*↓)
IDL	(~)	*↑ (*↑)	~ (*↑)
HDL particles (total)	(~)	*↑ (*↑)	*↑ (*↑)
Large HDL particles	(~)	*↑ (*↑)	*↑ (*↑)
Medium HDL particles	(~)	*↑ (*↑)	*↓ (↓)
Small HDL particles	(~)	*↑ (*↑)	*↑ (*↑)
Total triglycerides - calculated	(~)	*↑ (*↑)	*↑ (*↑)
VLDL triglycerides - calculated	(~)	*↑ (*↑)	*↑ (*↑)
HDL triglycerides - calculated	(~)	*↑ (*↑)	*↑ (*↑)
<b>Mean particle sizes</b>			
VLDL	(~)	*↑ (*↑)	~ (*↑)
LDL	(~)	*↑ (*↑)	*↑ (*↑)
HDL	(~)	*↓ (*↓)	~ (~)

Note: For a complete legend explaining how to interpret this table, please refer back to text of Section 12.3.2.4.5.

Abbreviations: HDL = high-density lipoprotein; IDL = intermediate density lipoprotein; LDL = low-density lipoprotein; NMR = nuclear magnetic resonance; VLDL = very low-density lipoprotein.

Source: Table JADV.14.250.

Legend

<sup>4</sup> Ip S et al. Systematic review: association of low-density subfractions with cardiovascular outcomes. *Ann Intern Med* 2009;150:474-84

<sup>5</sup> Krauss RM. Lipoprotein subfractions and cardiovascular disease risk. *Curr Opin Lipidol* 2010;21:305-11

<sup>6</sup> Davidson MH et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialist. *Journal of clinical lipidology* 2011;5:338-67.

- ↑ = increased compared to placebo.
- ↓ = decreased compared to placebo.
- ~ = similar to placebo.
- \* = statistically significant.
- Within-group changes for the placebo, baricitinib, and adalimumab groups are depicted as symbols in parentheses.
- For example (all relating to observed change from baseline at Week 12):
  - \*↓ (↓) = compared to placebo, statistically significantly decreased. A within-group decrease from baseline; the within-group change from baseline was not statistically significant.
  - ~ (\*↑) = compared to placebo, change from baseline similar; a statistically significant within-group increase from baseline.
  - \*↑ (~) = compared to placebo, statistically significantly increased; no notable within-group change from baseline.

Source: JADV CSR Table JADV.12.39

## Apolipoprotein Changes

In the phase 2 study, JADA, analyses were conducted on a variety of apolipoproteins (Table 11). As would be expected with the changes in LDL-C and HDL-C there were increases in apoB and apoA1, respectively.

Some have hypothesized that HDL can become dysfunctional during inflammation and may lose its anti-atherogenic properties.<sup>7</sup> Serum amyloid A, an acute phase reactant, increases during acute and chronic inflammation. SAA is transported in plasma by HDL. There is some evidence that SAA laden HDL-C has reduced cholesterol efflux capacity.<sup>8</sup> HDL-associated SAA decreased significantly compared to placebo with baricitinib treatment.

*Reviewer comment: It is not well understood if the lipid changes observed with RA treatment represent qualitative improvements in lipoprotein function. These analyses of apolipoproteins are considered exploratory and are not surrogates for cardiovascular risk.*

<sup>7</sup> Feingold KR, Grunfeld C. Effect of inflammation on HDL structure and function. *Curr Opin Lipidol* 2016

<sup>8</sup> Vaisar T et al. Inflammatory remodeling of the HDL proteome impairs cholesterol efflux capacity. *J Lipid Res* 2015;56:1519-30.

**Table 11. Change from Baseline in Apolipoprotein Results Phase 2 study JADA**

		Baricitinib		
		Placebo N=96	4-mg QD N=52	8-mg QD N=50
Apolipoprotein A-I (mg/dL)	Baseline	184.0 ± 5.5	188.0 ± 10	178.5 ± 8.5
	Percent change from baseline at Week 4	-1.9 ± 3.0	5.1 ± 4.1†,*	11.6 ± 3.9††,**
	Percent change from baseline at Week 12	1.1 ± 2.5	9.5 ± 3.8†,*	12.2 ± 3.0††,*
Apolipoprotein B (mg/dL)	Baseline	105.0 ± 3.0	110.5 ± 6.5	100.0 ± 6.5
	Percent change from baseline at Week 4	-4.5 ± 2.6†	3.6 ± 2.4*	0.85 ± 3.0*
	Percent change from baseline at Week 12	-4.5 ± 0.93†	6.8 ± 3.55*	7.14 ± 3.83*
Apo B/Apo A-I Ratio (mg/dL)	Baseline	0.6 ± 0.03	0.6 ± 0.03	0.6 ± 0.03
	Percent change from baseline at Week 4	-3.4 ± 2.5†	-2.69 ± 3.0	-9.8 ± 5.3*
	Percent change from baseline at Week 12	-6.6 ± 2.7†	-5.33 ± 2.7	-4.9 ± 6.2
Apolipoprotein CIII (mg/dL)	Baseline	8.3 ± 0.4	7.6 ± 0.7	7.4 ± 0.6
	Percent change from baseline at Week 4	-4.2 ± 4.3	17.0 ± 13.0	22.3 ± 10.5††,*
	Percent change from baseline at Week 12	-8.9 ± 4.3	23.0 ± 6.9†,*	19.7 ± 3.8††,**
LDL-C Associated Apolipoprotein CIII (mg/dL)	Baseline	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.1
	Percent change from baseline at Week 4	-20.8 ± 14.8	-4.7 ± 18.7	-1.3 ± 18.1
	Percent change from baseline at Week 12	0 ± 8.3	-4.5 ± 10.8	-9.0 ± 18.9
HDL-C Associated Serum Amyloid A (mg/L)	Baseline	5.7 ± 0.6	6.4 ± 0.9	11.1 ± 3.5
	Percent change from baseline at Week 4	12.0 ± 14.3	-51.3 ± 5.3††,**	-50.2 ± 7.5††,**
	Percent change from baseline at Week 12	11.3 ± 6.5	-36.0 ± 3.5†,*	-32.0 ± 16.1†,*
Lipoprotein (a) (mg/dL)	Baseline	8.4 ± 1.5	10.7 ± 3.0	11.1 ± 2.3
	Percent change from baseline at Week 4	0.7 ± 5.4	2.5 ± 7.4	-8.1 ± 6.5†,*
	Percent change from baseline at Week 12	-2.4 ± 3.9	-4.62 ± 4.5	-16.6 ± 2.6†

Abbreviations: QD – once-daily; LDL-C - low density lipoprotein; HDL-C- high density lipoprotein; SE - standard error.

Data are median ± SE due to skewed distribution.

†p<0.05 (within treatment)

††p<0.001 (within treatment)

\*p<0.05 vs. placebo

\*\*p<0.001 vs. placebo

Source: SCS Table 2.7.4.36

#### IV. Major Adverse Cardiovascular Events

All deaths and potential cardiovascular events, including adverse event terms that described an increase or abnormality in CPK or CPK-MB were adjudicated by an external cardiovascular endpoint committee (CEC). 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..

Overall at all doses, all treatment groups, all treatment periods, there were a total of 268 events that were sent to adjudication. Twenty-six events were attributed to 21 patients with adjudicated MACE: 8 CV death, 12 MI (11 patients), 6 stroke (6 patients).

From the placebo-controlled portion of phase 3 studies up to Week 24 (including data up to rescue), there were a total of 5 events adjudicated as MACE (2 in the placebo group and 3 in the baricitinib 4 mg group)Table 12. Brief narratives of these five events are listed below.

*Reviewer comment: The placebo-controlled portion of the phase 3 studies is of short duration – approximately up to 16 weeks before rescue was allowed, therefore, the lack of a long-term placebo-control group to compare rates of MACE is a major limitation of the data's ability to inform baricitinib-associated CV risk. The numbers are too small to draw any definitive conclusions regarding the effect of baricitinib on MACE compared to placebo.*

From the phase 3 active-controlled Study JADZ (MTX monotherapy, BARI 4 mg, BARI 4 mg + MTX) up to Week 52 (excluding events after rescue, if applicable for a given patient), MACE was reported in 2 patients in MTX monotherapy (1.1 events per 100 PY), 1 patient in BARI 4 mg monotherapy (0.7 event per 100 PY), and 0 patients in BARI 4 mg + MTX.

**Table 12. Number (%) of patients with events adjudicated by CEC as MACE by placebo-controlled phase 3 studies up to Week 24 (includes data up to rescue)**

	Placebo N=488 n (%)	JADV BARI 4 mg N=487 n (%)	ADA N=330 n (%)	Placebo N=176 n (%)	JADW BARI 2 mg N=174 n (%)	BARI 4 mg N=177 n (%)	Placebo N=288 n (%)	JADX BARI 2 mg N=299 n (%)	BARI 4 mg N=227 n (%)
MACE	0	1 (0.2)	0	0	0	2 (1.1)	2 (0.9)	0	0
CV Death	0	1 (0.2)	0	0	0	1 (0.6)	1 (0.4)	0	0
Cerebrovascular event	0	0	0	0	0	1 (0.6)	1(0.4)	0	0
Cardiovascular - other	0	1 (0.2)	0	0	0	0	0	0	0
MI	0	0	0	0	0	1 (0.6)	1 (0.4)	0	0
Stroke	0	0	0	0	0	1 (0.6)	1 (0.4)	0	0
Hemorrhagic	0	0	0	0	0	0	1 (0.4)	0	0
Ischemic	0	0	0	0	0	1 (0.6)	0	0	0
	0	0	0	0	0	0	0	0	0
Other CV event	1 (0.2)	1 (0.2)	0	0	1 (0.6)	0	2 (0.9)	1 (0.4)	0
Hosp unstable angina	0	0	0	0	0	0	0	0	0
Unchar ischemic event	0	1 (0.2)	0	0	0	0	0	0	0
Hosp heart failure	0	0	0	0	0	0	0	1 (0.4)	0
Serious arrhythmia	1 (0.2)	0	0	0	1 (0.6)	0	1 (0.4)	1 (0.4)	0
Resuscitated sudden death	0	0	0	0	0	0	0	0	0
Cardiogenic shock b/c MI	0	0	0	0	0	0	0	0	0
Coronary revascularization	0	1 (0.2)	0	0	0	2 (1.1)	1 (0.4)	0	0
Non-CV death	0	1 (0.2)	0	0	0	0	1 (0.4)	0	0
All-cause death	0	2 (0.4)	0	0	0	1 (0.6)	2 (0.9)	0	0

Source: JADV CSR Table JADV.14.136; JADW CSR Table JADW.14.95; JADX CSR Table JADX.14.140

Brief narratives of CEC adjudicated MACE from the placebo-controlled portion of Phase 3 studies (JADV, JADW, JADX) up to Week 24 (including data before rescue)

- **CV death (other)** ( [REDACTED] <sup>(b) (6)</sup> ) /**baricitinib 4 mg** 68 y/o female from Argentina randomized to baricitinib 4 mg, had the positively adjudicated MACE of cardiovascular death categorized under “cardiovascular-other” and the non-MACE of coronary revascularization surgery. Medical history of dyslipidemia (no treatment reported, LDL-C at baseline 146 mg/dL), hypertension, and obesity (BMI 31kg/m<sup>2</sup>). This event included a hospitalization due to MI and eventually death due to hospital-acquired pneumonia. One hundred sixty-four days after the first dose of baricitinib, the patient was hospitalized with a diagnosis of acute MI. Coronary catheterization showed multiple obstructions of the anterior descending coronary artery, circumflex artery, and right coronary artery (disease of 3 arteries). On that day, an SAE of MI was reported, and the study drug was permanently stopped. It was reported that the patient did not recover from the event and remained hospitalized. As corrective treatment, the patient had a revascularization bypass coronary surgery 22 days later, and on that same day was diagnosed with hospital-acquired postoperative pneumonia that resulted in death, 192 days after the first dose and 30 days after the last dose of baricitinib.
- **CV death – stroke** ( [REDACTED] <sup>(b) (6)</sup> ) /**baricitinib 4 mg** 76 y/o female from France experienced a basilar artery thrombosis 42 days after starting study drug and died 5 days later. Preexisting medical conditions included: steroid-induced type II diabetes, hypothyroidism, interstitial bilateral hypoxemic pneumopathy, delusions, depression, and dyslipidemia (on simvastatin 10 mg, baseline LDL-C 123 mg/dL. The patient was a nonsmoker with no prior thromboembolic disease or history of hypercoagulability. Forty-two days after starting study drug, the patient was found with an altered level of consciousness by her husband and was hospitalized. Clinical symptoms upon admission were mutism, somnolence, right hemiplegia, salivary stasis, and plantar reflex (flexion on the left and indifference on the right). A cranial computerized tomography scan showed partial opacification of 2/3 of the left proximal basilar artery trunk, complete thrombosis of 1/3 of the left distal basilar artery, and left vertebral artery thrombosis on V3 and V4 segment. The patient was treated with acetylsalicylate lysine and enoxaparin sodium. Two days after hospitalization, the patient presented with left bridge carotid ischemia on the terminal portion of the basilar trunk occlusion with left vertebral artery stenosis. The patient’s neurological condition progressively declined and she died 5 days after hospitalization.
- **MI** ( [REDACTED] <sup>(b) (6)</sup> ) /**baricitinib 4 mg** 45 y/o female from the United States experienced 2 positively adjudicated events: (1) MI was a positively adjudicated MACE and (2) coronary revascularization was considered the other positively adjudicated cardiovascular event. The patient was a nonsmoker, and current relevant medical conditions included diabetes mellitus and hypertension. Eighty-nine days after starting study drug, the patient presented to the emergency room with sudden-onset sub-sternal chest pain associated with shortness of breath. The patient was admitted to the hospital and diagnosed with non-ST elevation MI (NSTEMI) and coronary artery disease. The patient continued to have episodes of

chest pain. Coronary angiography revealed 99% stenosis in the right coronary artery. Successful PCI was performed with bare metal stent. The chest pain resolved after the procedure. The patient was also diagnosed with dyslipidemia during the hospitalization and began statin therapy (cholesterol 149 mg/dL, TG 234 mg/dL, HDL 36 mg/dL, LDL 66 mg/dL). The patient was discharged from the hospital with no further complications.

- **CV death – stroke** ( (b) (6) /placebo) 51 y/o female from Argentina experienced subarachnoid hemorrhage and death. The patient was a non-smoker, non-drinker, possible history of hypertension. 57 days after starting treatment, the patient developed symptoms of vomiting and headache. Brain CT revealed a subarachnoid hemorrhage. Six days after hospitalization, the patient developed intracranial hypertension and died.
- **MI** ( (b) (6) /placebo) experienced MI and coronary revascularization that led to discontinuation from study drug and from the study. Medical history included hypertension and type 2 diabetes mellitus. Seventy-two days after starting study drug the patient was hospitalized for an acute, inferior myocardial infarction and a cardiac catheterization with coronary angiography and percutaneous coronary intervention (PCI) was performed. Angiography showed 99% occlusion of the right coronary artery (RCA) at the junction of the proximal and middle thirds with diffuse irregularities noted distally. Diffuse irregularities were also noted in the LAD and left circumflex arteries. Successful PCI was performed with a drug eluting stent placed in the RCA. The patient recovered from the event without further complications.

The applicant provided the incidence rates of positively adjudicated MACE by different analysis set, including follow-up data where available.

From Study JADZ (MTX monotherapy, BARI 4-mg, BARI 4-mg + MTX), MACE were reported in 2 patients in MTX monotherapy (1.1 events per 100 PY), 1 patient in BARI 4-mg monotherapy (0.7 event per 100 PY), and 0 patients in BARI 4-mg + MTX.

From the Integrated Database, in the combined 6-study data set (BARI 4-mg RA PC), MACE were reported in 2 patients in PBO (0.5 events per 100 PYE) and 3 patients in BARI 4-mg (0.8 event per 100 PYE).

In the combined 4-study data set (BARI 2-mg vs 4-mg), MACE were reported in 2 patients in PBO (1.2 events per 100 PYE), 0 patients in BARI 2-mg, and 2 patients in BARI 4-mg (1.1 event per 100 PYE).

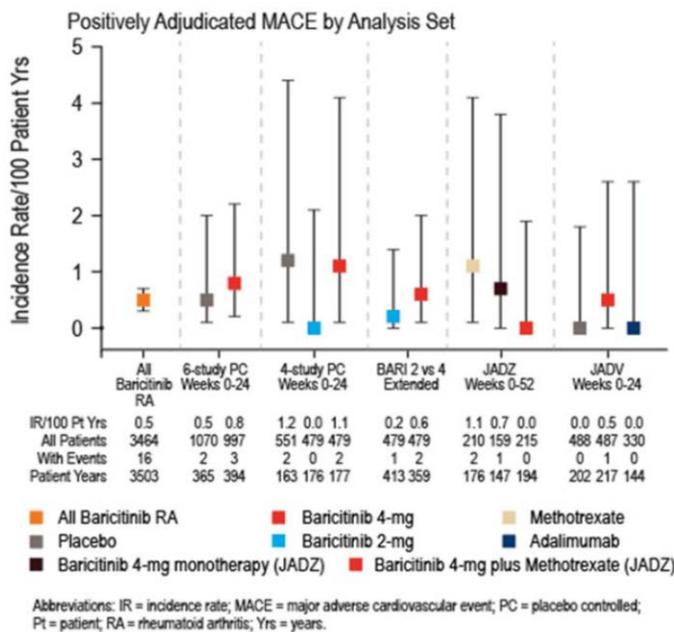
*Reviewer comment: With only 4 patients experiencing a MACE, the numbers are too small to determine a dose response for MACE between the 2 mg and 4 mg baricitinib dose.*

In the combined 4-study data set including data from the long-term extension study (Ext BARI 2-mg vs 4-mg RA), MACE were reported in 1 patient in BARI 2 mg (0.2 events per 100 PYE), 2 patients in BARI 4-mg group (0.6 event per 100 PYE).

*Reviewer comment: Due to study design, the 4 mg baricitinib group had a longer duration of exposure. The event rate has been adjusted for patient year exposure, however, the number of patients with an event is too small to draw definitive conclusions regarding a dose response.*

In the All BARI RA data set, All Phase 3 studies, MACE was reported in 16 patients (0.46 events per 100 PYE) who received BARI at any time, any dose including after rescuing or switching from ADA, MTX, and PBO.

*Reviewer comment: The number of overall MACE in baricitinib exposed patients from phase 3 studies at any time is very low. A total of only 16 baricitinib-treated patients in phase 3 studies (including long-term extension) experienced 20 positively adjudicated MACE (6 cardiovascular death, 10 myocardial infarction, 4 stroke).*



**Figure 3. Incidence rate of positively adjudicated MACE by analysis set in RA clinical studies**

Source: SCS Figure 2.7.4.23

*DMEP Reviewer’s Comment: The lack of a long-term placebo-control group to compare rates of MACE is a major limitation of the data’s ability to inform baricitinib-associated CV risk.*

## V. Recommendations

The following questions have been posed by DPARP to DMEP:

### Questions:

Baricitinib is a JAK inhibitor being developed for treatment in rheumatoid arthritis. As has been seen with other JAK inhibitors, an elevation in all lipid parameters (LDL, HDL, triglycerides) has been noted with baricitinib. Additionally, there is a suggestion of a possible dose response with more primary MACE events in the higher dose (4 mg daily) treatment arm as compared to the lower dose (2 mg daily); however, the overall exposure to the higher dose was much greater. Do you believe these lipid parameter changes are significant? Do you believe that they may be correlated with an increased risk of cardiovascular events? If so, do you feel that a post-marketing cardiovascular trial would address this possible concern? It should be noted that a currently approved JAK inhibitor (tofacitinib) has a post-marketing requirement to evaluate safety. The study will also assess the risk of serious cardiovascular events, e.g., stroke, non-fatal MI, cardiovascular death.

*DMEP Response: DMEP has offered our recommendations on this question relative to other RA treatment therapies, including a currently approved JAK inhibitor, tofacitinib, and most recently, sarilumab, an IL-6 receptor blocker. Review of the lipid changes observed with these therapies are directionally consistent (and generally similar in magnitude) with what was observed with baricitinib; therefore, much of this discussion is identical to our previous consults.*

*Patients with rheumatoid arthritis (RA), a chronic autoimmune inflammatory joint disorder are at 50% higher risk of cardiovascular disease compared to the general population.<sup>9</sup> The relationship between RA and increased CV disease is not fully explained by traditional assessments of cardiovascular risk (i.e. evaluating lipids and presence of various risk factors such as smoking, hypertension, family history, and diabetes). It has been hypothesized that the chronic pro-inflammatory state observed with RA is a primary contributor to cardiovascular pathology.<sup>10</sup> Indeed, targeting inflammation to reduce cardiovascular risk is the recent focus of clinical trials.<sup>11,12</sup> Ongoing CV outcomes trials are testing the effects of an anti-inflammatory therapy on CV risk (e.g., the Novartis-sponsored CANTOS trial [NCT01327846], which is testing canakinumab, a human mAb against IL-1 $\beta$ ).*

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<sup>9</sup> Avina-Zubieta JA et al. Risk of cardiovascular mortality in patients in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008;59:1690-7.

<sup>10</sup> Hannawi S et al. Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. *Arthritis Res. Ther* 2007; 9(6):R116

<sup>11</sup> Everett BM et al. Rationale and design of the cardiovascular inflammation reduction trial: a test of the inflammatory hypothesis of atherothrombosis. *Am Heart J*. 2013;166:199-207.e15.

<sup>12</sup> Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. *Circ Res*. 2016;118:145-56.

*Unlike the general population, where there is a linear association between LDL-C levels and cardiovascular risk, patients with RA tend to have lower total cholesterol and LDL-C, despite higher CV risk, in the setting of active inflammation. This relationship has been described as a “lipid paradox”.<sup>13</sup> Other disease conditions with inflammation have been associated with similar lipid changes and CV risk.<sup>14</sup> It has been noted, that with treatment of RA and favorable changes in RA disease activity, elevations in lipids occur. There has been interest in investigating whether these changes in lipids represent a more functional lipoprotein/anti-atherogenic profile in patients with RA. Some references provided by the applicant (mostly funded by Pfizer, sponsor of tofacitinib) have looked at HDL-C function via cholesterol efflux capacity and the concentration and size of lipoprotein subfractions in non-clinical and clinical studies in patients before and after treatment which have provided some preliminary evidence to suggest changes observed in this population (larger LDL particle size, decreased HDL-associated SAA) may be anti-atherogenic.<sup>15,16</sup> However, a recently published paper online showed net cholesterol efflux capacity was not significantly changed after 6 months of new RA therapy (MTX, adalimumab, and tocilizumab), despite significant improvement in disease activity.<sup>17</sup> While these results are interesting, further investigation is warranted, especially to further define what impact, if any, these biomarkers may have on cardiovascular events in patients with RA; at this time our Division considers these biomarkers exploratory and not surrogates of CV risk. These findings underscore the complex interplay of inflammation with lipid levels, lipoprotein structure/function, and CV risk and complicate conclusions about the clinical significance of the observed elevations in lipids with baricitinib, especially as they are occurring in tandem with reductions in inflammation and other changes in exploratory lipoprotein biomarkers.<sup>18</sup> Ultimately, the net effect on CV risk as a result of decreased inflammation (if any) and changes in the pro/anti-atherogenic profile of lipids in this population is unknown.*

*In general, of the lipid parameters, the evidence for LDL-C as a causal mediator of atherosclerosis and resultant cardiovascular disease is the most robust. A meta-analysis of statin trials estimated that each 1.0 mmol/L (~40 mg/dL) reduction in LDL-C results in*

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<sup>13</sup> Myasoedova E et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann. Rheum. Dis.* 2011; 70:482-87.

<sup>14</sup> Liu Y et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004; 291(4): 451-9.

<sup>15</sup> Charles-Schoeman C et al. Potential mechanism leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis&Rheumatology* 2015;67(3):616-625.

<sup>16</sup> McInnes I et al. Effects of tofacitinib (CP-690,550) on lipid biomarkers in rat adjuvant-induced arthritis (AIA) model and in patients with active rheumatoid arthritis [abstract]. In: The European League Against Rheumatism 2012 Annual Congress; 6-9 June 2012; Berlin (Germany). *Ann Rheum Dis.* 2013a;71(suppl 3):646. Abstract AB0160

<sup>17</sup> Ormseth MJ et al. Effect of drug therapy on net cholesterol efflux capacity of HDL-enriched serum in rheumatoid arthritis. *Arthritis&Rheumatology* 2016 March doi: 10.1002/art.39675. [Epub ahead of print]

<sup>18</sup> At 12 weeks, in individual phase 3 studies, JADV, JADW, JADX change in hsCRP 4 mg baricitinib versus placebo all  $p \leq 0.001$

*an approximate 22% reduction in major CV events.<sup>19</sup> In baricitinib placebo-controlled trials, relative to baseline, the LS mean change up to 16 weeks of treatment with baricitinib 4 mg was approximately 13 mg/dL (~12%), compared to -3 mg/dL (~-2.5%) in the placebo group. Although there was no direct comparison with tofacitinib within the baricitinib development, a previous DMEP consultative review of the lipid changes observed with tofacitinib showed there was an increase in LDL-C of approximately 15% to 20%.<sup>20</sup> It is not clear if this effect on lipids represents suppression of background inflammation, a specific effect of downstream signal blockade, or an off-target effect of these drugs.*

*Other drugs are associated with dyslipidemia, including anti-hypertensives (thiazide diuretics [increase cholesterol and TG] and certain beta blockers in some patients [increase TG, decrease HDL-C]), immunosuppressants (cyclosporine and tacrolimus), and protease inhibitors. The degree of cardiovascular risk as a result of pharmacologically induced dyslipidemia is not well understood, although it is most likely dependent on a multitude of factors including the disease condition, the drug's mechanism, baseline traditional risk factors, and duration of therapy and the resultant lipid abnormalities.<sup>21,22</sup>*

*In theory, if the statin-based relationship between LDL-C reduction and CV risk reduction were to hold for drug-induced increases in LDL-C and could be extrapolated to the RA population, the magnitude of change could be on the order of ~9% compared to placebo, assuming a mean LDL-C difference of 16 mg/dL. However, this quantification of risk is speculative, especially considering that baricitinib induces favorable changes in inflammation, which may be a key contributor to CV risk in patients with RA. We would like to emphasize, however, that our Division, at this time, does not consider a biomarker for inflammation such as hsCRP as a valid surrogate for CV risk.*

*We note that few patients were taking statins at baseline in this development program; however the applicant provided several analyses investigating the effect of statins (baseline statin therapy and statin initiation) on lipid abnormalities associated with baricitinib. Regardless of existing statin therapy, LDL-C increased with baricitinib 4 mg in both statin users and non-users. While the increase in LDL-C observed in baricitinib 4 mg compared to placebo was numerically smaller in statin users than in non-users, we would not go so far as the applicant with their suggestion that this pattern indicates “some blunting of the LDL-raising effect of baricitinib” as the treatment interaction was not statistically significant.*

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<sup>19</sup> Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; 376:1670-81.

<sup>20</sup> Chowdhury I, Colman E. DMEP Consult Tofacitinib, June 20, 2012 DARRTS ID 3148369

<sup>21</sup> Byington RP et al. Propranolol-induced lipid changes and their prognostic significance after a myocardial infarction: the beta-blocker heart attack trial experience. *Am J Cardiol.*1990;65(20):1287-91.

<sup>22</sup> Kannel WB et al. Long-term cardiovascular risk with protease inhibitors and management of the dyslipidemia. *Am J Cardiol* 2004;94:901-6.

*Among baricitinib-treated patients who started statin therapy, LDL-C levels fell to or slightly below baseline values, appearing to mitigate baricitinib-induced LDL-C elevations.*

*We note that baricitinib increases HDL-C, which was not affected by statin initiation, and could be considered favorable since epidemiologic studies have observed an inverse relationship between HDL-C and CV risk, but pharmacologic interventions to increase HDL-C have not consistently predicted cardiovascular benefit; therefore, it is unknown if the observed changes in HDL-C with baricitinib would ultimately be positive.<sup>23,24</sup> As mentioned above, whether the functional properties of HDL-C are improved with JAK inhibition or other RA therapies is under investigation. At this time, the impact of pharmacological changes on these exploratory biomarkers of HDL-C structure and function on cardiovascular events in the RA population is not known.*

*Similar uncertainty surrounds triglycerides. Although epidemiological evidence suggest elevated TG appears to be a risk factor for CVD, it is unknown whether drug-induced changes in TG will impact CV risk.<sup>25</sup> However, severe elevations in TG levels ( $\geq 500$  mg/dL) cause concern for a risk of acute pancreatitis. In the baricitinib development program, a very small proportion of patients had a triglyceride value of “very high” by NCEP criteria. There were 4 patients that reported pancreatitis, however, none had TG > 500 mg/dL and other factors may have contributed to the occurrence of pancreatitis.*

*Given the small number of events (total of 20 events adjudicated as MACE in 16 patients treated with any dose of baricitinib in phase 3 studies), this reviewer would consider any results generated regarding overall hazard ratios as preliminary and unstable.*

*If it is critical to characterize the effect of baricitinib on CV risk in order to determine whether the overall benefit/risk is favorable, a CVOT would be necessary. If a drug-induced increase in LDL-C confers an increase in CV risk of a magnitude similar to the expected CV risk reduction from a similar statin-induced change (decrease) in LDL-C, the LDL-C-mediated increase in risk may be ~9% assuming that the target patient population has similar baseline LDL-C values, on average, as the phase 3 program. Notably, it would very likely be infeasible to conduct a trial that aims to exclude this degree of risk (as opposed to a larger risk margin). Initiation of statins mitigated the lipid abnormalities associated with baricitinib; therefore, it is plausible that labeling could communicate that healthcare providers should follow lipid levels and treat accordingly. Of course, such an approach also assumes that the changes observed in lipids mediate any baricitinib-induced increase in CV risk, which may not be unreasonable if other signals have not been detected in the development program. Noting the precedent for*

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<sup>23</sup> AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. NEJM 2011;365:2255-67.

<sup>24</sup> Dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. NEJM 2012;367:2089-99.

<sup>25</sup> Rosenson RS et al. Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. JACC 2014;64:2525-40.

*requiring a CVOT to establish the CV safety of tofacitinib, however, it would appear that similar consideration would need to be given for baricitinib.*

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/s/  
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