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LIST OF ABBREVIATIONS

Abbreviation	Definition
μM	Micromole
1DMARD-IR	patients with inadequate response to 1 DMARD
2+DMARD-IR	patients with inadequate response to 2 or more DMARDs
ABA	abatacept
ACR	American College of Rheumatology
ACR20/50/70	20/50/70% improvement in American College of Rheumatology criteria
ADA	Adalimumab
AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0-\infty}$	area under the concentration versus time curve from zero to infinity
$AUC_{\tau,ss}$	area under the concentration time curve during one dosing interval at steady state
BARI	baricitinib
BCRP	breast cancer resistance protein
bDMARD	biologic disease-modifying antirheumatic drug
bDMARD-IR	patients with inadequate response to bDMARD(s)
BID	twice daily
Cav,ss	daily average concentration at steady state of dosing
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease-modifying antirheumatic drug
cDMARD-IR	patients with inadequate response to cDMARD(s)
CI	confidence interval
CL/F	apparent total clearance
CLnr/F	apparent nonrenal clearance
CLr/F	apparent renal clearance
COX-2	cyclooxygenase-2
CPK	creatine phosphokinase
CRL	complete response letter
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score in 28 joints-C-reactive protein
DDI	drug-drug interactions
DMARD	disease-modifying antirheumatic drug
DMARD-IR	patients with inadequate response to DMARD(s)
DVT	deep vein thrombosis
EAIR	exposure-adjusted incidence rate
EC50/80	concentration required to achieve 50/80% maximum response
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency (formerly EMEA)
EPO	erythropoietin
ePRO	electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life–5 Dimensions–5 Level

Abbreviation	Definition
E-R	Exposure-response
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
EU	European Union
EULAR	European League Against Rheumatism
EULAR28	European League Against Rheumatism responder index based on 28-joint count
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HAQ-DI	Health Assessment Questionnaire-Disability Index
HDL-C	high-density lipoprotein cholesterol
hERG	human ether-à-go-go-related gene
hsCRP	high-sensitivity C-reactive protein
IC_{50}	half-maximal inhibitory concentration
ICD-9	International Classification of Diseases 9
IFN	Interferon
IL	Interleukin
IMEDS	Innovation in Medical Evidence Development and Surveillance
IND	Investigational New Drug
IR	inadequate responder
IVRS	interactive voice-response system
JAK	Janus kinase
kg	Kilogram
L	Liter
LDA	low disease activity
LDL-C	low-density lipoprotein cholesterol
LE	linear extrapolation
Lilly	Eli Lilly and Company
LLN	lower limit of normal
LOCF	last observation carried forward
LS	least squares
LSM	least squares mean
MACE	major adverse cardiovascular events
MATE	multidrug and toxic extrusion protein
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mBOCF	modified baseline observation carried forward
MJS	Morning joint stiffness
mLOCF	modified last observation carried forward
Mono	monotherapy
MRI	magnetic resonance imaging
mTSS	modified Total Sharp Score
MTX	methotrexate
MTX-IR	patients with inadequate response to methotrexate
N	number of patients in the safety dataset
n	number of patients in the specified category
NCEP	National Cholesterol Education Program
nM	nanomole
NNT	number needed to treat

Abbreviation	Definition
NRI	non-responder imputation
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drug
OAT	organic anionic transporter
OATP	organic anion transporting polypeptide
PBO	placebo (for the pivotal Phase 3 studies, placebo treatment was generally in addition to background cDMARD therapy)
PBPK	physiologically-based pharmacokinetics
PC	placebo-controlled
PD	pharmacodynamic
PE	pulmonary embolism
PK	pharmacokinetic
PMSS	postmarketing safety study
PopPK	population pharmacokinetics
PRO	patient reported outcome
Ps	Psoriasis
PsA	psoriatic arthritis
PT	MedDRA preferred term
PY	person-years
PYE	patient-years of exposure
QD	once daily
Q2W	once every 2 weeks
QW	once per week
RA	rheumatoid arthritis
RR	relative risk
SAE	serious adverse event
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SE	Standard error
SJC	swollen joint count
SLE	systemic lupus erythematosus
SMQ	standardised MedDRA query
STAT	signal transducer and activator of transcription
$t_{½}$	terminal half-life
TCZ	tocilizumab
t_{max}	time to maximum observed drug concentration
TJC	tender joint count
TNF	tumor necrosis factor
TOF	tofacitinib
TPO	thrombopoietin
TQT	thorough QT
TYK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VAS	Visual analog scale
VTE	venous thromboembolic
wk	week
WPAI-RA	Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis

1. Synopsis

1.1. Executive Summary

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory autoimmune disease in which up to 90% of patients do not reach the treatment target of remission with current therapies (Smolen et al. 2016). Patients commonly report persistent and debilitating symptoms including pain, fatigue, and loss of function (Taylor et al. 2016). New therapies are needed to fill this unmet need.

Baricitinib is an orally administered Janus kinase (JAK) inhibitor under development by Eli Lilly and Company (Lilly) and Incyte Corporation for the treatment of adult patients with moderately to severely active RA. Baricitinib inhibits JAK1 and JAK2, thus reducing signals along multiple RA-associated cytokine pathways. Baricitinib is also being studied in a number of other chronic indications such as atopic dermatitis and systemic lupus erythematosus.

The baricitinib global RA development program included 19 clinical pharmacology studies, three Phase 2 studies, and four completed Phase 3 studies: two placebo-controlled studies of the 2-mg and 4-mg doses and two active comparator-controlled studies of the 4-mg dose. These Phase 3 studies enrolled 3100 patients, including patients naïve to disease-modifying antirheumatic drugs (DMARDs) and patients who had responded inadequately or were intolerant to conventional and/or biologic DMARDs (i.e., those who had failed cDMARDs and/or bDMARDs, respectively).

The Phase 3 studies demonstrated that both the 2-mg and 4-mg doses of baricitinib were superior to placebo. Both doses of baricitinib inhibited progression of joint damage and produced rapid improvements in signs and symptoms associated with RA. The most robust efficacy was seen for the 4-mg dose, with the dose response relationship most evident in patients who failed more than 1 DMARD. Baricitinib efficacy persisted in a long-term extension study. In head-to-head studies, baricitinib 4-mg was superior to standards of care (1. methotrexate as monotherapy and 2. adalimumab with a background of methotrexate) in reducing signs and symptoms, improving physical function, and improving additional patient reported outcomes (PROs) deemed important to patients (Taylor 2016). The long-term extension study also provided evidence that a majority of patients with well-controlled RA could be successfully tapered from the 4-mg to the 2-mg dose.

The baricitinib safety profile has been characterized with more than 7860 years of patient exposure. In head-to-head studies, the baricitinib safety profile appears generally comparable to standards of care (methotrexate as monotherapy and adalimumab with a background of methotrexate). The baricitinib safety profile also appears similar to other approved RA therapies according to literature and claims databases. The potential and identified risks of baricitinib are similar to other available therapies and the background risks in the RA population; rheumatologists are accustomed to managing these risks. The baricitinib risks will be described in product labeling.

Overall, these data demonstrate that baricitinib provides a needed treatment advance for patients unable to manage their moderately to severely active RA with current therapies.

1.2. Regulatory History

On 15 January 2016, Lilly submitted a New Drug Application for baricitinib as monotherapy or in combination with non-biologic DMARDs for the treatment of adult patients with moderately to severely active rheumatoid arthritis. The proposed dosing regimen in the initial submission was 4-mg as the recommended dose with 2-mg as an option for some patients.

On 12 April 2017, FDA sent a Complete Response Letter (CRL) to the application, indicating that the "*overall benefit-risk assessments of the baricitinib 2 and 4-mg once-daily doses have identified safety concerns that outweigh efficacy observed with the proposed dosing regimen*", specifically noting the potential serious risk of thrombosis. The letter also noted a lack of consistent efficacy benefits of 4-mg over 2-mg, stated that inadequate safety exposure at 2-mg precluded an adequate risk assessment at that dose, and recommended evaluating the benefit-risk of baricitinib at 1-mg or lower doses. The letter indicated that additional clinical data were necessary to address the concerns raised in the CRL. On 06 July 2017, a Type A post-action review meeting was held between Lilly and FDA to begin discussions on a path forward.

After subsequent meetings, Lilly and FDA agreed to the contents of a resubmission. In early December 2017, the resubmission was made to FDA that included the following:

- New baricitinib clinical safety data and analyses with longer exposure duration including data from 3492 patients receiving baricitinib for a total of 7860 patient-years of exposure (approximately a 90% increase from the initial submission); additional safety data from 3 recently finished studies (Phase 3 RA, Phase 2 atopic dermatitis, and Phase 2 systemic lupus erythematosus); postmarketing data and spontaneous adverse event (AE) reports data from countries where baricitinib is approved; and contextual information on deep vein thrombosis (DVT)/pulmonary embolism (PE) rates observed with other RA therapies, including from the FDA Sentinel system and Truven Marketscan. Proposed labeling associated with the potential risk for venous thromboembolism was also included.
- New assessments of observed and modelled exposure-response data across measures and populations which continue to indicate that baricitinib doses of 1-mg or lower would not have sufficient therapeutic potential to address the unmet needs of RA patients.
- A proposed dosing regimen based on pre-specified analyses from 1 prospective Phase 3 study, new complementary efficacy analyses from 2 Phase 3 studies that provide independent confirmation, and additional observed and modelled data evaluating dose-response. This effort identified a subgroup of patients who receive a greater benefit from an initial dose of 4-mg once daily. These individuals have more refractory disease, as defined by having failed 2 or more DMARDs.
- Planned prospective, retrospective, and registry post-approval studies were proposed which will evaluate up to 13,000 baricitinib-treated patients; some studies have begun in countries where baricitinib is approved.

The resubmission includes the following proposed indication:

> *OLUMIANT (baricitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.*

Considering the concerns raised by the FDA in the CRL regarding the dosing regimen in the initial submission, Lilly's resubmission proposes the following Dosing and Administration based on additional efficacy analyses that gives physicians the ability to manage their patients according to their history of DMARD use:

> *The recommended dose of OLUMIANT is 2-mg once daily. For patients with an inadequate response or intolerance to more than one DMARD, a dose of 4-mg once daily is recommended.*
>
> *Dose tapering to 2-mg once daily may be considered for patients who have achieved sustained control of disease activity with 4-mg once daily.*

Global Regulatory Approvals

Global marketing applications for baricitinib were submitted to regulatory authorities in 2016, with the first submission to FDA in January 2016. The applications emphasized the 4-mg dose as the recommended dose and the 2-mg dose as an option for some patients. Baricitinib received its first approval in the European Union, on 13 February 2017, as monotherapy or in combination with MTX for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to, one or more DMARDs. Since that time, baricitinib has been approved for the treatment of RA in more than 40 countries, including Japan in July 2017 and Australia in January 2018. For all countries where baricitinib is launched, both the 2-mg and the 4-mg doses are approved, with the recommended dose being 4-mg once daily; additionally, baricitinib may be used as a monotherapy or in combination with methotrexate.

1.3. Disease Background, Treatment Options, and Unmet Need

Estimates place the number of adults with RA at approximately 1.3 million in the United States, close to 3 million in Europe, and approximately 1.24 million in Japan (Hunter et al. 2017, Lundkvist et al. 2008; Yamanaka et al. 2014). The prevalence of RA is approximately 2 to 3 times higher in females than males; the disease affects people of all ethnicities and races (CDC 2010; Cross et al. 2014). Rheumatoid arthritis can present at any age and the average age of onset is 55 years (Yazici and Paget. 2000).

Patients with RA experience disruption of normal immune regulation that results in the targeting of synovial tissues by the immune system, generating severe damage. The systemic inflammation and destructive joint damage from inadequately treated RA results in reduced physical function, impaired quality of life including fatigue and sleep disturbances (Matcham et al. 2014), increased risk of comorbidities (Doran et al. 2002, Picerno et al. 2015, Simon et al. 2015), and reduced life expectancy (Listing et al. 2015). Sustained high disease activity is associated with loss of approximately 10 years of life (Listing et al. 2015). Multiple organ systems contribute to the

increased morbidity, which includes cardiovascular disease, serious infections, and malignancies (Doran et al. 2002, Picerno et al. 2015, Simon et al. 2015). Importantly, signs and symptoms of RA are often reversible with appropriate treatment, but joint damage and the associated disability typically are not.

As published in current treatment guidelines, the goal of RA treatment is disease remission or low disease activity in every patient (Singh et al. 2015; Smolen et al. 2017). Treatments achieving remission or low disease activity inhibit structural damage and lessen disease burden. However, the majority of patients in the established phase of disease fail to achieve and sustain these ideal treatment goals over time. From the viewpoint of patients, their primary concern is control of debilitating and persistent symptoms such as pain and fatigue, and to maintain function (Taylor 2016).

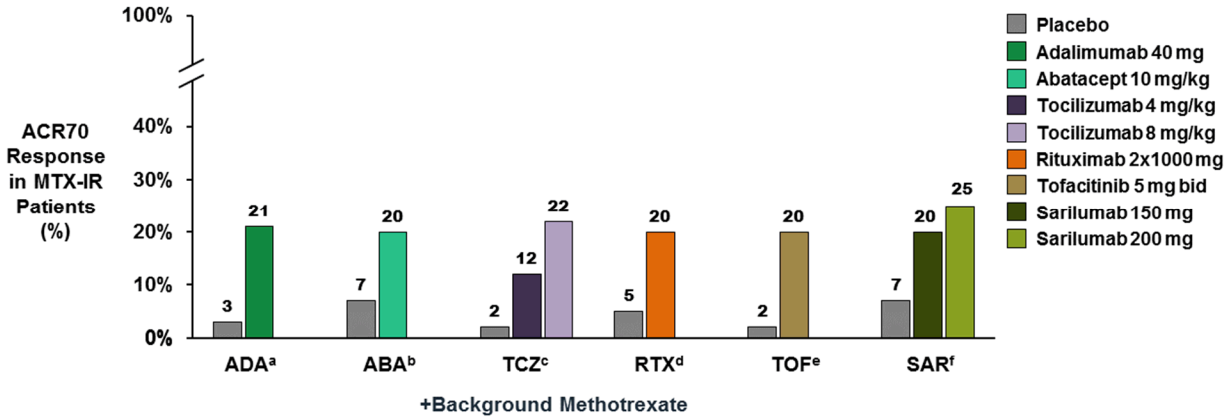
The current RA treatment guidelines recommend initiation of DMARDs at RA diagnosis and change of DMARD therapy if treatment goals are not reached in a timely manner (Singh et al. 2015; Smolen et al. 2017). DMARD options include conventional synthetic (small molecule) DMARDs (cDMARDs), biologic DMARDs (bDMARDs), and the targeted synthetic DMARD tofacitinib (a JAK inhibitor). Non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, and corticosteroids may be used to help improve symptoms associated with RA.

Methotrexate (MTX), a cDMARD, is the most frequent first-line therapy after RA diagnosis; however, for many patients, it has limited efficacy and has tolerability and safety issues. For patients with an inadequate response to MTX, the next treatment is typically combination therapy of cDMARDs with a bDMARD or tofacitinib. Existing DMARDs have been associated with a range of risks such as serious infections, heart failure, gastrointestinal perforation, and demyelinating disorders (Ruderman et al. 2012).

To ensure that the treatment target is reached, monitoring should be frequent in active disease (every 1 to 3 months); if there is no improvement by 3 months or the treatment target has not been reached by 6 months, therapy should be adjusted (Smolen et al. 2017). In patients achieving sustained remission, both American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines recommend considering dose tapering but not discontinuation of RA therapies (Singh et al. 2015; Smolen et al. 2017).

Despite the approvals of a number of novel DMARDs in recent years, ~20% of MTX-IR patients achieve ACR70, a proxy for remission (Figure 1). For bDMARD-IR patients, the ACR70 response rates are even lower. Many patients lose response over time (e.g., due to development of anti-drug antibodies for biologics) or discontinue treatment because of tolerability issues or side effects (Montag 2011; Singh 2015; Taylor 2016). In addition, 40% of RA patients use prescription opioids regularly (Curtis et al. 2017). This has advanced during the targeted DMARD era, high disease activity and high pain were the largest predictors of use (Lee et al. 2017).

Figure 1: ACR70 Response from Various DMARD MTX-IR Clinical Studies: 75% to 80% Do Not Achieve ACR70 Response



Abbreviations: ACR70 = 70% improvement in American College of Rheumatology criteria; DMARD = disease-modifying anti-rheumatic drug; MTX-IR = patients with inadequate response to MTX.

[a] Adalimumab: Keystone et al. 2004. [b] Abatacept: Kremer et al. 2006. [c] Tocilizumab: Smolen et al. 2008. [d] Rituximab: Emery et al. 2006. [e] Tofacitinib: van Vollenhoven et al. 2012. [f] Sarilumab: Genovese et al. 2015.

Incorporation of patients' perspectives is increasingly important in drug product development and regulatory decision-making (FDA 2017). In late 2017, Lilly conducted a study to assess patients' perspectives to identify, characterize, and quantify the unmet needs of RA patients that still exist despite many available treatment options. US patients with RA were identified and recruited through CreakyJoints, an online patient support community, and ArthritisPower, an online patient research registry. The sample included 258 patients currently receiving treatment with RA of whom 90% had experience with a biologic medication. Fewer than half (46%) were satisfied with the way their medication relieved their symptoms. On a scale of 0 to 10, with higher scores indicating worse status and a maximal score of 2 being an acceptable status, the study sample reported a mean (SD) of 5.06 (2.0) (Rheumatoid Arthritis Impact of Disease Score; Dougados et al. 2012). Overall 67% of patients reported moderate to severe pain, 61% reported difficulty with daily physical activities, and 74% reported moderate to severe fatigue resulting from their RA in the prior 7 days (Curtis et al 2018). Thus, these important patient symptoms are not adequately addressed with current treatments, highlighting the unmet need existing in this population.

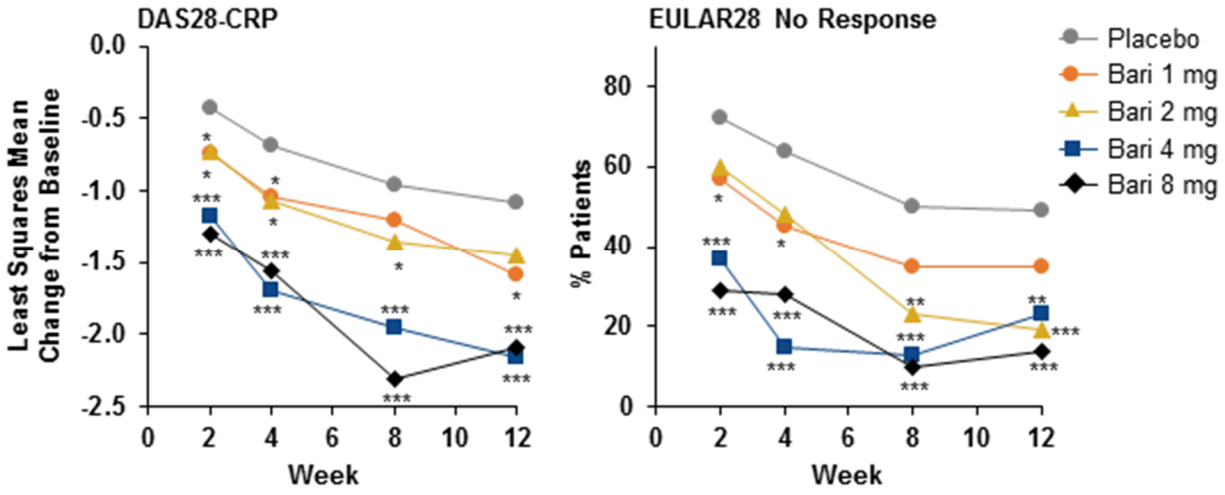
In conclusion, in order to optimize short and long-term health outcomes, achieving timely and sustained remission (or LDA) is the treatment goal for all patients. Patients who do not achieve treatment goals require treatment escalation, commonly changing to a treatment with a different mechanism of action. Therefore, the need exists for new therapeutic alternatives offering substantial efficacy—including effect on disease activity and protection against progression of joint damage—with an acceptable safety profile.

1.4. Phase 3 Dose Selection from Observed and Modelled Dose Ranging Data

Two Phase 2 studies were conducted in patients with RA to facilitate dose selection for Phase 3 (JADC and JADA). A third Phase 2 study was conducted in Japan and the results supported the earlier findings (JADN).

The initial proof-of-concept study, JADC, showed that the 4-mg dose was efficacious as compared to placebo, and suggested that higher doses of 7 mg and 10 mg did not provide additional benefit. The Phase 2b study, JADA, showed improvements in disease activity over time for the 1- and 2-mg doses, and the greatest improvements for the 4- and 8-mg doses, which were comparable to each other (DAS28-CRP Panel, Figure 2). When looking at the proportion of patients with no response at each time-point, the highest proportion (other than for placebo) was seen for 1-mg, with improvement seen for the 2-mg dose and the most rapid and consistent benefit observed with the 4-mg and 8-mg doses (EULAR28 No Response Panel, Figure 2). A similar pattern was seen in the Japan Phase 2b study, JADN.

Figure 2: Dose Ranging Efficacy from Study JADA



Abbreviations: Bari = baricitinib; DAS28-CRP = Disease Activity Score in 28 joints-C-reactive protein; EULAR28 = European League Against Rheumatism responder index based on 28-joint count.
p-value versus placebo: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.
Study JADA (N = 301) included methotrexate inadequate responders in US, Europe, India, and Mexico.
Imputation methods: observed data for DAS28-CRP. NRI for EULAR28 No Response.

Exposure-response (E-R) analysis was conducted for DAS28-CRP based on data from Study JADA to inform Phase 3 dose selection. The E-R relationship showed that concentrations for 4-mg resided predominantly on the flat portion of the E-R curve, where patients have an optimal probability of achieving a response (Figure 3). Concentrations for 2-mg were lower and encompassed the ascending portion of the curve. Concentrations for 1-mg reside almost entirely on the ascending portion of the curve, where many patients would not achieve a robust response.

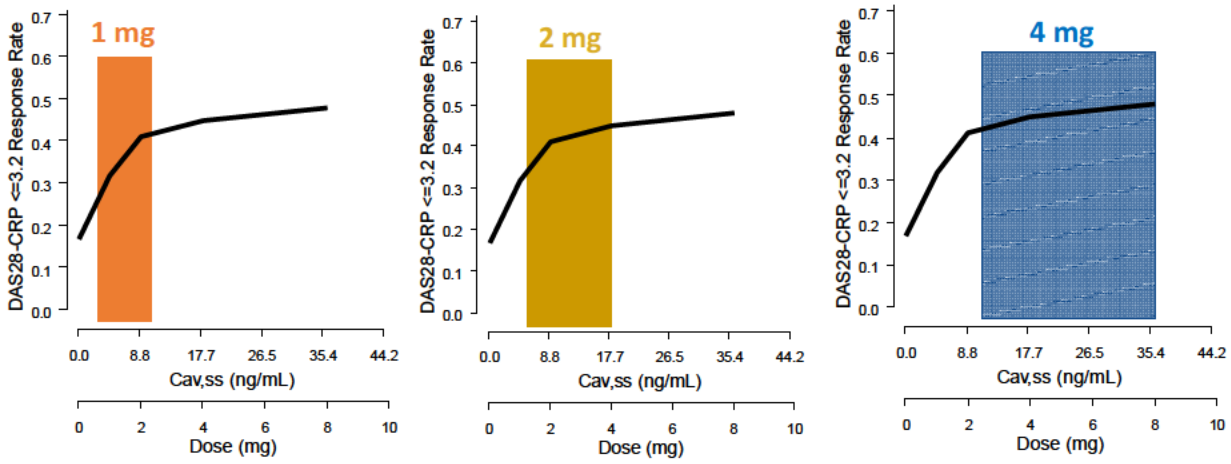
These findings supported the choice of 4-mg once daily as the primary dose to be tested in Phase 3 and 2-mg as a second dose that might be suitably effective for some patients. Further evaluation of 1-mg or lower doses would not offer patients an acceptable probability of

achieving treatment goals recommended by contemporary guidelines (to rapidly induce sustained control) (Singh et al. 2015; Smolen et al. 2017).

Accordingly, both 2-mg and 4-mg were included in 2 adequate and well-controlled studies vs placebo. The 4-mg dose was also included in 2 studies versus oral and injectable standard of care DMARDs, as this dose had the highest probability of potentially showing superiority to these active comparators. Use of a single dose in these studies also allowed for group sizes and analysis schemes that facilitated robust comparisons between the active treatments.

Final E-R analyses that incorporated available data from all phase 2 and 3 studies further confirmed the phase 2 findings (Section 5.7). See Section 4 for additional data and discussion of dose selection.

Figure 3: Estimated Exposure-Response Relationship of DAS28-CRP <=3.2 at Week 12 in cDMARD-IR Patients based on the Phase 2 Study JADA

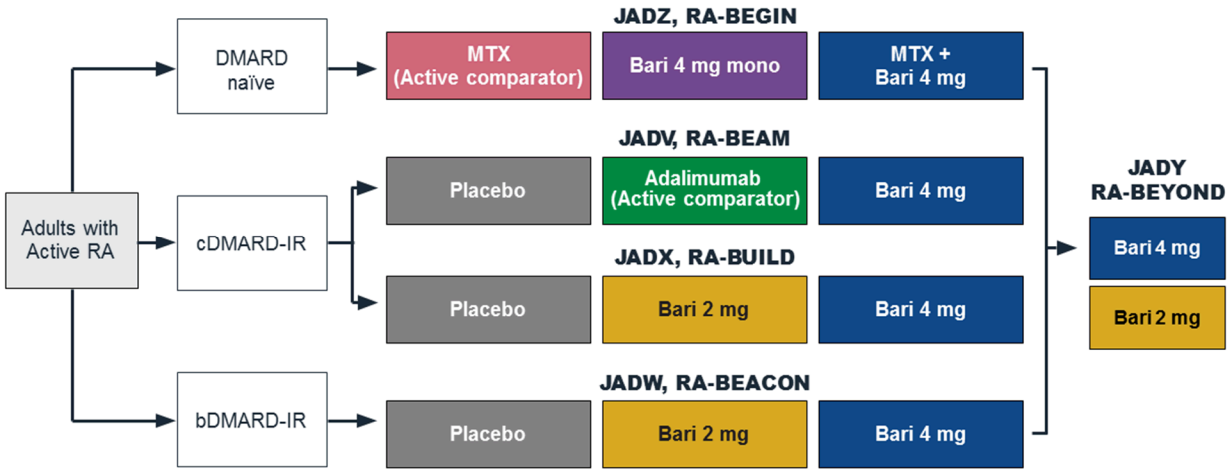


Abbreviations: Cav,ss = daily average concentration at steady state of dosing; cDMARD = conventional disease-modifying antirheumatic drug; CRP = C-reactive protein; DAS28= Disease Activity Score based on the 28 diarthrodial joint count; IR =inadequate responder.
Shaded areas indicate the range (5^{th}-95^{th} percentile) of Cav,ss for the corresponding doses.

1.5. Efficacy

The Phase 3 program for baricitinib includes four completed randomized, controlled trials (JADW, JADX, JADV, and JADZ) and one ongoing long-term extension study (JADY) that incorporates a randomized dose taper component (Figure 4 and Table 1). Patients who completed the Phase 3 studies as well as the Phase 2 Study JADA could enter the long-term extension study JADY. A summary of key findings related to efficacy is presented as part of this Synopsis, with additional detail provided about each study in Section 5.

Figure 4: Overview of Baricitinib Phase 3 Studies



Abbreviations: Bari = baricitinib; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; DMARD = disease-modifying anti-rheumatic drug; IR = inadequate responder; mono = monotherapy; MTX = methotrexate; RA = rheumatoid arthritis.
For JADZ: Indicated treatment did not include a background DMARD.
For JADV: Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
For JADX: Indicated treatment is in addition to existing (0-2) background cDMARDs.
For JADW: Indicated treatment is in addition to existing (1-2) background cDMARDs.

Table 1: Key Features of Baricitinib Phase 3 Studies

	JADW N=527	**JADX N=684**	**JADV N=1305**	**JADZ N=584**
Patient Population (History of prior RA therapy)	bDMARD-IR (cDMARD-IR[a])	cDMARD-IR (bDMARD-naïve)	cDMARD-IR (bDMARD-naïve)	DMARD-Naïve
Background DMARD Therapy During Study	1 or 2 cDMARD	0 to 2 cDMARD	MTX ±1 other cDMARD	None
Treatment Arms	Placebo Bari 2-mg Bari 4-mg	Placebo Bari 2-mg Bari 4-mg	Placebo Adalimumab Bari 4-mg	MTX Bari 4-mg mono MTX + Bari 4-mg
Timepoint of Primary Endpoint (ACR20)	Week 12	Week 12	Week 12	Week 24
Primary Objective	Superiority of 4-mg vs placebo	Superiority of 4-mg vs placebo	Superiority of 4-mg vs placebo	Non-inferiority of 4-mg vs MTX
Study Duration (Weeks)	24	24	52	52
Structure Assessed	No	Yes	Yes	Yes
Primary Publication	Genovese et al. 2016	Dougados et al. 2016	Taylor et al. 2017	Fleischmann et al. 2017
PRO Publication	Smolen et al. 2017	Emery et al. 2017	Keystone et al. 2017	Schiff et al. 2017

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; Bari = baricitinib; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; DMARD = disease-modifying anti-rheumatic drug; IR = inadequate responder; mono = monotherapy; MTX = methotrexate; PRO = patient-reported outcome; RA = rheumatoid arthritis, vs = versus.
[a] JADW patients were inadequate responders to both bDMARDs and cDMARDs.

1.5.1. Efficacy Endpoints

The pivotal Phase 3 studies measured efficacy using endpoints that encompass four key domains of RA: signs and symptoms (including achievement of clinical remission of disease activity), physical function or disability, other patient-reported outcomes (PROs), and radiographic progression of structural joint damage. See Section 5.1 for details about the components of the composite scores and other measures of efficacy as well as the clinical relevance and importance of these efficacy measures. Secondary endpoints that were controlled for multiplicity are referred to as the **key secondary endpoints**.

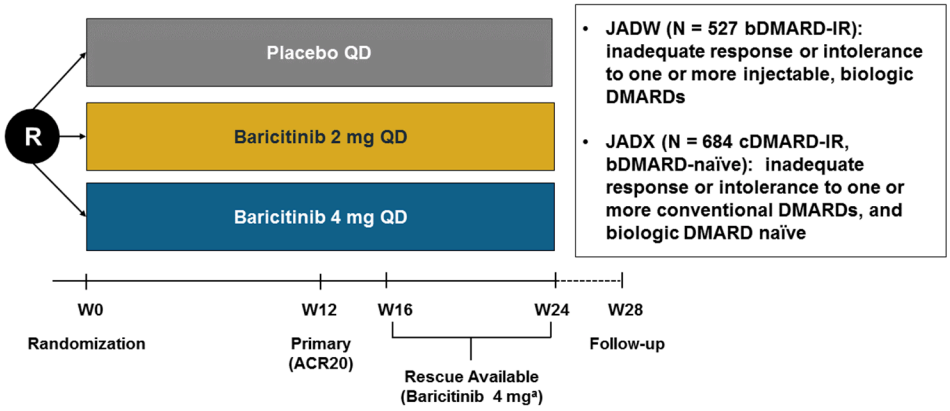
1.5.2. Efficacy Results

1.5.2.1. Phase 3 Studies JADW, JADX, JADZ, and JADV

In all of the Phase 3 studies, the primary objectives were met. Compared to placebo in Studies JADW, JADX, and JADV and active comparator in Studies JADZ (methotrexate) and JADV (adalimumab), baricitinib demonstrated rapid, durable improvements for relevant domains of efficacy across the RA treatment continuum.

The designs for the 2 studies comparing baricitinib 2-mg and 4-mg to placebo, JADW and JADX, were very similar, with the main difference being the patient population (Figure 5).

Figure 5: Study Design for JADW and JADX



Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; DMARD = disease-modifying anti-rheumatic drug; IR = inadequate responder; QD = once daily; R = randomization; W = week.
[a] Initial treatment assignment remained blinded.
For JADW: Indicated treatment is in addition to existing (1-2) background cDMARDs.
For JADX: Indicated treatment is in addition to existing (0-2) background cDMARDs.

Study JADW (bDMARD-IR and cDMARD-IR) included 527 randomized and treated patients who had all failed a biologic DMARD, with approximately 40% having failed multiple classes of bDMARDs. The primary objective was met: 4-mg was superior to placebo based on ACR20 (Table 2). All key secondary objectives were met except for simplified disease activity index (SDAI) remission at Week 12, which is a challenging endpoint to achieve in such a refractory population, particularly after this relatively short duration of treatment. However, improvements were seen for other stringent efficacy measures including ACR70 response rate. A dose-response

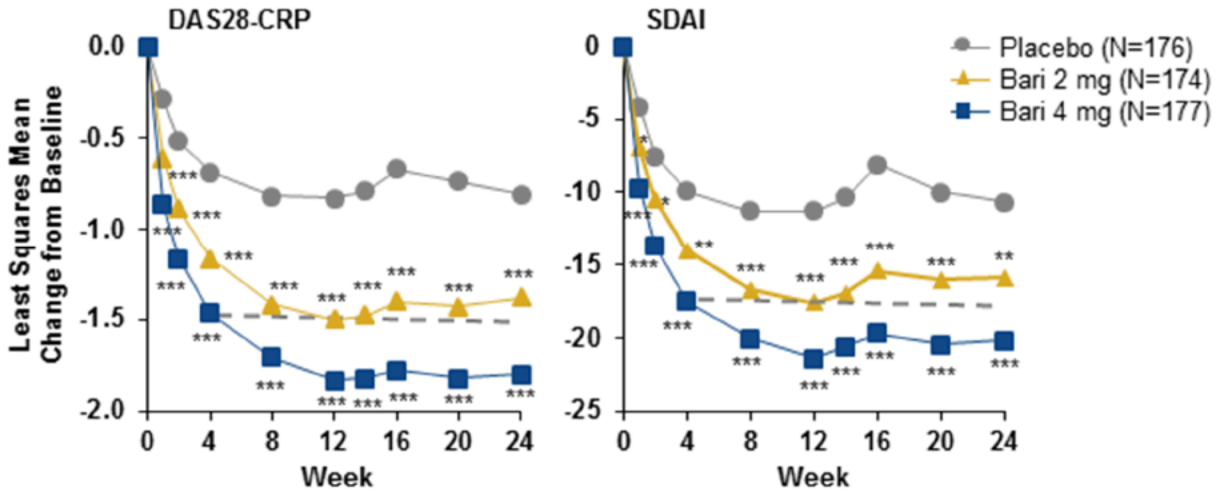
relationship was also observed. When evaluated by continuous measures, which are most sensitive to detect differences between treatment groups, both the 2-mg and 4-mg doses showed significant improvement over placebo as early as Week 1 (Figure 6). However, throughout the study the 4-mg dose produced improvements in disease activity that were at least 1.5x as large as the treatment effect of 2-mg over placebo. By 4 weeks, 4-mg produced a degree of improvement that was as large as 2-mg ever achieved during the full 6 months (Figure 6, indicated by the dashed horizontal line).

Table 2: Summary of Primary and Secondary Endpoint Results in Study JADW (bDMARD-IR and cDMARD-IR)

				p-value for Indicated Dose Compared to Placebo	
Endpoint	**Placebo[a] N=176**	**BARI 2-mg[a] N=174**	**BARI 4-mg[a] N=177**	**BARI 2-mg[b]**	**BARI 4-mg[b]**
ACR20	27.3%	48.9%	55.4%	≤0.001	≤0.001
Δ DAS28-CRP	-0.83	-1.49	-1.79	≤0.001	≤0.001
Δ HAQ-DI	-0.17	-0.37	-0.40	≤0.001	≤0.001
SDAI Remission	1.7%	2.3%	5.1%	0.723	0.140
SDAI LDA	9.1%	22.4%	28.2%	≤0.001	≤0.001
ACR50	8.0%	20.1%	28.2%	0.002	≤0.001
ACR70	2.3%	12.6%	11.3%	≤0.001	0.002

Abbreviations: Δ=least squares mean change from baseline; ACR20/50/70=20/50/70% improvement in American College of Rheumatology criteria; BARI=baricitinib; DAS28-CRP=Disease Activity Score in 28 joints-C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=low disease activity; SDAI=Simplified Disease Activity Index.
a Indicated treatment is in addition to existing (1-2) background cDMARDs
b Colored cells indicate results for key objectives, i.e. those included in the multiplicity control plan. Green = significant with multiplicity control. Yellow = significant but without multiplicity control. Orange = not significant. Cells without highlighting indicate secondary endpoints not included in multiplicity control.
Data shown are from Week 12.
Imputation methods: mBOCF for Δ DAS28-CRP and Δ HAQ-DI. NRI for other endpoints.

Figure 6: Improvements in Disease Activity in Study JADW (bDMARD-IR and cDMARD-IR)

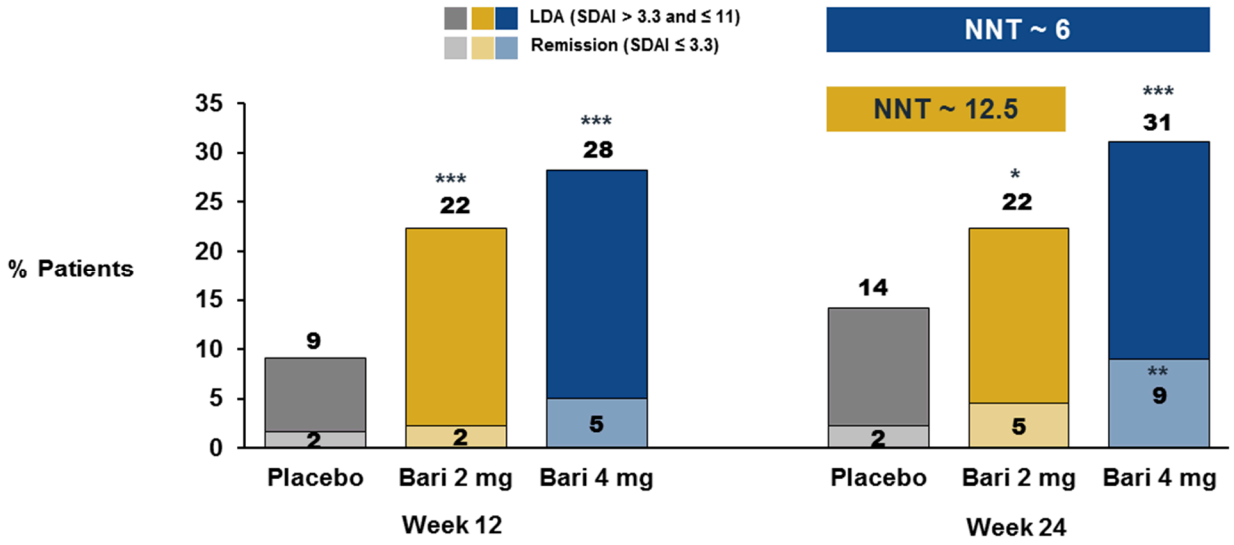


Abbreviations: Bari=baricitinib; bDMARD-IR=biologic disease-modifying anti-rheumatic drug inadequate responder; cDMARD-IR=conventional disease-modifying anti-rheumatic drug inadequate responder; DAS28-CRP=Disease Activity Score in 28 joints-C-reactive protein; N=number of patients; SDAI=simplified disease activity index.
P-value versus Placebo: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

Indicated treatment is in addition to existing (1-2) background cDMARDs.
Dashed horizontal lines indicate level of response seen for baricitinib 4-mg at Week 4.
Imputation method: mLOCF.

The achievement of treatment targets, represented with SDAI remission (SDAI ≤3.3) and low disease activity (SDAI ≤11) were evaluated (Figure 7). At Week 12, neither baricitinib group showed a significant improvement in SDAI ≤3.3 response rate compared to placebo. However, both baricitinib groups showed a significant improvement in SDAI ≤11 response rate at Week 12 (p≤0.001 for both doses). The 4-mg group showed significant improvement in SDAI ≤3.3 response rate compared to placebo beginning at Week 14 through later timepoints, including Week 24. The responses for SDAI were consistent across the completed Phase 3 studies (Figure 44, Figure 50, and Figure 57).

Figure 7: SDAI Response Rates in JADW (bDMARD-IR and cDMARD-IR)



Abbreviations: Bari = baricitinib; bDMARD-IR = biologic disease-modifying anti-rheumatic drug inadequate responder; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; LDA = low disease activity; NNT = number needed to treat; SDAI = Simplified Disease Activity Index.
p-value versus placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001.
Total height of each bar = SDAI ≤11. Lower (paler) portion of each bar = SDAI ≤3.3.
Indicated treatment is in addition to existing (1-2) background cDMARDs.
Imputation method: NRI.

Study JADX (cDMARD-IR and bDMARD-naïve) had a design similar to JADW. This study included 684 randomized and treated patients with inadequate response or intolerance to one or more conventional DMARDs (Figure 5). The primary and all key secondary objectives were met for both doses of baricitinib compared to placebo (Table 3). Dose-response in JADX was present (Figure 8), but less marked than in the more refractory JADW population (Figure 6).

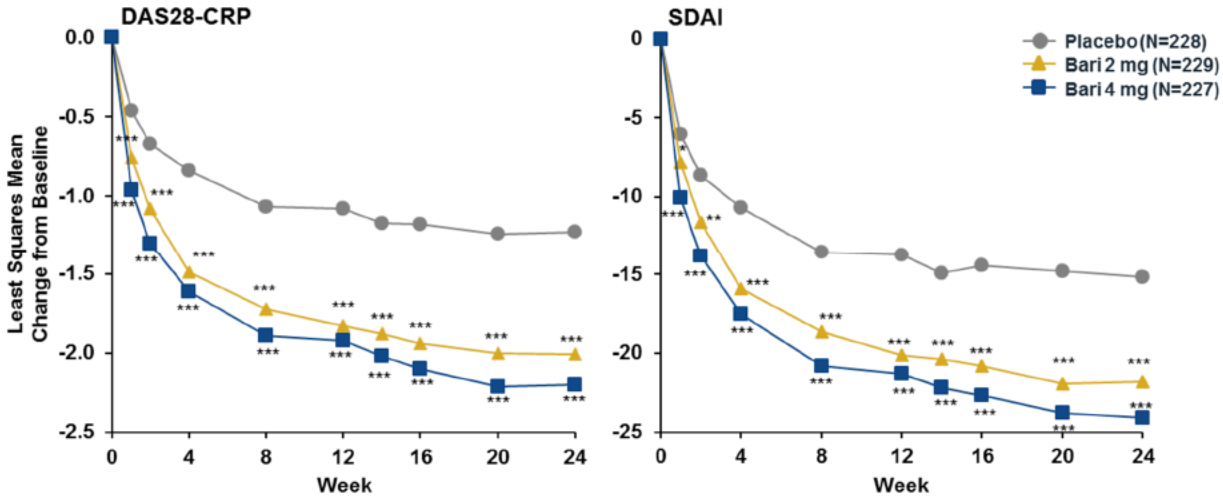
Compared to placebo, a statistically significant decrease in radiographic progression of joint damage based on mTSS was observed at Week 24 for the baricitinib groups (p=0.043 for 2-mg and p=0.004 for 4-mg) (Figure 9). The comparison of 4-mg to placebo remained statistically significant in analyses using all observed data as randomized.

Table 3: Summary of Primary and Secondary Endpoint Results in Study JADX (cDMARD-IR and bDMARD-naïve)

Endpoint	Placebo N=228	BARI 2-mg N=229	BARI 4-mg N=227	p-value for Indicated Dose Compared to Placebo	
				BARI 2-mg	BARI 4-mg
ACR20	39.5%	65.9%	61.7%	≤0.001	≤0.001
Δ DAS28-CRP	-1.1	-1.8	-1.9	≤0.001	≤0.001
Δ HAQ-DI	-0.34	-0.54	-0.53	≤0.001	≤0.001
SDAI Remission	0.9%	9.2%	8.8%	≤0.001	≤0.001
MJS Duration, mins	60.0	44.4	34.6	0.002	≤0.001
MJS Severity NRS	4.1	3.5	3.4	0.002	≤0.001
Worst Joint Pain NRS	4.7	3.8	3.8	≤0.001	≤0.001
Worst Tiredness NRS	4.5	4.1	4.0	0.049	0.027
SDAI LDA	19.7%	33.2%	34.8%	0.002	≤0.001
ACR50	12.7%	33.6%	33.5%	≤0.001	≤0.001
ACR70	3.1%	17.9%	18.1%	≤0.001	≤0.001

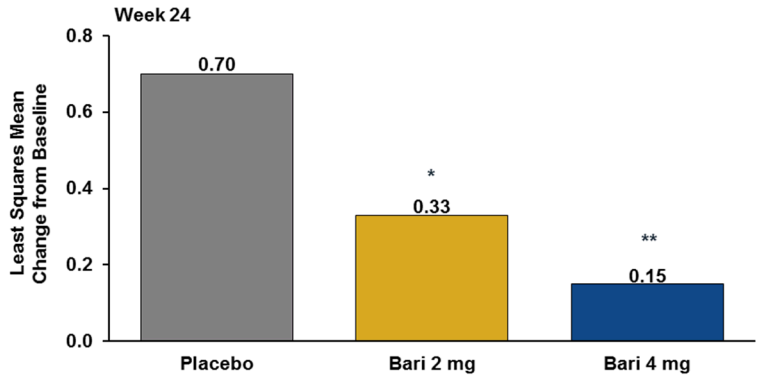
Abbreviations: Δ=least squares mean change from baseline; ACR20/50/70=20%/50%/70% improvement in American College of Rheumatology criteria; DAS28-CRP=Disease Activity Score in 28 joints-C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=low disease activity; MJS=morning joint stiffness; NRS=numeric rating scale; SDAI=Simplified Disease Activity Index.
Colored cells indicate results for key objectives, i.e. those included in the multiplicity control plan. Green = significant with multiplicity control. No highlighting = secondary endpoint not included in multiplicity control.
Values shown are Week 12. MJS duration values are median, other diary values are LS mean.
Indicated treatment is in addition to existing (0-2) background cDMARDs
Imputation methods: mBOCF for Δ DAS28-CRP and Δ HAQ-DI. LOCF for diary data. NRI for other endpoints.

Figure 8: Improvements in Disease Activity in Study JADX (cDMARD-IR and bDMARD-naïve)



Abbreviations: Bari=baricitinib; bDMARD-IR=biologic disease-modifying anti-rheumatic drug inadequate responder; cDMARD-IR=conventional disease-modifying anti-rheumatic drug inadequate responder; DAS28-CRP=Disease Activity Score in 28 joints-C-reactive protein; N=number of patients; SDAI=simplified disease activity index.
P-value vs. Placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001
Indicated treatment is in addition to existing (0-2) background cDMARDs
Imputation method: mLOCF.

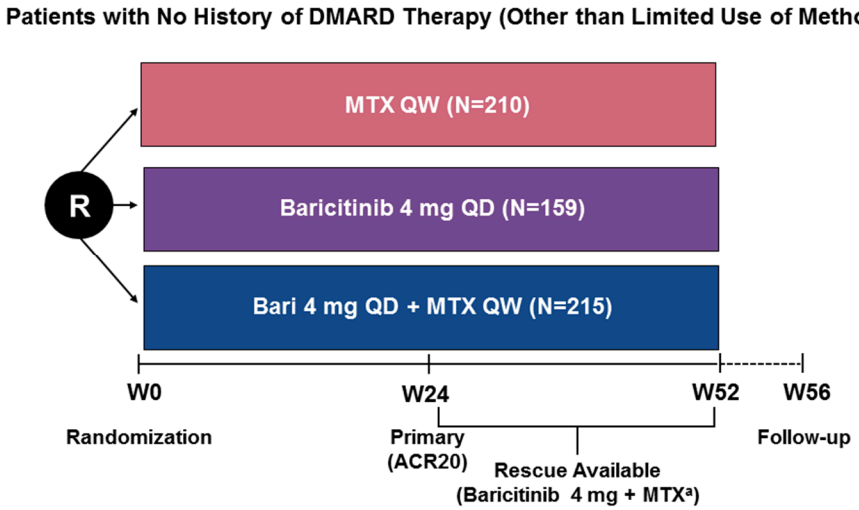
Figure 9: mTSS Change from Baseline to Week 24 in JADX (cDMARD-IR and bDMARD-naïve)



Abbreviations: Bari = baricitinib; bDMARD=biologic disease-modifying anti-rheumatic drug; cDMARD-IR=conventional disease-modifying anti-rheumatic drug inadequate responder; mTSS = modified Total Sharp Score
*p≤0.05, **p≤0.01 vs placebo.
Imputation method: LE.
Indicated treatment is in addition to existing (0-2) background cDMARDs

Study JADZ (DMARD-naïve) included 584 randomized and treated patients and compared baricitinib 4-mg alone or in combination with oral methotrexate to methotrexate alone in patients who were DMARD-naïve (Figure 10). The primary objective was met: 4-mg was superior to MTX based on ACR20 response (Table 4). When administered alone or in combination with MTX, baricitinib 4-mg was superior to MTX alone on all clinical efficacy measures at Week 24. For slowing radiographic joint damage, baricitinib monotherapy was numerically (but not significantly) better than MTX, which is itself a DMARD that slows joint damage. Baricitinib plus MTX was superior to MTX alone for slowing radiographic joint damage.

Figure 10: Study Design for JADZ (DMARD-naïve)



Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; QD = once daily; QW = once per week; W = week.
[a] Initial treatment assignment remained blinded.
Indicated treatment did not include a background cDMARD.

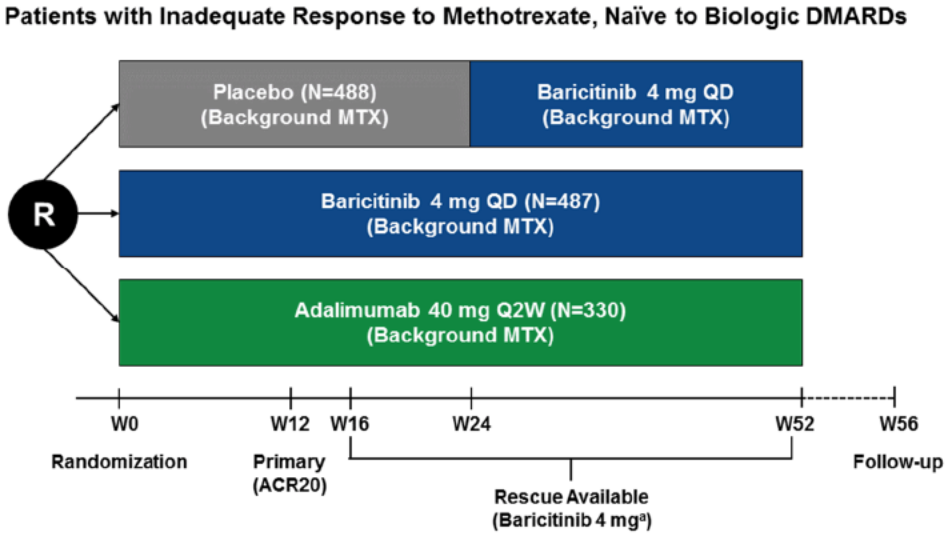
Table 4: Summary of Primary and Secondary Endpoint Results in Study JADZ (DMARD-naïve)

				p-value for Indicated Comparisons	
Endpoint	**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**
ACR20	61.9%	76.7%	78.1%	0.003	≤0.001
Δ DAS28-CRP	-2.06	-2.75	-2.84	≤0.001	≤0.001
Δ HAQ-DI	-0.72	-1.00	-0.95	≤0.001	≤0.001
SDAI Remission	10.5%	22.0%	22.8%	0.003	≤0.001
Δ mTSS	0.6	0.4	0.3	0.158	0.026
ACR50	43.3%	59.7%	63.3%	0.002	≤0.001
ACR70	21.4%	42.1%	39.5%	≤0.001	≤0.001

Abbreviations: Δ = least squares mean change from baseline; ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; mTSS = modified Total Sharp Score; SDAI = Simplified Disease Activity Index.
Colored cells indicate results for key objectives, i.e. those included in the multiplicity control plan. Green = significant with multiplicity control. Orange = not significant. No highlighting = secondary endpoint not included in multiplicity control.
Values shown are from Week 24.
Treatment did not include a background cDMARD.
Imputation methods: mBOCF for Δ DAS28-CRP and Δ HAQ-DI. LE for Δ mTSS. NRI for other endpoints.

Study JADV (cDMARD-IR and bDMARD-naïve) included 1305 randomized and treated patients and compared baricitinib 4-mg to placebo and to adalimumab (Figure 11). All patients continued their stable background methotrexate to allow optimal efficacy of adalimumab. Rescue was available from Week 16; patients randomized to placebo who were not rescued were switched to baricitinib 4-mg after 24 weeks. The primary objective was met: baricitinib 4-mg was superior to placebo for ACR20 response (Table 5). All key secondary objectives comparing baricitinib 4-mg to placebo were also met. Additionally, 2 key secondary objectives comparing baricitinib 4-mg to adalimumab with background methotrexate, were both met. Importantly, adalimumab with background methotrexate performed well compared to placebo, in line with the expectations used to power the study (Breedveld et al. 2006). Both therapies separated clearly from placebo, but with significantly larger improvements for baricitinib 4-mg compared to adalimumab that were sustained over the year of treatment (DAS28 and SDAI in Figure 12). For PROs drawn from daily electronic diary evaluations, both therapies produced improvements over placebo, with significantly greater improvements for baricitinib compared to adalimumab across each symptom (Figure 13).

Figure 11: JADV (cDMARD-IR and bDMARD-naïve) Study Design



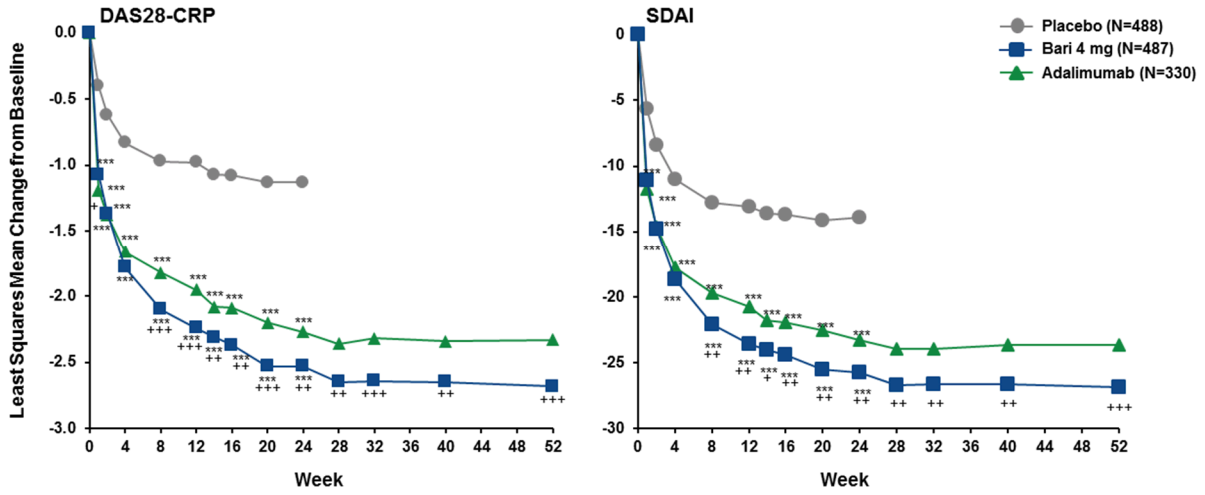
Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; MTX = methotrexate; Q2W = once every 2 weeks; QD = once daily; W = week.
[a] Initial treatment assignment remained blinded.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.

Table 5: Summary of Primary and Secondary Endpoint Results in Study JADV (cDMARD-IR and bDMARD-naïve)

				p-value for Indicated Comparisons	
Endpoint	**Placebo N=488**	**Bari 4-mg N=487**	**ADA N=330**	**4-mg vs PBO**	**4-mg vs Ada**
ACR20	40.2%	69.6%	61.2%	≤0.001	0.014
Δ DAS28-CRP	-0.96	-2.19	-1.91	≤0.001	≤0.001
Δ HAQ-DI	-0.34	-0.65	-0.55	≤0.001	≤0.001
SDAI Remission	1.8%	8.4%	7.3%	≤0.001	0.600
MJS Duration, mins	60.0	27.1	36.6	≤0.001	0.024
MJS Severity NRS	4.1	3.0	3.5	≤0.001	0.002
Worst Joint Pain NRS	4.6	3.4	4.0	≤0.001	≤0.001
Worst Tiredness NRS	4.3	3.6	3.9	≤0.001	0.028
Δ mTSS (Wk 24)	0.9	0.4	0.3	≤0.001	0.594
ACR50	16.8%	45.0%	34.8%	≤0.001	≤0.001
ACR70	4.7%	18.9%	12.7%	≤0.001	≤0.001

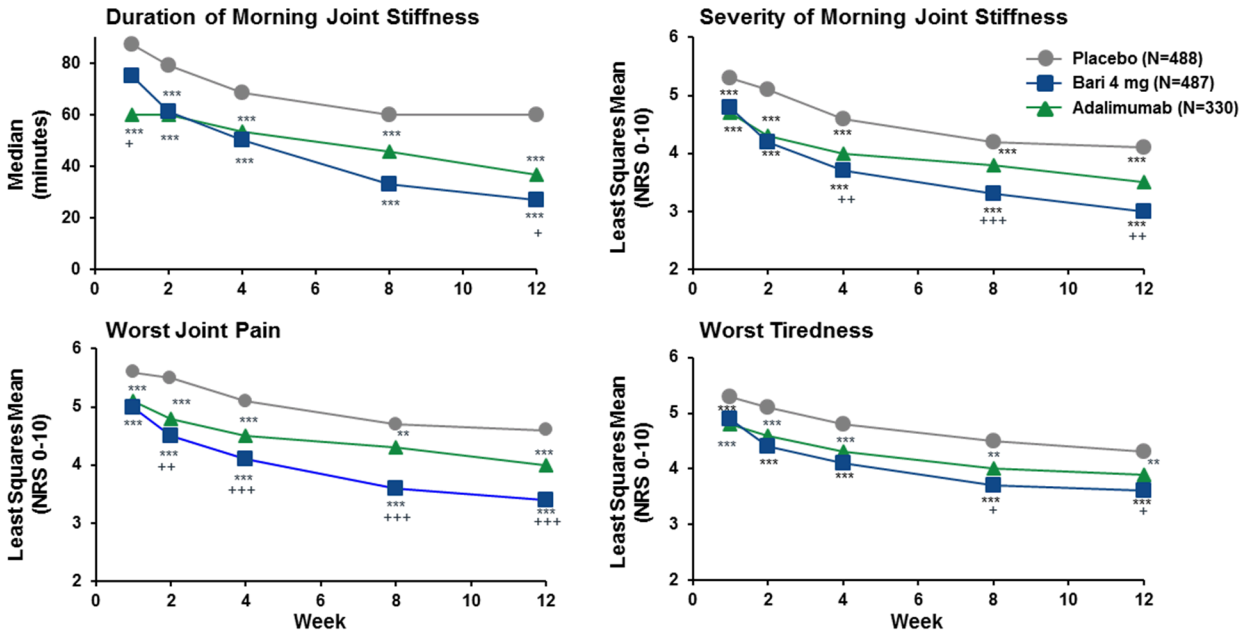
Abbreviations: Δ = least squares mean change from baseline; ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; Bari = baricitinib; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug inadequate responder; HAQ-DI = Health Assessment Questionnaire-Disability Index; MJS = morning joint stiffness; NRS = numeric rating scale; SDAI = Simplified Disease Activity Index.
Colored cells indicate results for key objectives, i.e. those included in the multiplicity control plan. Green = significant with multiplicity control. No highlighting = secondary endpoint not included in multiplicity control.
Values shown are from Week 12 unless otherwise specified.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
MJS duration values are median, other diary values are LS mean.
Imputation methods: mBOCF for Δ DAS28-CRP and Δ HAQ-DI. LE for Δ mTSS. LOCF for diary data. NRI for other endpoints.

Figure 12: JADV (cDMARD-IR and bDMARD-naïve) Improvements in Disease Activity



Abbreviations: Bari = baricitinib; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; SDAI = Simplified Disease Activity Index.
P-value vs. placebo: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001; P-value vs. Adalimumab: + p ≤ 0.05; ++ p ≤ 0.01; +++ p ≤ 0.001.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
Imputation method: mLOCF.

Figure 13: Patient Reported Outcomes Assessed by Electronic Diary through Week 12 in JADV (cDMARD-IR and bDMARD-naïve)



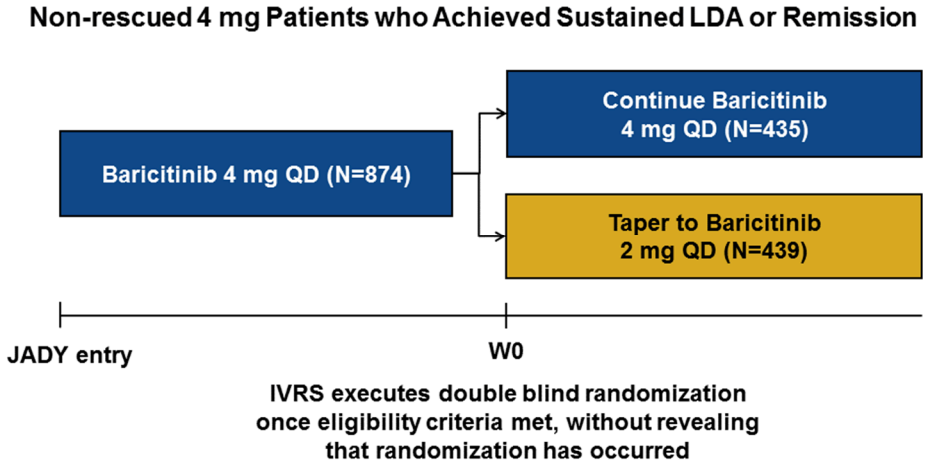
Abbreviations: Bari = baricitinib; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; NRS = numeric rating scale.
P-value vs. placebo: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001; P-value vs. Adalimumab: + p ≤ 0.05; ++ p ≤ 0.01; +++ p ≤ 0.001.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
Imputation method: LOCF.

1.5.2.2. Extension Study JADY

Patients completing any of the pivotal Phase 3 studies were eligible for the long-term extension, Study JADY. Sustained efficacy was observed in Study JADY across relevant measures over an additional 96 weeks of treatment following completion of the originating study (Figure 60).

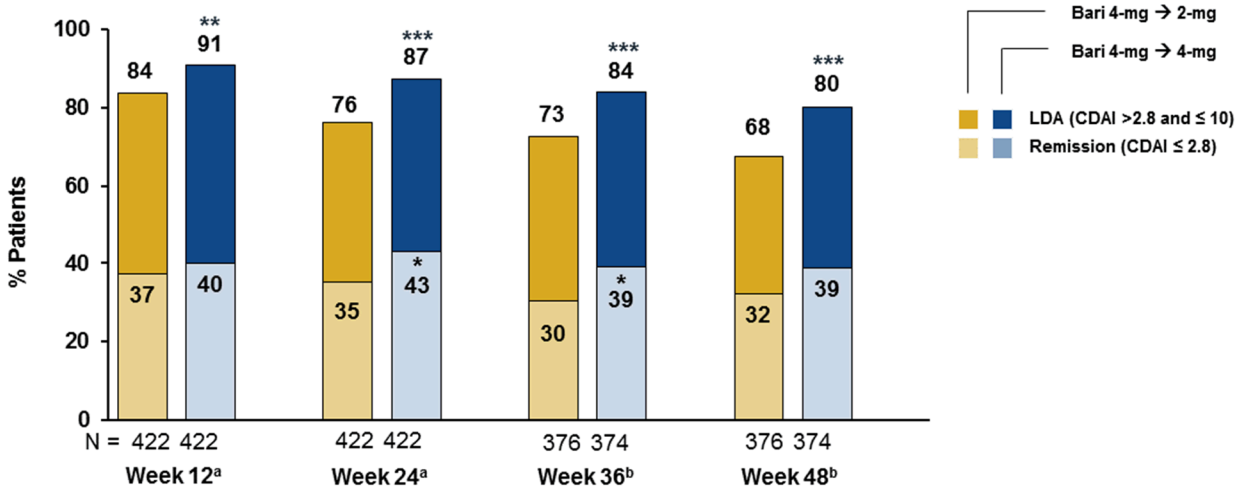
JADY included a substudy to assess the ability to dose taper from baricitinib 4-mg to 2-mg after achieving sustained disease control (Figure 14). Dose taper after induction of sustained remission is a treatment strategy recommended in professional guidelines (Singh et al. 2015, Smolen et al. 2017). Patients eligible for dose taper included those who had received baricitinib 4-mg for at least 15 months, had not been rescued, and achieved sustained LDA or remission. These patients were randomized to continue on baricitinib 4-mg or to taper to 2-mg, without knowledge of the investigator or patient, and with dose-blinding. The Clinical Disease Activity Index (CDAI) was used to determine dose taper eligibility and was also used as the principal outcome measure. The CDAI includes the same components as SDAI, except for CRP, is well accepted, is validated, and as it requires no laboratory results to calculate, it permits immediate determination of eligibility at study visits. In the dose taper substudy, 874 DMARD-IR patients in sustained LDA or remission on 4-mg (92% with a background of MTX) were randomized as of 01 April 2017. The proportions of patients maintaining LDA or remission were significantly higher with continued 4-mg compared to 2-mg dose taper (Figure 15). These randomized, blinded findings further establish that the efficacy of 4-mg significantly exceeds that of 2-mg. However, most patients in both treatment groups maintained LDA or remission, supporting the dose taper treatment strategy. Fewer than 1 in 5 patients required rescue following dose taper. Among patients who did require rescue, by Week 24 post-rescue two-thirds were able to recapture their prior level of disease control; of the remaining patients, approximately two-thirds were able to recapture their prior level of disease control beyond Week 24.

Figure 14: JADY Randomized Dose Taper Substudy Design



Abbreviations: IVRS = interactive voice-response system; LDA = low disease activity; QD = daily; W = week.
Includes patients from Studies JADV, JADX, and JADW.

Figure 15: CDAI Remission and Low Disease Activity Rates after Dose Taper through Week 48, Patients from Studies JADW, JADX, and JADV Continuing in JADY



Abbreviations: Bari = baricitinib; CDAI = Clinical Disease Activity Index; LDA = low-disease activity.
Total height of each bar = CDAI ≤ 10 (LDA or remission). Data are from DMARD-IR studies: JADW, JADX, JADV. Patients from JADZ are not included in this analysis (patients in JADZ were DMARD-naïve and had a different randomization criterion [remission]).
P-value between groups: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$
a Week 12 and 24 includes patients who had been randomized 24 weeks prior to the datacut.
b Week 36 and 48 includes patients who had been randomized 48 weeks prior to the datacut.
Imputation method: NRI.

1.5.3. Dose-Response Evaluation Based on RA Patient Population

Differences in efficacy by baricitinib dose were observed in both JADW (bDMARD-IR and cDMARD-IR) and JADX (cDMARD-IR and bDMARD-naïve). The largest differences were observed in JADW (Figure 6), in which all patients had prior treatment experience that included at least one cDMARD and at least one TNFi. When considering the results of JADX (Figure 8) alongside JADW (Figure 6), the difference between doses was largest in patients with more refractory disease, based on history of prior DMARD-IR. To further explore this finding, patients from Study JADX were separated into groups who had failed a single DMARD (1DMARD-IR; 44% of the total) or 2 or more DMARDs (2+DMARD-IR; 56% of the total). Other than treatment history, baseline characteristics between these groups were comparable (Table 35).

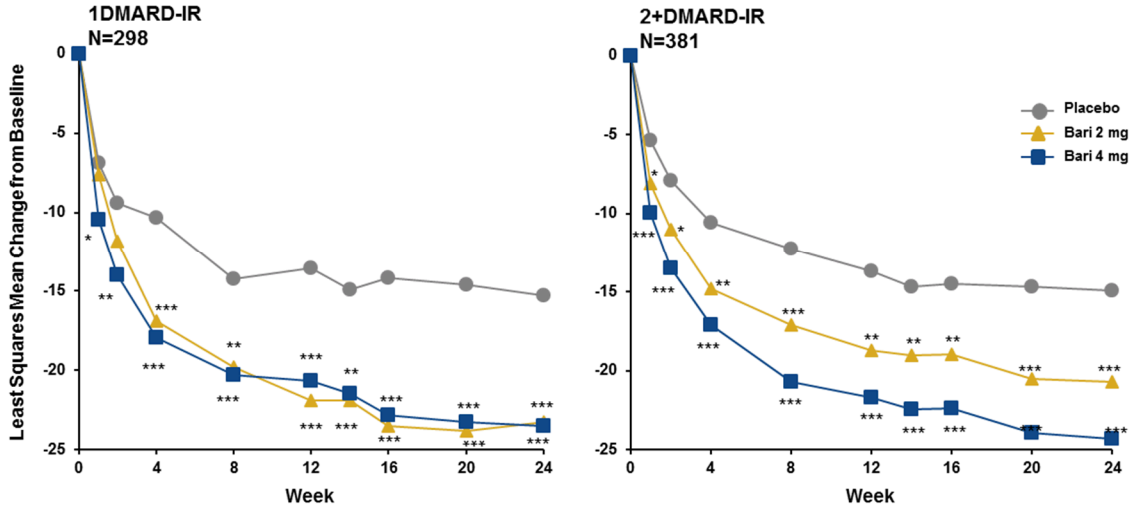
As observed in the a priori results from JADW and JADX, improvements in disease activity for the 2- and 4-mg doses appeared generally similar in the less refractory, 1DMARD-IR subgroup from JADX (Figure 16). In contrast, there was a clear dose response in the more refractory, 2+DMARD-IR subgroup from JADX (Figure 16). These observations support the dose response findings in JADW; specifically that in the 2+DMARD-IR group the treatment effect of 4-mg versus placebo commonly added >50% relative improvement compared to the treatment effect of 2-mg versus placebo in SDAI. Examination of between-dose differences in JADW and the 2+DMARD-IR group from JADX showed that the 4-mg dose had significantly larger improvement in DAS28-CRP and SDAI compared to the 2-mg dose at most timepoints through Week 24. When using area under the curve analysis, which accounts for the totality of the data

over time, the difference between doses was also significant for both JADW and the 2+DMARD-IR group from JADX.

Supporting the observations from Studies JADW and JADX, exposure-response analyses based on all Phase 2 and Phase 3 data show that the more refractory bDMARD-IR and 2+cDMARD-IR patients had higher EC50 and EC80 (concentrations required to achieve 50% and 80% maximum response, respectively) values than the less refractory 1cDMARD-IR patients. It indicates that the more refractory patients (bDMARD-IR and 2+cDMARD-IR) need higher baricitinib concentrations to achieve the same efficacy as the less refractory patients (Section 5.7, Figure 65).

The data from two Phase 3 RA studies (JADW and JADX) provide complementary and confirmatory evidence that there is a benefit of 4-mg over 2-mg in patients who have failed more than 1 DMARD, a patient population with high unmet need.

Figure 16: SDAI Change from Baseline through 24 Weeks for the 1DMARD-IR and 2+DMARD-IR Subgroups of Patients from JADX



Abbreviations: 1DMARD-IR = patients who have failed or had inadequate response to a single DMARD; 2+DMARD-IR = patients who have failed or had inadequate response to 2 or more DMARDs; Bari = baricitinib; DMARD = disease-modifying anti-rheumatic drug; mLOCF = modified last observation carried forward; SDAI = simplified disease activity index.
Baricitinib dose vs placebo: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001.
Imputation method: mLOCF.

1.6. Safety

Within the Complete Response Letter (CRL) issued by FDA, a request was made to include a safety update from all nonclinical and clinical studies for baricitinib regardless of indication, dosage form, or dose level. Additionally, the CRL noted that the "*overall benefit-risk assessment of baricitinib 2-mg and 4-mg for rheumatoid arthritis is not favorable given the potential serious risk for thrombosis*." As part of the resubmission, a thorough evaluation of the cumulative integrated RA safety data was conducted to characterize the safety profile of baricitinib, including a comprehensive assessment of the potential serious risk for thrombosis.

The integrated safety database includes data from all patients enrolled in RA studies, whether treated with placebo, active comparator, or baricitinib, and covers the entire exposure period,

including the long-term extension study. As of the resubmission data cutoff, 01 April 2017, 3492 RA patients were treated with baricitinib at any dose with a total of 7860 patient-years of exposure (PYE) (Table 6) and 7993 patient-years of observation, including follow-up time after last dose of treatment. This is nearly a 90% increase in PYE since the initial submission in January 2016 that summarized 4214 PYE from 3464 RA patients. Over 50% of these patients were treated for >2 years.

Table 6: Summary of Safety Exposure

	Placebo	Randomized to Bari 2-mg	Randomized to Bari 4-mg	Ever Exposed to Bari 2-mg[a]	Ever Exposed to Bari 4-mg[a]	Bari All Doses
Number of patients	1070	479	1371	1005	3107	3492
Patient-years of exposure	394	617	2951	1275	6392	7860
Number of patients exposed for ≥52 weeks	-	177	1126	494	2490	2723
Number of patients exposed for ≥104 weeks	-	126	705	210	1633	2182

Abbreviations: Bari = baricitinib.
a Number of patients ever exposed to that dose, irrespective of censoring; some patients are counted in both dose columns
Data cutoff: 01 April 2017.

The safety resubmission focused on updates to the safety overview and important safety topics of serious infection, malignancy, major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and gastrointestinal perforations along with key laboratory changes. Analyses from the initial submission were updated with any new information from the placebo controlled dataset (revised VTE analyses were provided) and long-term extension data for each dose and in total based on additional PYE. This document focuses on the datasets described in Table 7. Data presentations concentrate on the most relevant dataset for each safety topic. In general, the additional safety data from added patient years of exposure is most robustly evaluated in the ALL BARI RA dataset representing all patients ever treated with baricitinib at any dose. The EXTENDED dataset evaluates long-term safety differences by dose, even though patient data are censored at dose change. Another way to look for possible safety differences by dose has been included based on events reported by patients when treated with either 2-mg or 4-mg baricitinib within the ALL BARI RA dataset. The results of these analyses by dose will be labeled “as-treated”. Incidence rates are presented per 100 patient years of exposure.

Table 7: Integrated Safety Datasets

Analysis Purpose	Dataset Name	Description	Data Pool	N	Patient-Years
Short-term Safety of 2-mg and 4-mg vs Placebo	**PC Dataset**	This Placebo-Controlled dataset includes only the 4 placebo-controlled studies with randomization to both 2-mg and 4-mg. Placebo-controlled data from the studies that included a 4-mg dose and placebo (but no 2-mg dose) are not included (JADV and JADC).	**Two Phase II Studies**: JADA and JADN, Weeks 0-12 **Two Phase III Studies:** JADW and JADX, Weeks 0-16	Total: 1509 Placebo: 551 2-mg: 479 4-mg: 479	Total: 425 Placebo: 150 2-mg: 137.3 4-mg: 137.6
Long-term Safety of 2-mg vs 4-mg	**EXTENDED Dataset**	The Extended dataset includes the long-term follow-up data from patients included in the Placebo-Controlled dataset and the 2 placebo-controlled studies that did not include a 2-mg dose (with data censored at dose change) with the addition of patients from Study JADZ. It provides cumulative estimates of safety risks by dose across longer duration of treatment. The extended dataset does not allow comparisons to placebo because placebo-treated patients were switched to active treatment by Week 24.	**All Phase II Studies:** JADC, JADA/Y*, JADN **All Phase III Studies:** JADV/Y*, JADX/Y*, JADW/Y*, JADZ/Y* *including extension up to database lock	Total: 1850 2-mg: 479 4-mg: 1371	Total: 3568 2-mg: 617.2 4-mg: 2950.8
Safety Across All Exposure	**ALL BARI RA Dataset**	The All BARI RA dataset includes safety outcomes for all RA patients exposed to baricitinib at any dose, for the entire duration of exposure with no censoring; and provides the most stable estimate of potential safety risks associated with baricitinib treatment.	**1 Phase 1 RA Study:** JADB **All Phase II Studies:** JADC, JADA/Y*, JADN **All Phase III Studies:** JADV/Y*, JADX/Y*, JADW/Y*, JADZ/Y* *including extension up to database lock	Total: 3492	Total: 7860 Exposure plus follow-up may be up to: 7993[a]
Short-term Safety of 4-mg vs Placebo	**PC 4-mg Dataset**	The Placebo-Controlled dataset includes the 6 placebo-controlled studies with randomization to 4-mg.	**Three Phase II Studies**: JADC, JADA, JADN, Weeks 0-12 **Three Phase III Studies:** JADW, JADX, JADV, Weeks 0-24	Total: 2067 Placebo: 1070 4-mg: 997	Total: 803.2 Placebo: 393.8 4-mg: 409.4

[a] Patient years may be up to 7993 PYE due to inclusion of post-treatment observation time that varies for each safety topic
JADC=Phase 2 study of baricitinib 4-mg, 7-mg, and 10-mg QD vs placebo in cDMARD- and bDMARD-IR patients. JADA=Phase 2 study of baricitinib 1-mg, 2-mg, 4-mg, and 8-mg QD and 2-mg BID vs placebo in MTX-IR and bDMARD-naïve patients. JADN=Phase 2 study of baricitinib 1-mg, 2-mg, 4-mg, and 8-mg QD vs placebo in MTX-IR and bDMARD-naïve patients.

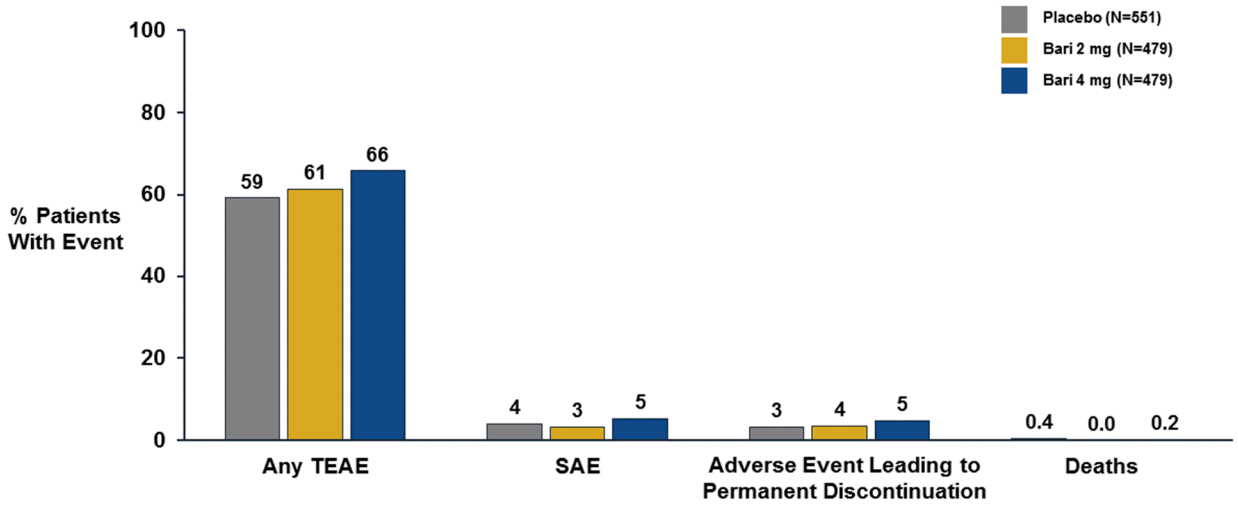
1.6.1. Adverse Events

In the PC dataset, the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to permanent discontinuation were generally similar to placebo (Figure 17). Three deaths were reported, one for a patient on 4-mg baricitinib and 2 for patients treated with placebo.

In the ALL BARI RA dataset, deaths occurred at an incidence rate of 0.35 events per 100 patient-years (Figure 18). For 2-mg-treated patients the incidence rate was 0.16, and for 4-mg-treated patients it was 0.34 in the EXTENDED dataset. These rates are lower than for patients treated with placebo (1.3) or 4-mg (0.7) in the PC dataset and are within the range of what has been reported from the abatacept, tocilizumab, adalimumab, and tofacitinib RA submissions (Figure 18).

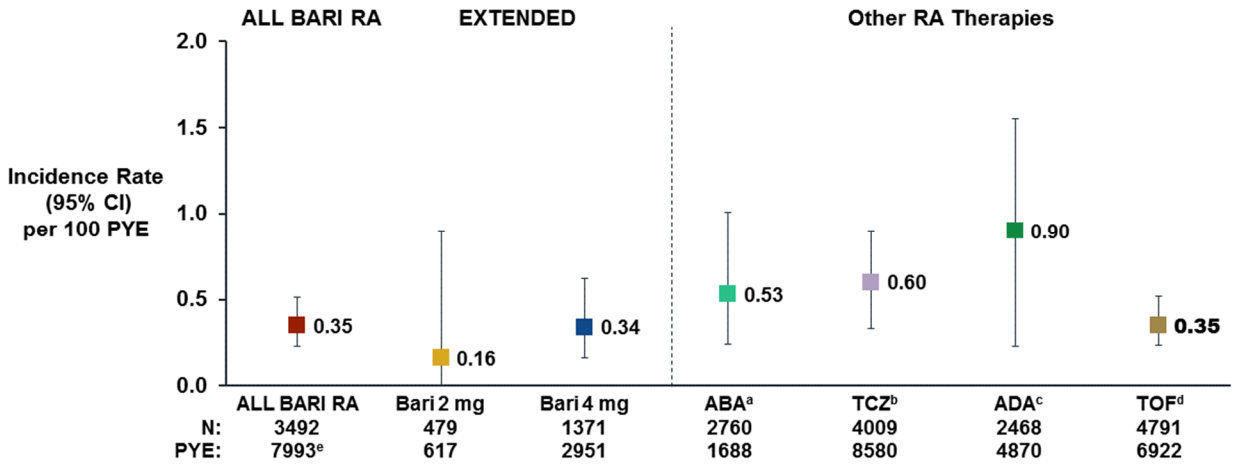
Serious adverse events occurred at an incidence rate of 8.9 events per 100 patient-years in the ALL BARI RA dataset (Figure 19). From the EXTENDED dataset, the incidence rates were 10.1 for 2-mg and 9.2 for 4-mg. These incidence rates are within the range reported from other RA registration programs.

Figure 17: Overview of Safety, PC Dataset



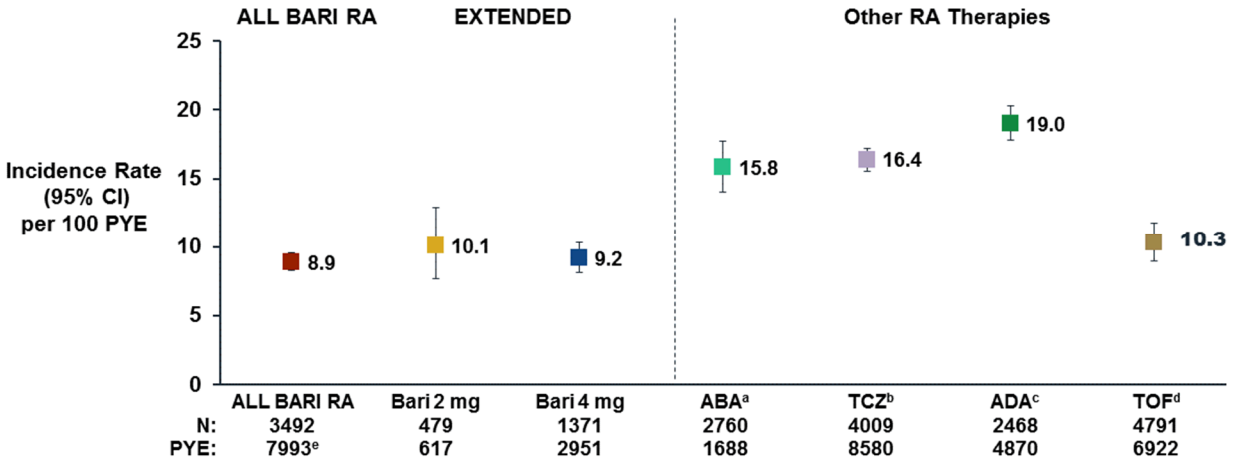
Abbreviations: Bari = baricitinib; N = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Figure 18: Overview of Deaths



Abbreviations: ABA = abatacept; ADA = adalimumab; CI = confidence interval; N=number of patients; PYE = patient years exposure; TCZ = tocilizumab; TOF = tofacitinib.
a FDA 2005 (briefing document for abatacept). b FDA 2009 (tocilizumab clinical review of the complete response). c FDA (update on TNF-blocking agents). d FDA 2012 (tofacitinib advisory committee briefing document). e Includes follow up time.

Figure 19: Overview of Serious Adverse Events



Abbreviations: ABA = abatacept; ADA = adalimumab; CI = confidence interval; N=number of patients; PYE = patient years exposure; TCZ = tocilizumab; TOF = tofacitinib.
a FDA 2005 (briefing document for abatacept). b FDA 2009 (tocilizumab clinical review of the complete response). c FDA 2003 (adalimumab advisory committee briefing document). d FDA 2012 (tofacitinib advisory committee briefing document). e Includes follow up time.

1.6.2. Infections

Infections were an adverse event of special interest. In the PC dataset, non-serious infections were frequently reported (Figure 20) and upper respiratory tract infections; herpes zoster and herpes simplex have all been classified as adverse drug reactions.

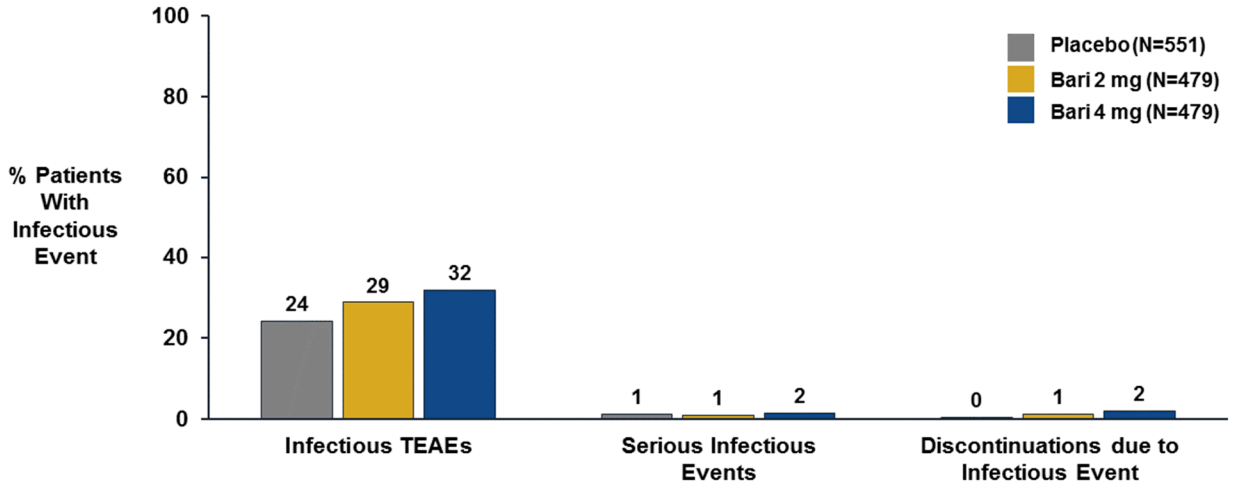
For serious infections, no differences were noted in frequency or incidence rates between baricitinib and placebo, or between baricitinib 2- and 4-mg dose groups in the placebo-controlled period (Figure 20). From the ALL BARI RA dataset, the overall incidence rate of serious infections was 3.0 (Figure 21) and the most common serious infections were pneumonia and

herpes zoster (each reported by approximately 1% of patients). From the EXTENDED dataset, there was no dose-response over time, with an incidence rate of serious infections of 3.3 for 2-mg and 3.2 for 4-mg. The incidence rates of serious infections for baricitinib are within the range from other RA registration programs (Figure 21).

From the PC dataset, the proportion of patients reporting herpes zoster was higher in the baricitinib groups than in the placebo group (Figure 22). From the PC dataset a dose-response was observed, with more patients who received 4-mg reporting herpes zoster than patients who received 2-mg. From the ALL BARI RA and EXTENDED dataset, the incidence rate for all herpes zoster was similar for 2-mg and 4-mg and for all baricitinib doses (Figure 22). The majority of herpes zoster events were mild or moderate (94%).

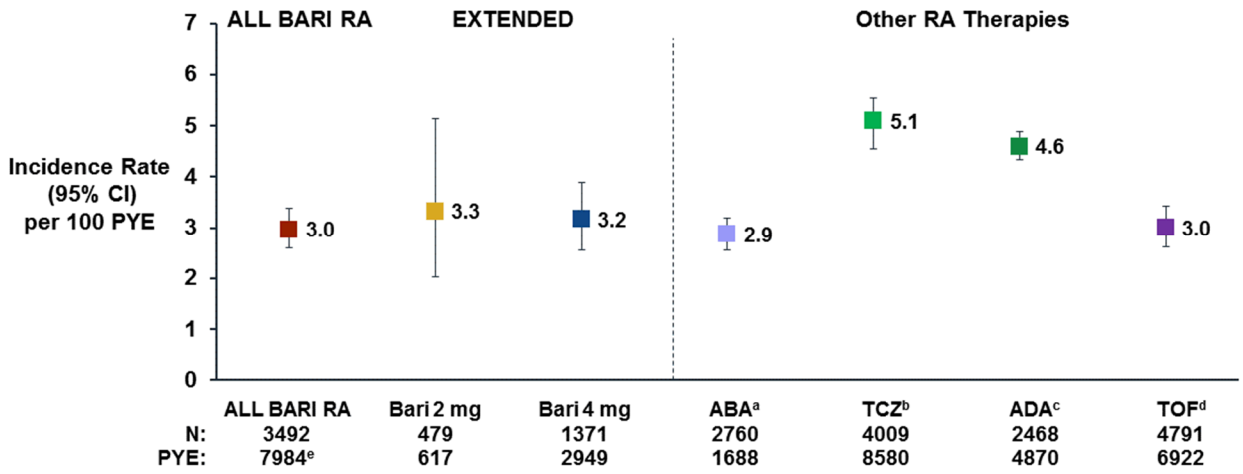
Other potential opportunistic infections were infrequent, not different between baricitinib and placebo in the PC 4-mg dataset and were not different by dose in the EXTENDED dataset (summary in Section 6.2.5.1.4).

Figure 20: Overview of Infections, PC Dataset



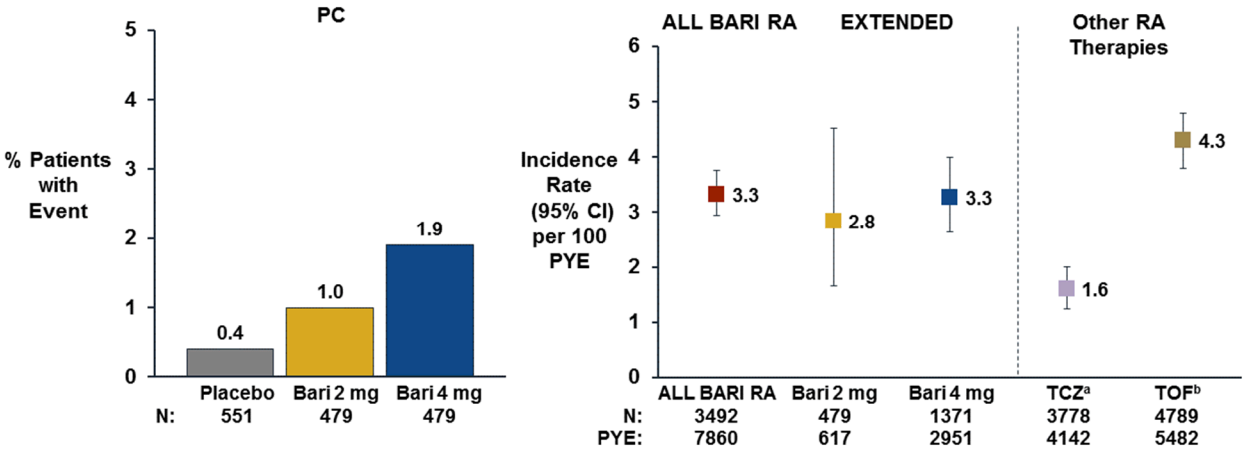
Abbreviations: Bari=baricitinib; N = number of patients; TEAE=treatment-emergent adverse event.

Figure 21: Overview of Serious Infections



Abbreviations: ABA = abatacept; ADA = adalimumab; CI = confidence interval; N=number of patients; PYE = patient years exposure; TCZ = tocilizumab; TOF = tofacitinib.
a Alten et al. 2014. b FDA 2009 (tocilizumab clinical review of the complete response). c Burmester et al. 2013. d FDA 2012 (tofacitinib advisory committee briefing document). e Includes follow up time.

Figure 22: Herpes Zoster Proportion and Incidence Rates from PC, ALL BARI RA, and EXTENDED Datasets and from Other RA Therapies



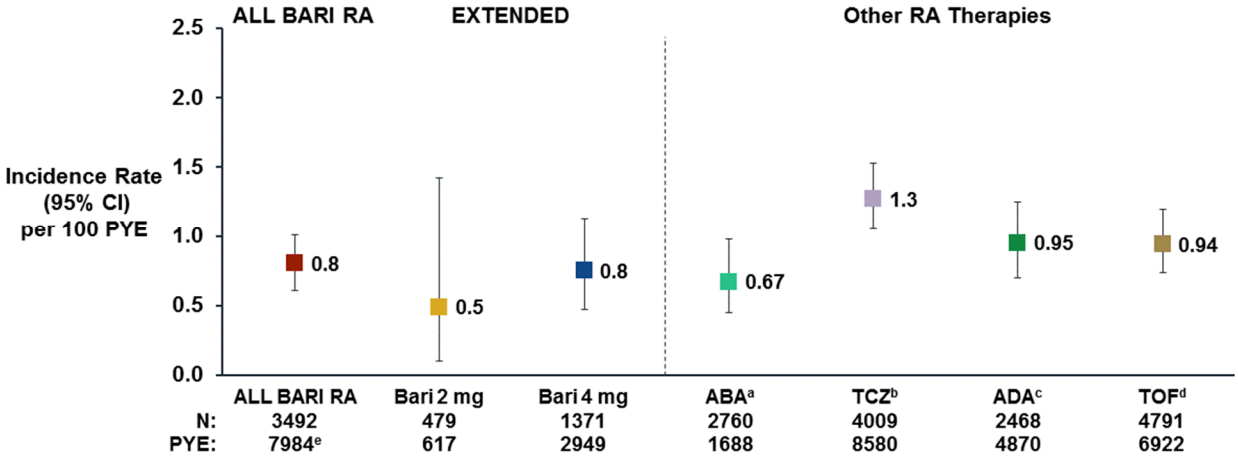
Abbreviations: CI = confidence interval; N=number of patients; PYE = patient years exposure; TCZ = tocilizumab; TOF = tofacitinib.
a FDA 2008 (tocilizumab advisory committee slides). b Winthrop et al. 2014.

1.6.3. Malignancy

For malignancy the EXTENDED and ALL BARI RA datasets were utilized as the primary datasets of interest, as only 1 malignancy (2-mg) was reported in the PC dataset. The incidence rate in the EXTENDED dataset was 0.5 in the 2-mg group and 0.8 in the 4-mg group (Figure 23). The incidence rate for the ALL BARI RA dataset was 0.8. For lymphoma, specifically, 6 events were reported for an incidence rate of 0.08 in the All BARI RA dataset. These incidence rates are within the range reported in other RA registration programs (Figure 23). The most commonly reported malignancies (Table 25) are consistent with those frequently seen in the RA

population (Ekstrom et al. 2003; Chen et al. 2011; Lin et al. 2015), including breast, lung, colorectal, kidney, and prostate.

Figure 23: Summary of Malignancy Rates (Excluding NMSC)



Abbreviations: ABA = abatacept; ADA = adalimumab; CI = confidence interval; N=number of patients; NMSC = nonmelanoma skin cancer; PYE = patient years exposure; TCZ = tocilizumab; TOF = tofacitinib.
a FDA 2005 (briefing document for abatacept). b FDA 2009 (tocilizumab clinical review of the complete response). c FDA 2003 (adalimumab advisory committee briefing document). d FDA 2012 (tofacitinib advisory committee briefing document). e Includes follow up time.

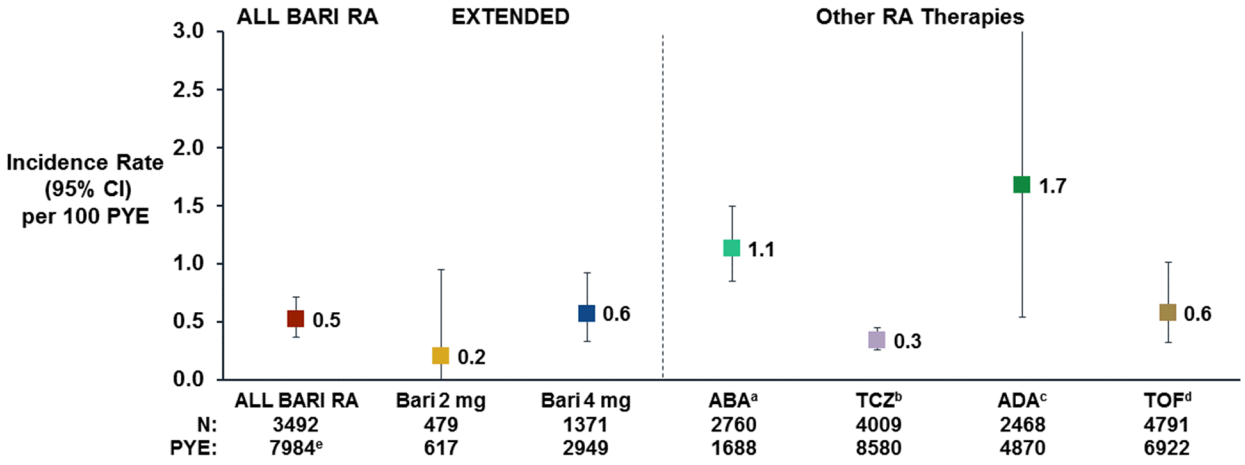
1.6.4. MACE

Patients with RA have an increased cardiovascular risk (Kume et al. 2014). Accelerated atherosclerosis caused by inflammation is the hallmark of cardiovascular disease in RA (Sen et al. 2014). Increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) have been observed in studies with baricitinib, the JAK inhibitor tofacitinib (Souto et al. 2015), the IL-6 receptor monoclonal antibody tocilizumab (Roberston et al. 2013), and MTX in various RA clinical studies (Navarro-Millan et al. 2013). Cardiovascular events and lipids were specifically evaluated in the baricitinib RA development program because of noted changes in lipid parameters with baricitinib treatment and the lipid paradox in RA (i.e., RA patients have low serum lipids and increased cardiovascular risk; effective control of RA appears to reduce cardiovascular risk with a paradoxical increase in serum lipids [Myasoedova et al 2011]).

Potential major adverse cardiovascular events (MACE), including stroke, myocardial infarction (MI), and cardiovascular death, were externally adjudicated in the Phase 3 program. From the PC dataset, 4 events were reported: 2 with placebo (1 MI, 1 stroke) and 2 with baricitinib 4-mg (1 MI and 1 stroke). From the EXTENDED dataset, the incidence rate was 0.2 for 2-mg (1 event) and 0.6 for 4-mg (16 events) (Figure 24). From the ALL BARI RA dataset, there were 38 MACE across all doses and exposure durations, resulting in an incidence rate of 0.5 per 100 patient-years. This incidence rate is within the range reported from other RA registration programs (Figure 24) and from RA patients in general (Michuad et al 2016, Ogdie et al. 2015; Liao et al. 2015).

Changes in lipids and their relationship to MACE are addressed in the laboratory analytes section (Section 1.6.7).

Figure 24: Summary of MACE Rates



Abbreviations: ABA = abatacept; ADA = adalimumab; CI = confidence interval; MACE = major adverse cardiovascular events; N=number of patients; PYE = patient years exposure; TCZ = tocilizumab; TOF = tofacitinib.
a Alten et al. 2014. b Rao et al. 2015. c FDA 2012 (tofacitinib advisory committee briefing document). d FDA 2012 (tofacitinib advisory committee briefing document). e Includes follow up time.

1.6.5. Venous Thromboembolism (VTE)

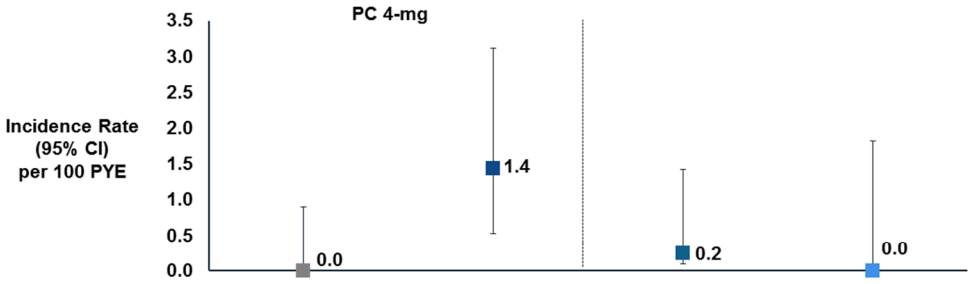
Venous thromboembolism was evaluated and discussed in the initial submission, in a variety of regulatory interactions, and was noted as an issue in the FDA CRL. Because of an imbalance in the placebo-controlled time-period and serious nature of these events, VTE is classified as an important potential risk; meaning it could not be confirmed based on further investigation, nor could it be ruled out. The key results for this topic are presented here with more details included in Section 6.2.5.4.

From the PC 4-mg dataset, an imbalance of VTE was observed during Weeks 0 to 24 with 6 events reported in the baricitinib 4-mg group (incidence rate=1.4, N=997) and no events in the placebo group (N=1070) (Figure 25). Three events were considered serious due to hospitalization (1 DVT and 2 PE), and the other 3 events did not require hospitalization and/or were not reported as serious (2 DVT and 1 PE); for details of each case see Table 8. This imbalance was an unexpected finding.

To investigate if patients were at an increased risk of VTE upon initial exposure, which can be supportive of a possible causal association with baricitinib, patients who were randomized to placebo and then rescued or switched to baricitinib 4-mg were evaluated for occurrence of VTE. For this group of 928 patients, during their 24 weeks of initial exposure to baricitinib, 1 VTE was reported (incidence rate=0.2) (Figure 25). This DVT was 2 days after a femoral fracture; the patient was treated with aspirin, recovered and continued baricitinib treatment . Additionally, among the 451 patients that were randomized to either methotrexate or adalimumab with a background of methotrexate and then rescued or switched to baricitinib 4-mg; none reported a VTE during their initial 24 weeks of baricitinib exposure (incidence rate=0) (Figure 25). These

findings were in contrast to the placebo controlled incidence rate of VTE risk upon first exposure to baricitinib.

Figure 25: VTE Incidence Rates during First 24 Weeks of Baricitinib Exposure for the PC 4-mg Dataset and Rescued or Switched Groups



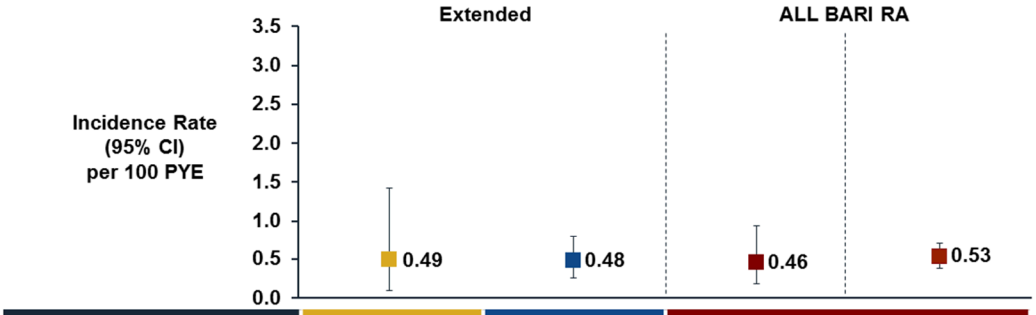
Treatment	PBO	BARI 4 mg	PBO→BARI 4 mg	Active→BARI 4 mg
Time Period	24 wks post-randomization		24 wks post-switch or rescue	24 wks post-switch or rescue
# of Patients	1070	997	928	451
# of Patients with Event(s)	0	6	1	0
PYE	406	418	410	203

Abbreviations: BARI = Baricitinib; CI = confidence interval; PBO = placebo; PYE = patient years exposure; VTE = venous thromboembolism.

Likewise, other findings that would support a causal relationship to treatment were not present for baricitinib, for example:

- lack of a clear dose response with an incidence rate of 0.49 (95% CI; 0.10,1.43) for 2-mg and 0.48 (95% CI; 0.26,0.80) for 4-mg baricitinib (Figure 26; EXTENDED dataset) events were identified in controlled period of 2/8 RA studies
- events were not clustered in temporal association with baricitinib initiation, instead accumulating at a consistent annual incidence of approximately 0.5%, as shown in the Kaplan-Meier plot with near constant slope (Figure 27); and time from first baricitinib dose to event ranged from 37 to 1658 days (42 events; ALL BARI RA dataset)
- most patients continued baricitinib treatment without recurrence and for those with a recurrence (2/28), the events were 1-2 years after the initial event with precipitating factors (fracture with post-procedural complications; discontinuation of anti-coagulant)

Figure 26: VTE Incidence Rates for Extended and All BARI RA Datasets



Treatment	Bari 2 mg	Bari 4 mg	ALL BARI RA	
Time Period	Overall		0-24 wks	Overall
# of Patients	479	1371	3492	3492
# of Patients with Event(s)	3	14	7	42
PYE	615	2936	1533	7949[a]

Abbreviations: BARI = Baricitinib; CI = confidence interval; PYE = patient years exposure; VTE = venous thromboembolism.
a Includes follow up time

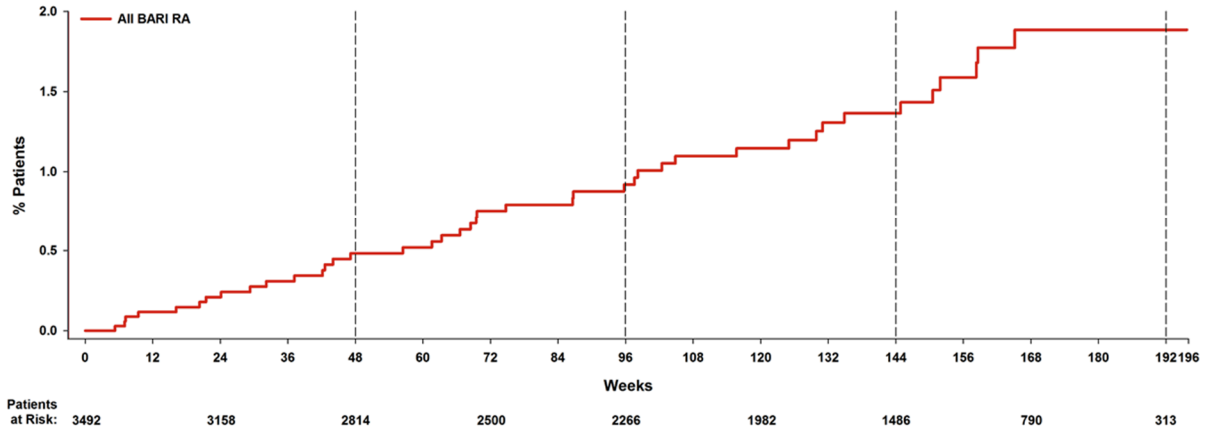
Table 8: Details of Each Individual VTE Case during the Placebo Controlled Period

	Age	Event	Serious	Days from Start of Baricitinib Treatment to Event	Body Mass Index (kg/m^2)	Relevant Medical History and Risk Factors	Baricitinib Status	VTE Treated with Anti-Coagulant
1	62	PE	N	37	37	Hypertension, chronic obstructive pulmonary disease, pulmonary fibrosis, varicose veins Concomitant MTX and steroid	Receiving baricitinib at time of event. Continued baricitinib throughout event and recovery.	Y
2[a]	38	DVT	Y	49	20	Concomitant oral contraceptive and MTX	Receiving baricitinib at time of event. Interrupted baricitinib for 36 days and then resumed.	Y
3	66	PE	Y	50	45	Hypertension, peripheral edema, family history of PE, selective IgG subclass deficiency Concomitant MTX and steroid	Received baricitinib for 3 weeks, discontinued due to AE of hypersensitivity ~1 month prior to PE event.	Y
4	65	PE	Y	66	52	Hypertension, rib fractures 9-10 months prior Concomitant MTX and steroid	Receiving baricitinib at time of event. Interrupted baricitinib for 3 weeks and then resumed.	Y
5	53	DVT	N	113	36	Peripheral edema, tobacco use Concomitant MTX and steroid	Receiving baricitinib at time of event. Continued baricitinib throughout event and recovery.	N
6	58	DVT	N	150	39	Prior DVT, peripheral edema Concomitant MTX	Receiving baricitinib at time of event. Interrupted baricitinib for 4 days and then resumed.	Y

Abbreviations: DVT=deep vein thrombosis; MTX=methotrexate; N=no; PE=pulmonary embolism; VTE=venous thromboembolism; Y=yes.

[a]Reported as thrombophlebitis by the investigator.

Figure 27: Kaplan-Meier Curve of Venous Thromboembolism Events; Accruing ~ 0.5% Annually



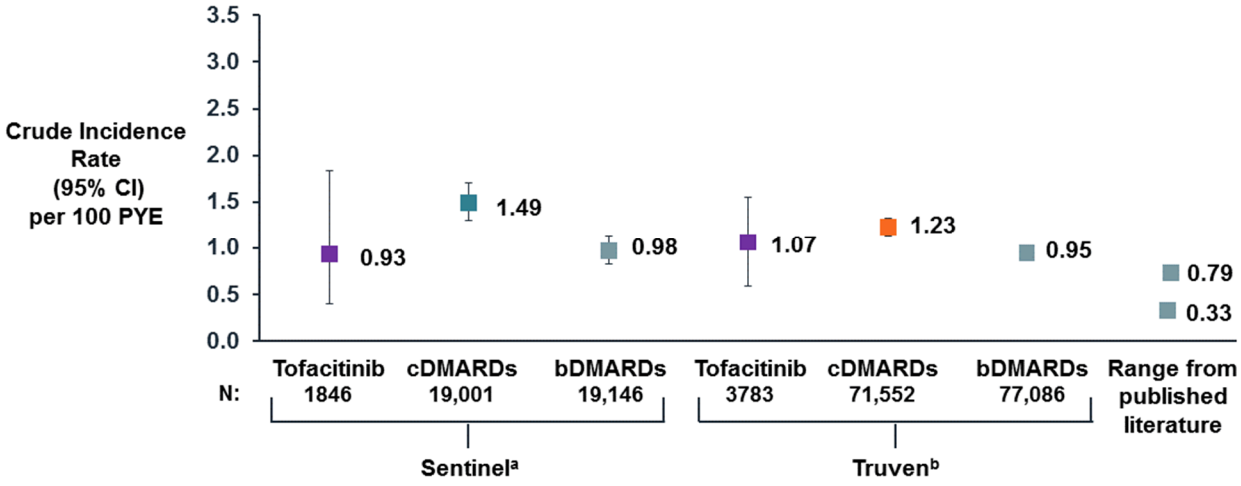
For patients with an event, data was censored at the event start date; for patients without an event, data was censored at the last observation or data cutoff date.

The ALL BARI RA dataset is the largest, includes all patients with a VTE event (N=42) over the entire duration of exposure (7949 PYE with inclusion of follow up events and observation time), and offers the most stable estimate of VTE incidence rate: 0.53 (95% CI: 0.38, 0.71). Because this dataset includes about a 10-fold increase in exposure versus the PC dataset; it yields a much tighter estimate of VTE incidence rate in this population. Possible VTE risk factors for patients with and without an event were evaluated and patients with an event tended to have a history of previous DVT/PE, were receiving cyclooxygenase-2 (COX-2) inhibitors, had higher body mass index, and were older (Figure 66).

For other RA therapies, finding complete information on counts of serious and non-serious DVT/PE events along with the number of patients and duration of exposure in patient-years is difficult as these data are not included in many publications or summary safety findings. Submission data from 3 recently FDA-approved drugs for RA (tocilizumab, tofacitinib, and sarilumab) were located and evaluated for the number of serious PE and DVT events during the controlled periods (Table 29 and Table 30). Serious venous thromboembolism was reported in these programs at overall incidence rates similar to baricitinib, although frequencies were not imbalanced compared to placebo in the placebo-controlled period.

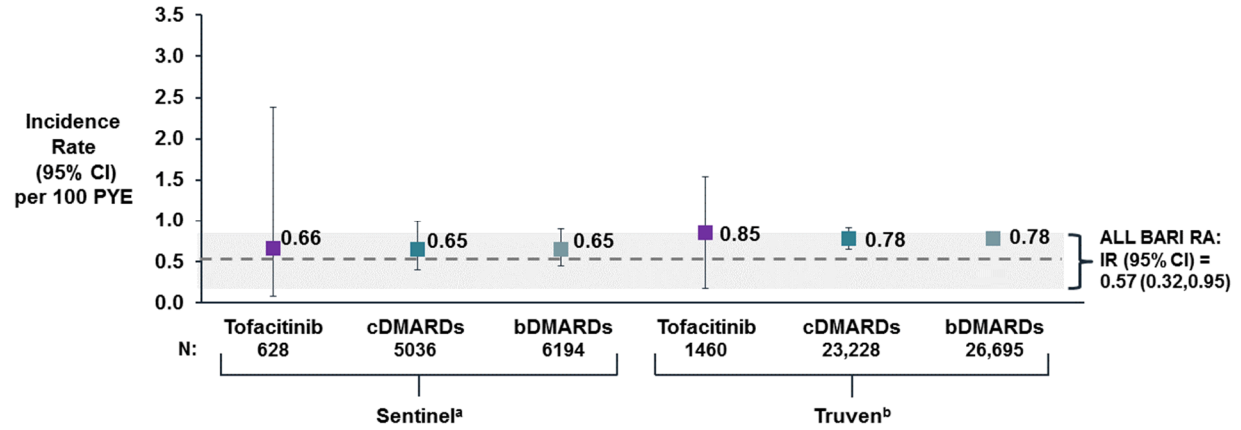
To further contextualize the VTE incidence rate found for baricitinib, VTE incidence rates for the RA population from FDA's Sentinel program, Truven Marketscan administrative claims data, and results from published observational studies (Figure 28) were evaluated. Both Sentinel and Truven administrative claims databases contain information on patients enrolled in US health plans. A subset of the Sentinel program representing 75 million enrolled patients identified over 69,000 users of RA medications. Truven represents over 110 million patients, from which over 205,000 patients with RA medications were identified. VTE incidence rates for RA patients treated with conventional and biologic DMARDs from Sentinel, Truven, and the published literature, while not directly comparable with results from the baricitinib clinical trial program, appear to be within a similar range (Figure 28), especially when comparing data by age (age-restricted data presented for 50-59 year age group; Figure 29).

Figure 28: Incidence Rates of VTE among Patients with RA from Sentinel Data Partners, Truven Marketscan Database, and Published Literature



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CI = confidence interval; PYE = patient years exposure; RA = rheumatoid arthritis, VTE = venous thromboembolism.
a Results from 5 Sentinel System data partners, offered through the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program.
b Results from Truven Marketscan database.

Figure 29: VTE Incidence Rates among RA Patients Aged 50-59 from Sentinel Data Partners, Truven Marketscan Database, and Baricitinib



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CI = confidence interval; PYE = patient years exposure; RA = rheumatoid arthritis, VTE = venous thromboembolism.
a Results from 5 Sentinel System data partners, offered through the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program
b Results from Truven Marketscan database
ALL BARI RA data is the age-restricted data for the 50-59 year age group.

While caution must be used in comparing clinical trial results to epidemiology studies, the epidemiology confirms that the background rate of VTE, regardless of treatment, is greater than zero, and the overall baricitinib VTE incidence rate is not greatly different than the expected background.

In summary, the incidence rate of VTE during baricitinib treatment is most accurately estimated at 0.53 events/100 patient years (95% CI: 0.38, 0.71). While it is not currently possible to

exclude some incremental treatment-induced effect, thorough investigation has not confirmed such an effect and review of disease state data support that at least some of the observed rate should reflect background. However, as the association suggested by the imbalance in the placebo-controlled dataset cannot be fully excluded, VTE is an important potential risk. By classifying VTE as an important potential risk, information is included as Warning and Precaution in draft labeling. VTE will be further evaluated in postmarketing observational studies (Section 6.5), through review of spontaneous adverse event reports and in clinical trials for other indications. Several post-approval studies are proposed to FDA and have already begun in countries where baricitinib is approved.

1.6.6. Gastrointestinal Perforations

Gastrointestinal (GI) perforations are a rare but serious adverse event observed in patients with RA and have been seen with all combinations of RA therapies (Curtis et al. 2011; Závada et al. 2014). GI perforations were infrequent in the ALL BARI RA dataset (n=3), resulting in an incidence rate of 0.04. In the EXTENDED dataset, there were no reports at 2-mg and 1 event at 4-mg (incidence rate = 0.2). The incidence rate for the ALL BARI RA dataset is within the range of published rates in patients receiving a variety of RA therapies (0.07 [based on hospital discharge codes; Xie et al. 2016] to 0.19 [adjudicated; Monemi et al. 2016]).

1.6.7. Clinical Laboratory Observations

Baricitinib treatment was associated with a number of changes in laboratory data and most associated adverse events were uncommon. Changes from baseline to Week 16 for the 2-mg and 4-mg doses compared to placebo using the PC dataset are summarized below using within group least squares mean (LSM). Common terminology criteria for adverse events (CTCAE) grade changes by dose are summarized in Table 9. See Section 6.2.6 for detailed review of clinical laboratory observations.

- **Hemoglobin** (Figure 69): At Week 16, the within-group change from baseline was -0.21, -0.23 and -0.32 g/dL for placebo, baricitinib 2- and 4-mg, respectively . Mean hemoglobin returned toward baseline values with continued treatment.
- **Lymphocytes** (Figure 70): Baricitinib treatment was associated with an increase in circulating absolute lymphocyte count within the first week of treatment, and counts returned to baseline or below within 12 to 24 weeks and remained stable. At Week 16, the within group change from baseline was -0.08, 0.04 and 0.07 x 10^9/L for placebo, baricitinib 2- and 4-mg, respectively. Worsening of lymphopenia was associated with an increase in infections (Table 33).
- **Neutrophils** (Figure 71): Absolute neutrophil count decreased in the first 4-8 weeks, mostly within the normal range, and remained stable thereafter. At Week 16, the within-group change from baseline was -0.03, -0.76 and -0.94 x 10^9/L for placebo, baricitinib 2- and 4-mg, respectively. Values returned to baseline after baricitinib was discontinued. In the PC dataset, neutropenia less than 1.0 x 10^9/L was uncommon at 0.6% at 2-mg and 0.2% at 4-mg baricitinib (Table 9).
- **Platelets** (Figure 72): Baricitinib treatment was associated with an increase in mean platelet count within the first 2 weeks (51 x 10^9/L for 4-mg) that then returned towards

baseline and remained stable over time. At Week 16, the within-group change from baseline was 3, 12, and 28 x 10^9/L for placebo, baricitinib 2- and 4-mg, respectively.

- **Liver Chemistry** (Figure 73): Baricitinib treatment was associated with mean increases of approximately 6 U/L for both Alanine Aminotransferase (ALT) and Aspartate aminotransferase (AST) that plateaued around Week 4. Elevations to >3x ULN were noted in less than 2% of baricitinib-treated patients regardless of dose. At Week 16, for ALT the within-group change from baseline was 0, 3.2 and 5.3 U/L for placebo, baricitinib 2- and 4-mg, respectively. Change in AST was consistent with that of ALT. All patients with elevations in ALT or AST at least 3x the upper limit of normal (ULN) and total bilirubin at least 2x ULN were examined. No cases met Hy's Law, and all had a reason other than study treatment for these elevations, resulting in no identified cases of drug-induced liver injury.
- **Creatine Phosphokinase (CPK)** (Figure 74): Increases were noted within 1 week of treatment in a dose-related manner and plateaued at 8-12 weeks. Median increases at the 4-mg dose were approximately 50 U/L. At Week 16, the within-group change from baseline was 4, 37, and 57 U/L for placebo, baricitinib 2- and 4-mg, respectively. Discontinuations due to CPK elevation were less than 1%. TEAEs related to muscle injury were reported at frequencies of 1-2% for placebo- and baricitinib-treated patients in the placebo-controlled time-period with no rhabdomyolysis associated with baricitinib.
- **Lipids** (Figure 75): Evaluation of serum lipids showed dose-dependent mean increases for triglycerides and cholesterol within the first 12 weeks that then remained stable over continued exposure. Mean increase in LDL cholesterol was 8% and 14% for the 2-mg and 4-mg doses by Week 12. Increases to ≥ 160 mg/dL were noted for 7.8, 11.3 and 13.6 percent of placebo, 2-mg and 4-mg baricitinib-treated patients, respectively (Table 9). The mean LDL/HDL ratio did not change. No association between the lipid changes and MACE was identified; patients who initiated statin therapy had reductions in total cholesterol and LDL-C to baseline levels, although HDL-C remained elevated. The increases in LDL are primarily due to increases in larger LDL particles and decreases in smaller LDL particles that are generally thought to be more atherogenic.

Table 9: Summary of Categorical Laboratory Changes in PC Dataset

Analyte	Impact	Placebo N=551 n (%)	2-mg N=479 n (%)	4-mg N=479 n (%)
Hemoglobin	CTCAE Grade 3^+ (< 8.0 g/dL)	1 (0.2)	2 (0.4)	0
Neutrophils (neutropenia)	CTCAE Grade 3^+ (< 1.0 x10^9/L)	0	3 (0.6)	1 (0.2)
Lymphocytes (lymphopenia)	Grade 3^+ (< 0.5x10^9/L)	2 (0.4)	4 (0.8)	3 (0.6)
Platelets	Increased to (> 600 x10^9/L)	7 (1.3)	5 (1.1)	11 (2.3)
ALT[a]	≥ 3x ULN	2 (0.4)	8 (1.7)	6 (1.3)
Creatine Phosphokinase (increased)	CTCAE Grade 3^+ (> 5x ULN)	3 (0.6)	4 (0.8)	7 (1.5)
LDL (NCEP Criteria)	≥ 160 mg/dL; High and Very High	24 (7.8)	38 (11.3)	44 (13.6)

Abbreviations: ALT = alanine aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; LDL= low-density lipoprotein; NCEP = National Cholesterol Education Program; ULN = upper limit of normal
a This row includes all patients with post-baseline values greater than 3xULN regardless of baseline ALT value.

1.6.8. Risk Mitigation and Risk Assessment

Several identified and potential risks for baricitinib will be described in proposed labeling, including risks related to infection and changes in laboratory analytes. Many of these risks are similar to other approved RA therapies and familiar to prescribers (Table 10).

The ongoing open-label extension study, JADY, will continue to provide data on long-term exposure to baricitinib and associated risks. In addition, postmarketing surveillance, including several observational studies, will further characterize the long-term safety profile of baricitinib where information may be missing or for important potential risks including serious infections, malignancy, MACE, VTE, and hepatotoxicity (Section 6.5). Planned post-approval studies will evaluate an estimated 13,000 baricitinib-treated patients; some studies have already begun in countries where baricitinib is approved.

Routine pharmacovigilance activities will also capture reported cases and aid in further characterization of important potential risks and missing information in the postmarketing setting, including from spontaneous postmarketing reports, clinical trial reports for ongoing studies of RA or other indications, review of medical literature including published studies and meeting abstracts and disproportionality testing of spontaneous data for safety signals.

Table 10: Comparison of Safety Labeling within Commonly Prescribed Rheumatoid Arthritis Therapies

Risks Identified in Labeling	Tofacitinib	Tocilizumab	Abatacept	Adalimumab	Methotrexate[a]
Serious infections	✓	✓	✓	✓	✓
Opportunistic infections	✓	✓	—	✓	✓
Herpes zoster	✓	✓	✓	✓[b]	✓
Tuberculosis	✓	✓	✓	✓	—
Malignancies	✓	✓[c]	✓[c]	✓	✓
Lymphoma	✓	—	✓	✓	✓
Elevated liver enzymes	✓	✓	—	✓	✓
Venous thromboembolism	—	—	—	✓	✓
Hyperlipidemia, LDL Increase, or Triglycerides	✓	✓	—	✓	—
Thrombocytosis or thrombocytopenia	—	✓	—	✓[e]	✓
Neutropenia	✓	✓	—	✓[b]	✓
Gastrointestinal perforations	✓	✓	—	✓[d]	✓

Abbreviations: LDL = low-density lipoprotein.
All information obtained from approved United States Prescribing Information.
Note: "—" indicates that data or information are not included in the USPI.
a Data from Methotrexate tablet (DAVA PHARMS INC).
b In Juvenile Idiopathic Arthritis study.
c Listed under "Immunosuppression" subheading of Warnings and Precaution.
d Listed under Postmarketing Experience.
e Listed as an example under Hematologic Reactions within Warnings and Precautions.

1.7. Benefit-Risk Conclusions

Benefits: Baricitinib consistently demonstrated statistically significant and clinically meaningful improvements in signs and symptoms (across composite scores and components), measures of LDA and remission, physical function, and additional patient-reported outcomes including pain and morning joint stiffness. Across relevant domains of efficacy, improvements were seen over

placebo for both the 2-mg and 4-mg doses, and 4-mg showed significant improvements over the leading oral and injectable standards of care, MTX and adalimumab used with background MTX. Improvements occurred rapidly (within a week) and were sustained during long-term treatment. Baricitinib also showed significant inhibition of radiographic joint damage in 3 studies where radiographic progression was evaluated.

In patients who had failed multiple prior DMARDs, the added benefits of 4-mg were particularly evident and consistent. In bDMARD-IR patients, baricitinib 4-mg showed significant benefit across domains of efficacy, even for those most refractory patients failing multiple bDMARDs of differing mechanisms. For these difficult-to-manage patients with limited treatment options, the magnitude of its enhanced benefit over the 2-mg dose was large, often adding more than 50% relative to 2-mg versus placebo effects on RA disease activity. The benefits of the 4-mg dose for patients with multi-DMARD refractory disease were also consistently demonstrated in a corroborative analysis from the corresponding Phase 3 cDMARD-IR population. Additionally, in the study comparing baricitinib to adalimumab, the 4-mg dose showed significantly improved efficacy over adalimumab in multi-DMARD-refractory patients. This superiority to adalimumab demonstrates the potential benefit that baricitinib 4-mg may offer to refractory patients compared to a typical targeted second-line treatment option.

For patients with potentially less-difficult-to-treat RA (those who had not failed multiple DMARDs), analyses of observed clinical (Study JADX) and supportive PK/PD modelling data showed that both the 2- and 4-mg initial doses produced comparable rapid, large, and statistically significant levels of improvement in disease activity versus placebo.

In patients for whom sustained disease control was induced with 4-mg, a large, randomized, blinded study provided robust data to inform consideration of tapering to a lower dose for maintenance. While the efficacy of 4-mg significantly exceeded that of 2-mg, most patients in both treatment groups maintained LDA or remission. Moreover, among patients who did require rescue, by Week 24 post-rescue two-thirds were able to recapture their prior level of disease control with the 4-mg dose. Data from this study support use of baricitinib according to the dose taper treatment strategy advocated in ACR/EULAR RA treatment guidelines (Sing et al. 2015, Smolen et al. 2017).

Risks: A thorough evaluation of the cumulative safety data was conducted to evaluate the risks associated with baricitinib treatment. Results from 3492 patients with a combined 7860 patient-years of exposure confirm that the 2- and 4-mg doses of baricitinib have a similar safety profile, with reported risks that are also similar to other approved RA therapies. The baricitinib RA clinical development program does not show an increased risk for serious infections with baricitinib in comparison to placebo. The incidence rate for malignancies observed with baricitinib is consistent with background rates in patients with RA, and there is no evidence of an increase in MACE relative to the expected rate in RA patients. The rates of serious infections, malignancies, and MACE do not increase with extended baricitinib exposure. VTE events were noted with baricitinib (but not placebo) during the controlled phase of integrated studies; however, the overall incidence rate is stable over time and within the incidence rates for the disease state as a whole, including for other approved RA therapies, published literature, and

observational data. While not able to establish a clear association between venous thromboembolic events and baricitinib, VTEs are considered an important potential risk addressed with a warning in proposed labeling. Measures of tolerability, including adverse drug reactions, appeared generally similar for baricitinib and active comparators. A dose relationship between baricitinib treatment groups (4-mg and 2-mg) was observed for some laboratory parameters. Common adverse reactions include upper respiratory tract infections, nausea, herpes zoster and herpes simplex.

The potential risks identified in the baricitinib program are generally consistent with risks identified for other approved RA therapies (Table 10), while the common adverse reactions are routinely encountered and managed by practitioners in the clinical setting. Proposed labeling for baricitinib will describe these risks, including appropriate warnings and precautions, in a similar way to applicable US labeling for approved therapies.

Safety topics of special interest will be monitored closely through routine pharmacovigilance efforts as well as ongoing and planned clinical trials and planned observational studies to ensure that long-term exposure to baricitinib is not associated with increased risk.

Benefit-Risk Conclusion: Baricitinib provides a needed treatment advance for patients who have struggled to manage their moderate to severe rheumatoid arthritis with current therapies, including those who have failed multiple prior therapies. Baricitinib demonstrated greater efficacy and a similar safety profile relative to standards of care. The data from studies JADX and JADW provide complementary and confirmatory evidence that there is a benefit of 4-mg over 2-mg in patients who have failed multiple DMARDs, a patient population in which the needs are the greatest. Moreover, two dosing options allow physicians greater ability to achieve optimal clinical outcomes by considering the individual patient in a way that is supported by data and aligns with practice guidelines. In the context of unmet needs and the benefits and risks of available therapies, once-daily oral baricitinib is a valuable addition to the treatment options for US patients struggling with this common and disabling disease.

2. Product Background

- Baricitinib is an orally administered JAK1/JAK2 inhibitor with low selectivity for JAK3 and TYK2.
- Toxicology data do not reveal genotoxic or carcinogenic potential, and the adverse events in the repeat-dose studies are consistent with JAK inhibition and immunosuppression.

2.1. Pharmacological Class

Baricitinib, administered orally, belongs to the pharmacological class of Janus kinase (JAK) inhibitors. Two other JAK inhibitors are currently available for human use in several countries: ruxolitinib, a JAK1/JAK2 inhibitor for the treatment of myelofibrosis and polycythemia vera, and tofacitinib, a JAK1/JAK3 inhibitor with lesser activity at JAK2 for the treatment of RA and psoriatic arthritis.

2.2. Mechanism of Action

Baricitinib represents a selective inhibitor of the JAK family of protein tyrosine kinases with selectivity for JAK1 and JAK2, and less selectivity for JAK3 or TYK2 (Fridman et al. 2010). Janus kinases are a family of 4 protein tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that play an important role in cytokine signal transduction. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2 and JAK3 with IC_{50} values of 5.9, 5.7, 53 and >400 nM, respectively.

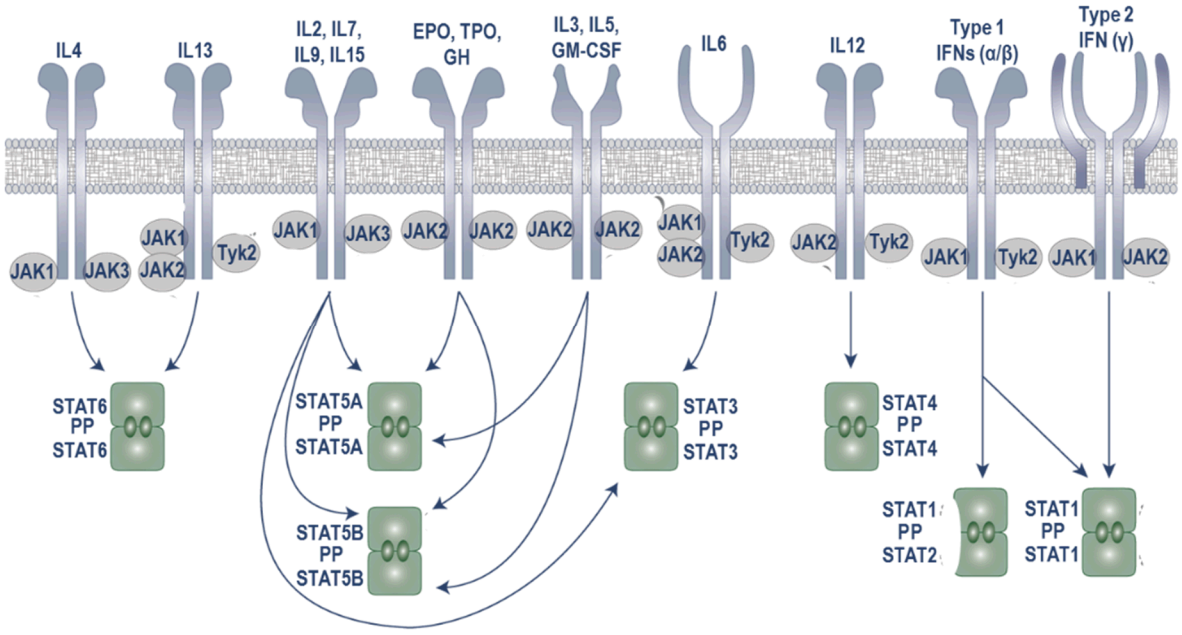
Janus kinases are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis (e.g., erythropoietin [EPO]), inflammation (e.g., interleukin [IL]-6), and immune function (e.g., IL-12, IL-23, granulocyte macrophage colony-stimulating factor [GM-CSF]). Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signaling pathways by specifically inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs. Functional JAK inhibition would be expected to reduce phosphorylated STAT (pSTAT) levels within the cell. As baricitinib is a JAK1/JAK2 inhibitor and cytokines such as IL-6 signal via a JAK1/JAK2 heterodimer, an IL-6 stimulated pSTAT assay was developed and used in early clinical pharmacology studies as a marker of target engagement. Many of the pro-inflammatory cytokines implicated in the pathogenesis of RA, including IL-6 (JAK1/JAK2), GM-CSF (JAK2/JAK2), and interferons (JAK1/JAK2, JAK1/TYK2), signal via the JAK-STAT pathway. Thus, inhibition of JAK1 and JAK2 signaling can target multiple RA-associated cytokine pathways, and thereby reduce inflammation, cellular activation, and proliferation of key immune cells (Figure 30).

Baricitinib was found to inhibit IL-6-induced STAT3 phosphorylation in whole blood from healthy subjects. In single and multiple dose studies, maximal pSTAT inhibition in healthy adults was observed at approximately 1 to 2 hours postdose, coincident with the observed time to reach C_{max}, and ranged from approximately 40% at the lowest dose (1-mg) to approximately 70% to 80% at the highest dose (20-mg). By 24 hours, pSTAT returned to control levels, confirming that baricitinib administered once daily produces inhibition of relevant (IL-6) cytokine activity

that is partial (less than 100%) and reversible and intermittent (for only a portion of the daily dosing interval).

The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

Figure 30: JAK1/JAK2 Inhibition Targets Multiple Pathways



Abbreviations: EPO = erythropoietin; GH = growth hormone; GM-CSF = granulocyte-macrophage colony stimulating factor; IFN = interferon; IL = interleukin; JAK = Janus kinase; PP = phosphorylation; STAT = signal transducer and activator of transcription; TPO = thrombopoietin; Tyk = tyrosine kinase.

2.3. Nonclinical Safety Pharmacology

Safety pharmacology studies were performed to assess cardiac, central nervous system, and respiratory function. Changes observed in the studies were not considered to impact clinical safety since they were observed at exposures significantly above the clinically efficacious dose and were generally mild and monitorable. The risk for QT prolongation due to human ether-a-go-go related gene (hERG) blockade is minimal since the IC_{50} is 1400-fold greater than the clinical C_{max} and is supported by a lack of QT effects in the human study.

2.4. Nonclinical Toxicology

The toxicologic and toxicokinetic profiles of baricitinib were characterized in oral studies of up to 6 months in rats and 9 months in dogs. Genetic toxicology, safety pharmacology, embryo-fetal toxicology studies in rats and rabbits, a rat fertility study, a rat pre-postnatal study and a phototoxicity study have been conducted to support registration.

Decreases in lymphocytes and eosinophils as well as lymphoid depletion in organs/tissues of the immune system were observed in mice, rats and dogs. Opportunistic infections related to demodicosis (mange) were observed in dogs at exposures approximately 7 times the human

exposure. Decreases in red blood cell parameters were observed in mice, rats and dogs at exposures approximately 6 to 36 times the human exposure.

Baricitinib did not produce compound-related adverse changes in plasma lipids (cholesterol and triglycerides), coagulation parameters (prothrombin time, activated partial thromboplastin time, platelets, histological evaluation of blood vessels), or the liver (ALT, AST, histopathology).

Baricitinib was not genotoxic in in vitro and in vivo assays. Administration of baricitinib to rats and mice in carcinogenicity studies did not produce baricitinib-related neoplasms at any of the administered doses. In the 2-year rat study, baricitinib administration was associated with increased survival and decreases in proliferative and neoplastic changes.

The toxicology data do not reveal carcinogenic potential or baricitinib-related effects on coagulation, and the adverse events in the repeat-dose studies are consistent with JAK inhibition and immunosuppression. In conclusion, the overall findings from the nonclinical toxicology program support the clinical dose regimen proposed for baricitinib treatment of adults with moderately to severely active RA.

3. Clinical Pharmacology Overview

- Baricitinib has an absolute bioavailability of 79% and is rapidly absorbed, with a median t_{max} of 1 hour and $t_{1/2}$ of 12.5 hours. Administration with meals was not associated with a clinically relevant effect on exposure.
- Baricitinib is primarily excreted in the urine as unchanged drug (69%) and is minimally cleared through hepatic metabolism (<10% identified as metabolites).
- None of the patient factors of body weight, age, sex, race, ethnicity, or hepatic impairment had a clinically relevant effect on the PK of baricitinib.
- The recommended dose of baricitinib in patients with moderate renal impairment is 2-mg once daily. Baricitinib is not recommended for use in patients with severe renal impairment (eGFR<30 mL/min) or end-stage renal disease (ESRD); no dose adjustment is needed for patients with mild renal impairment.
- Baricitinib is a substrate of the renal transporter Organic Anion Transporter 3 (OAT3). The recommended dose of baricitinib in patients taking strong OAT3 inhibitors, such as probenecid, is 2-mg once daily. There is a low likelihood of other transporter-mediated drug-drug interactions (DDI) with baricitinib as either the victim or perpetrator.
- Baricitinib is a substrate of CYP3A4. There is a low likelihood of CYP-mediated DDI with baricitinib as either the victim or perpetrator.

The clinical pharmacology of baricitinib was evaluated in 19 clinical pharmacology studies, three Phase 2 studies, four Phase 3 studies, and a series of in vitro studies using human biomaterials. Across the clinical pharmacology studies, single doses of baricitinib were administered over a range of 1 to 40 mg. Multiple doses were administered up to 20-mg once daily for 10 days, up to 10-mg daily for 28 days (either 10-mg once daily or 5-mg twice daily) and up to 15-mg once daily for 28 days. Clinical pharmacology studies included healthy subjects and patients with RA, and special population studies included subjects with renal or hepatic impairment.

3.1. Pharmacokinetics

Following oral administration of baricitinib, a dose-proportional increase in systemic exposure was observed in the therapeutic dose range. The PK of baricitinib is linear with respect to time. Steady state was typically reached between the second and third doses. Accumulation during QD dosing was minimal, with an accumulation ratio of 1.11- and 1.15-fold for C_{max} and AUC, respectively. Pharmacokinetics after multiple doses were predictable from single-dose data.

Absorption: Following oral administration, baricitinib is rapidly absorbed with a median time to maximum observed drug concentration (t_{max}) of approximately 1 hour (range 0.5 - 3.0 h). The absolute bioavailability of baricitinib is 78.9% (90% CI: 76.9% to 81.0%). Food intake led to a decreased exposure by up to 14%, a decrease in C_{max} by up to 18% and delayed t_{max} by 0.5 hours. Administration with meals was not associated with a clinically relevant effect on exposure.

Distribution: Mean volume of distribution following intravenous infusion administration was 76 L, indicating distribution of baricitinib into tissues. Baricitinib is approximately 50% bound to plasma proteins.

Biotransformation: Baricitinib metabolism is mediated by CYP3A4, with less than 10% of the dose identified as undergoing biotransformation. No metabolites were quantifiable in plasma. In a clinical pharmacology study, baricitinib was excreted predominately as the unchanged active substance in urine (69%) and feces (15%) and only 4 minor oxidative metabolites were identified (3 in urine; 1 in feces) constituting approximately 5% and 1% of the dose, respectively. In patients with mild or moderate hepatic impairment, there was no clinically relevant effect on the PK of baricitinib. The use of baricitinib has not been studied in patients with severe hepatic impairment.

Elimination: Renal elimination is the principal mechanism for baricitinib's clearance through glomerular filtration and active secretion via OAT3, Pgp, BCRP and MATE2-K. In a clinical pharmacology mass balance study where 95% of the total dose was recovered, approximately 75% of the administered dose was eliminated in the urine, while about 20% of the dose was eliminated in the feces. Mean apparent clearance (CL/F) and half-life in patients with RA was 9.42 L/hr (CV = 34.3%) and 12.5 hrs (CV = 27.4%), respectively. The CL/F in patients with RA is approximately 46% lower than that in healthy subjects.

Renal Impairment: Renal impairment significantly affected baricitinib exposure. In a clinical pharmacology study conducted in otherwise healthy subjects with renal impairment, the geometric mean ratio of area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$) was 1.41, 2.22, and 4.05 for the mild, moderate, and severe renal impairment cohorts, respectively, compared with healthy subjects with normal renal function.

The Primary Phase 2/3 PopPK Analysis showed a less pronounced effect of estimated glomerular filtration rate (eGFR) (calculated using the Modification of Diet in Renal Disease (MDRD) equation) on the exposure of baricitinib in patients with RA compared to the observations in non-RA subjects. The estimated mean ratios (lower MDRD-eGFR : normal renal function) for area under the concentration versus time curve during one dosing interval at steady state ($AUC_{\tau,ss}$) in patients with RA were 1.30 and 1.62 for mild and moderate renal impairment, respectively (Table 11). Renal impairment has a minimum effect on the peak concentration at steady state ($C_{max,ss}$) of baricitinib (Table 11).

Table 11: Estimated mean ratios (lower MDRD-eGFR: normal renal function) for $AUC_{\tau,ss}$ and $C_{max,ss}$ in patients with RA based on the Primary Phase 2/3 PopPK Analysis

Renal impairment group	MDRD-eGFR (mL/min/1.73 m^2)	Mean Ratio (90% CI) for $AUC_{\tau,ss}$	Mean Ratio (90% CI) for $C_{max,ss}$
Mild	60-<90	1.30 (1.06 – 1.73)	1.08 (1.00 – 1.17)
Moderate	30-<60	1.62 (1.37 – 2.14)	1.17 (1.10 – 1.28)

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration time curve during one dosing interval at steady state; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; PopPK = population pharmacokinetics; RA = rheumatoid arthritis.

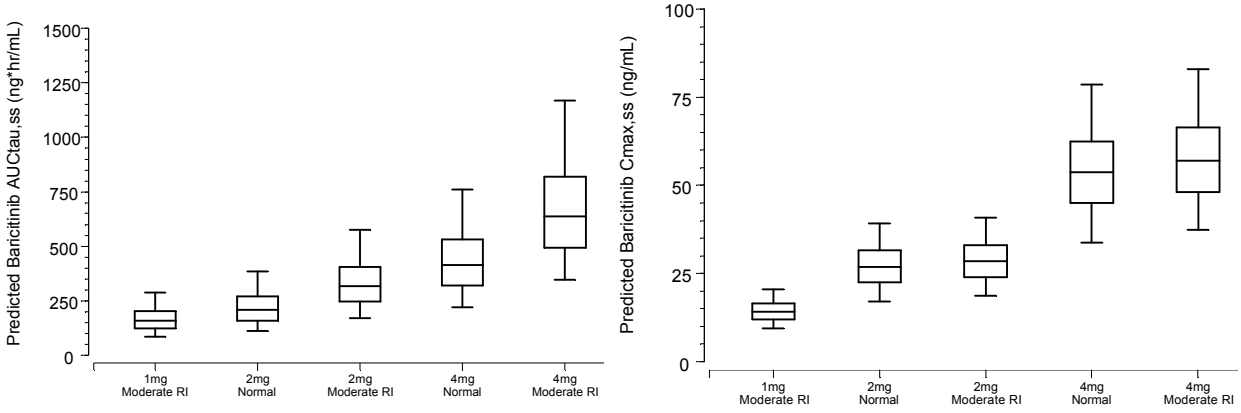
Estimates for $AUC_{\tau,ss}$ and $C_{max,ss}$ at 1-, 2-, and 4-mg doses are compared for patients in various renal function groups based on the Primary Phase 2/3 PopPK Analysis (Figure 31). When the dose was reduced from 4-mg to 2-mg for patients with moderate renal impairment (MDRD = 30

to <60 mL/min/1.73 m2), the resulting exposures ($AUC_{\tau,ss}$ and $C_{max,ss}$) were between those of 2-mg and 4-mg in patients with normal renal function. On the other hand, a dose reduction to 1-mg for patients with moderate renal impairment would result in exposures lower than the 2-mg exposures in patients with normal renal function. The lower exposures reside on the slope portion of the E-R curve of DA28-CRP<=3.2 estimated for the 1cDMARD-IR patient subgroup (for whom a 2-mg dose was recommended) as shown in Figure 32, resulting in more patients not achieving a low disease activity. Therefore, a dose of 2-mg is recommended as a suitable dose for patients with moderate renal impairment.

No dose adjustment is needed for patients with mild renal impairment. Baricitinib is not recommended for use in patients with severe renal impairment or end-stage renal disease (ESRD).

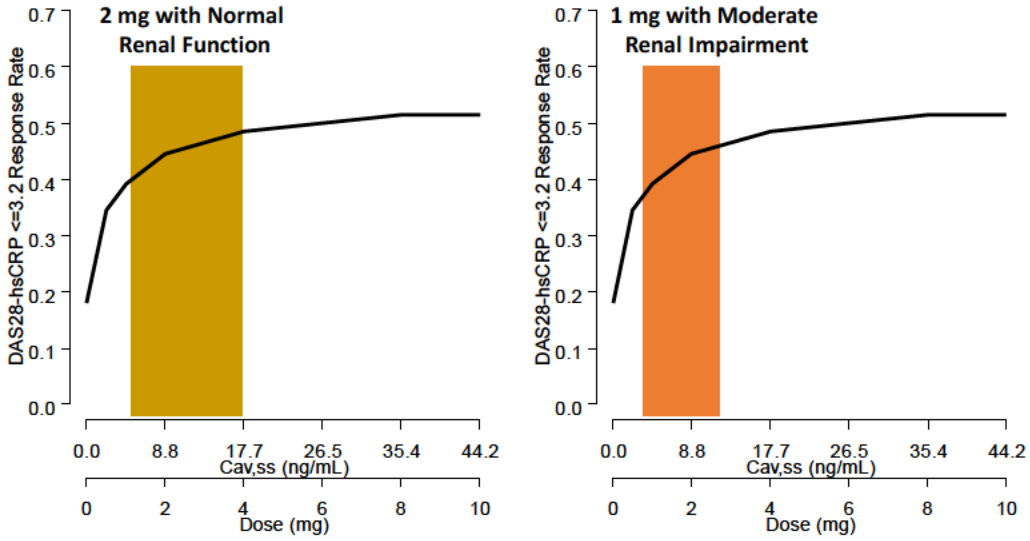
Other Intrinsic Factors: None of the patient factors of body weight, age, sex, race, ethnicity, or hepatic impairment had a clinically relevant effect on the PK of baricitinib. Figure 33 summarizes the impact of intrinsic factors associated with baricitinib and includes the proposed dosing recommendation.

Figure 31: Box Plots Comparing Baricitinib (1-mg, 2-mg, and 4-mg Doses) Plasma $AUC_{\tau,ss}$ and $C_{max,ss}$ for Different Renal Function Groups



Abbreviations: AUCτ,ss = area under the concentration time curve during one dosing interval at steady state; Cmax,ss = maximum observed drug concentration during a dosing interval at steady state; RI = renal impairment.
Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.

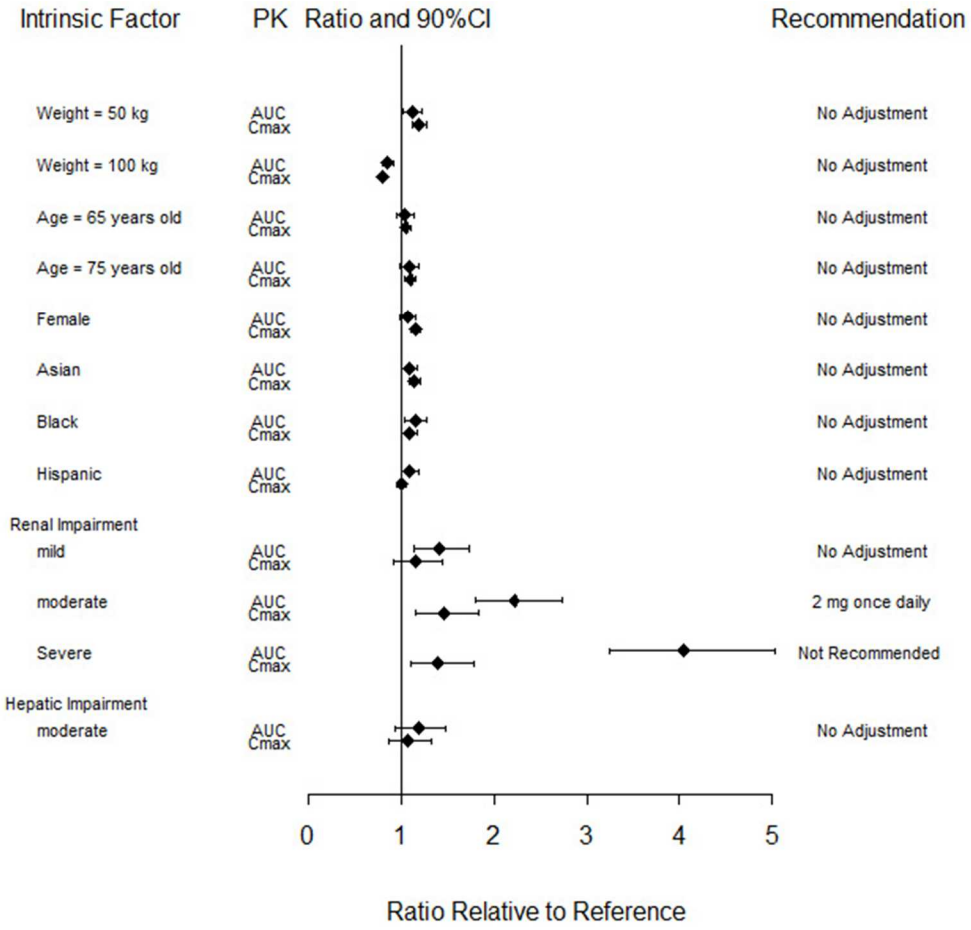
Figure 32: Exposure range of 1-mg in moderate renal impairment on the estimated E-R curve for DAS28-CRP<=3.2 in the less refractory patients (1-cDMARD-IR)



Abbreviations: Cav,ss = average concentration during a dosing interval at steady state; cDMARD = conventional disease-modifying antirheumatic drug; CRP = C-reactive protein; DAS28 = Disease Activity Score based on the 28 diarthrodial joint count; IR= inadequate responder.

Solid black lines are model-predicted mean response rate of DAS28-CRP<=3.2 in the 1cDMARD-IR patient. Yellow and orange shaded area indicate baricitinib concentration range (5^{th} – 95^{th} percentiles) for 2-mg with normal renal function and 1 mg with moderate renal impairment, respectively.

Figure 33: Impact of Intrinsic Factors on Baricitinib Pharmacokinetics[a,b]



a Reference values for weight, age, gender, and race comparisons are 70 kg, 54 years, male, and white, respectively; reference groups for renal and hepatic impairment are subjects with normal renal and hepatic function, respectively.

b Effects of renal and hepatic impairment on baricitinib exposure were summarized from dedicated renal and hepatic impairment studies, respectively. Effects of other intrinsic factors on baricitinib exposure were summarized from population PK analysis.

3.2. Drug-Drug Interaction Potential

Potential for other medicinal products to affect the pharmacokinetics of baricitinib

Cytochrome P450 enzymes: In vitro, baricitinib is a CYP3A4 substrate although less than 10% of the dose is metabolized via oxidation. In clinical pharmacology studies, coadministration of baricitinib with ketoconazole (strong CYP3A inhibitor) resulted in no clinically meaningful effect on the PK of baricitinib. Coadministration of baricitinib with fluconazole (moderate CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampicin (strong CYP3A inducer) resulted in no clinically meaningful changes to baricitinib exposure.

Transporters: In vitro, baricitinib is a substrate for OAT3, P-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and multidrug and toxic extrusion protein (MATE)2-K. In a clinical pharmacology study in healthy volunteers, dosing of probenecid (an OAT3 inhibitor with strong inhibition potential) resulted in approximately a 2-fold increase in AUC(0-∞) with no change in t_{max} or C_{max} of baricitinib. Using physiologically-based pharmacokinetics (PBPK) simulations,

the effect of probenecid resulted in a smaller (approximately 1.4-fold) increase in AUC in RA patients, likely due to a smaller fraction of the OAT3-mediated renal clearance in RA patients compared to healthy subjects. Consequently, the recommended dose in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid, is 2-mg once daily, irrespective of the baricitinib dose prior to concomitant use with probenecid.

No clinically relevant interactions with the OAT3 inhibitors ibuprofen and diclofenac, which have less inhibition potential compared to probenecid, were observed in Phase 2/3 based on PopPK, as well as PBPK simulations. Coadministration of baricitinib with cyclosporine (Pgp/BCRP inhibitor) or methotrexate (substrate of several transporters including organic anion transporting polypeptide 1B1 [OATP1B1], OAT1, OAT3, BCRP, MRP2, MRP3, and MRP4) resulted in no clinically meaningful effects on baricitinib exposure.

Gastric pH modifying agents: Elevating gastric pH with omeprazole had no clinically significant effect on baricitinib exposure.

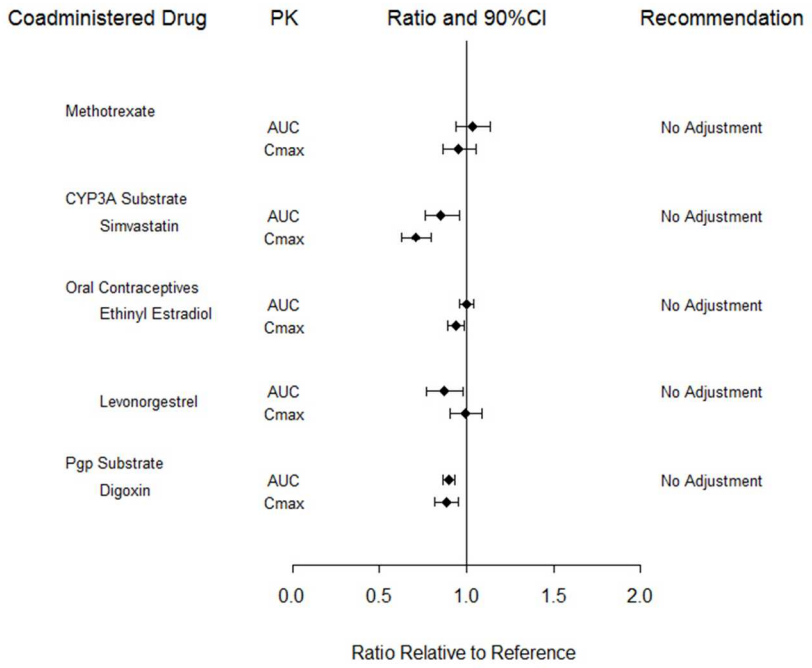
Potential for baricitinib to affect the pharmacokinetics of other medicinal products

Cytochrome P450 enzymes: In vitro inhibition and induction studies suggest a low likelihood of CYP-mediated, clinically relevant drug-drug interactions with baricitinib. In clinical pharmacology studies, coadministration of baricitinib with the CYP3A substrates simvastatin, ethinyl estradiol, or levonorgestrel resulted in no clinically meaningful changes in the PK of these medicinal products. Dose alterations of sensitive CYP substrates, as well as drugs with a narrow therapeutic range, such as warfarin, are not needed.

Transporters: In vitro, baricitinib did not inhibit OATP1B1 or Pgp, although baricitinib did inhibit OAT1, OAT2, OAT3, organic cationic transporter (OCT) 1, OCT2, OATP1B3, BCRP and MATE1 and MATE2-K. However, clinically meaningful changes in the PK of medicinal products that are substrates for these transporters are unlikely based on standard in vitro-in vivo correlation methods. Furthermore, in clinical pharmacology studies there were no clinically meaningful effects on exposure when baricitinib was co-administered with digoxin (Pgp substrate) or methotrexate (substrate of several transporters).

Figure 34 summarizes the exposure changes of drugs following co-administration with baricitinib and includes the proposed dosing recommendation.

Figure 34: Impact of Baricitinib on the Pharmacokinetics of Other Drugs[a]



Abbreviations: AUC=area under the concentration versus time curve; C_{max}=maximum plasma concentration; CYP=cytochrome P450; Pgp=P-glycoprotein

a Reference group is administration of concomitant drug alone.

4. Exposure Response Evaluation and Dosing Recommendation

- Three Phase 2 studies included doses ranging from 1-mg to 10 mg.
- Observed and modeled data informed the decision to study 4-mg as the optimally effective dose with an acceptable safety profile, and 2-mg as a potentially efficacious dose for some patients.

4.1. Phase 2 Studies and Phase 3 Dose Selection

Dose selection for Phase 3 was based on the results of the Phase 2 studies: Study JADC and Study JADA (Section 4.1.1), as well as PK/PD modeling (Section 1.4).

Baricitinib 4-mg once daily resided on the plateau of the efficacy dose response curve for all domains of efficacy and higher doses did not increase the observed or modelled treatment benefit. The 1-mg dose of baricitinib was biologically active, but the observed and modelled treatment benefits were not considered compelling in the context of available therapies for RA. Therefore, further evaluation of 1-mg or lower doses was not appropriate, as it would not offer study patients an acceptable probability of achieving contemporary treatment goals. As doses larger than 4-mg did not offer meaningful increased benefit, both the 2-mg and 4-mg doses, which were well-tolerated, were taken into Phase 3.

4.1.1. Phase 2 Dose-Ranging Evaluation

Dose-ranging data were reviewed from Phase 2 studies of baricitinib in RA patients that included 1-mg, 2-mg, 4-mg, and 8-mg: Study JADA (N = 301 in US, Europe, India, Mexico) and Study JADN (N = 145 in Japan).

- ACR responses were assessed; ACR20 was the primary outcome measure in each study, and ACR50 was evaluated as a more clinically relevant, higher level of response (FDA 2013).
- As ACR responses have been noted to discriminate suboptimally between active treatments, more sensitive continuous measures including DAS28 and CDAI were evaluated (FDA 2013, EMA 2015, Felson et al. 2007).
- Measures of low disease activity / remission were also evaluated, as these are the established targets of therapy for patients (Smolen et al. 2017; Singh et al. 2015).
- Composite score components were evaluated to assure that composite effects were not established without effect on all components (FDA 2017). These included physician- and PRO measures as well as objective measures of acute-phase response.
- To better capture possible differences between doses, evaluation included early timepoints before the therapeutic plateau (FDA 2013, EMA 2015). Timely achievement of treatment goals is advocated in RA guidelines (Smolen et al. 2017; Singh et al. 2015), and patients prefer rapid onset of benefit, which can improve adherence (Alldred and Emery 2001; Fraenkel et al. 2004; Neame and Hammond 2005; Strand et al. 2015; Louder et al. 2016).
- Safety findings, including adverse events and laboratory evaluations, were assessed

Results

Overall, the onset and consistency of improvement vs. placebo in Studies JADA and JADN was most robust for baricitinib 4-mg and 8-mg and least robust for the 1-mg dose. Onset and consistency of statistical separation of composite measures of disease activity and the components of those composite endpoints are summarized in Table 13.

Composite measures (Figure 35)

- Baricitinib 4-mg and 8-mg showed statistically significant improvement in ACR20 compared to placebo.
- Baricitinib 4-mg and 8-mg showed the largest improvements in ACR50 response rates and DAS28, which were significant compared to placebo from the earliest weeks of treatment in both studies.
- Baricitinib 2-mg was not significantly different from placebo based on ACR50 response at any point in Study JADA and it showed improvement only at Week 12 in Study JADN. For DAS28, baricitinib 2-mg showed significant improvement compared to placebo across timepoints in Study JADN, but only at Week 4 in Study JADA.
- For 1-mg, improvement in DAS28 was noted at earlier timepoints and at Week 12, but improvement for ACR50 response rates was only noted at Week 12 in both studies.
- Similar results were observed for composite measures without acute phase reactants.

Physician-reported composite measure components (Figure 36)

- Baricitinib 4-mg and 8-mg showed the largest improvements in TJC, SJC, and physician's global assessment, which were significant from the earliest weeks of treatment in both studies.
- Baricitinib 2-mg showed significant improvements compared to placebo at various timepoints prior to Week 12 in Study JADN, but at only a single or no timepoints in Study JADA.
- For the 1-mg dose, improvement was noted at selected timepoints in Study JADN, but at no timepoints in Study JADA.

Patient-reported composite measure components (Figure 37)

- Baricitinib 4-mg and 8-mg showed significant improvements compared to placebo in HAQ-DI, patient's assessment of pain, and patient's global assessment from the earliest weeks of treatment in both studies.
- Baricitinib 2-mg showed significant improvements compared to placebo at various timepoints prior to Week 12 in Study JADN, but at only a single or no timepoints in Study JADA.
- Baricitinib 1-mg showed significant improvements compared to placebo at selected timepoints across measures; significant improvement in HAQ-DI was seen only at Week 12 in both studies.

Safety

The Phase 2 dose-ranging studies were included in the integrated safety evaluation, the results of which are described in Sections 1.6 and 6. Dose-specific safety considerations from the dose-ranging studies include:

- All assessed doses were well-tolerated (Table 12); few SAEs (including serious infections) or AEs leading to discontinuation were reported at any dose level.
- Some additional signals were seen above 4-mg, including for TEAEs and changes in selected laboratory analytes.
- In conjunction with the efficacy profile described above, these findings supported 4-mg and 2-mg as the appropriate doses to advance to confirmatory evaluation.

Table 12: Phase 2b Studies JADA and JADN, Safety in Placebo-Controlled Period

	Study JADA					Study JADN				
	Pbo N=98	**1 mg N=49**	**2-mg N=52**	**4-mg N=52**	**8 mg N=50**	**Pbo N=49**	**1 mg N=24**	**2-mg N=24**	**4-mg N=24**	**8 mg N=24**
TEAE, n (%)	45 (46)	20 (41)	24 (46)	22 (42)	26 (52)	26 (53)	11 (46)	12 (50)	13 (54)	18 (75)
SAE, n (%)	3 (3)	0	3 (6)	0	1 (2)	1 (2)	0	1 (4)	0	1 (4)
Serious infection, n (%)	0	0	2 (4)	0	0	0	0	0	0	0
Adverse event leading to permanent discontinuation, n (%)	5 (5)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (4)	0	0	0
Mean change in hemoglobin[a]	-0.14	0.12*	-0.09	-0.15	-0.54**	-0.13	0.11	-0.02	-0.16	-0.21

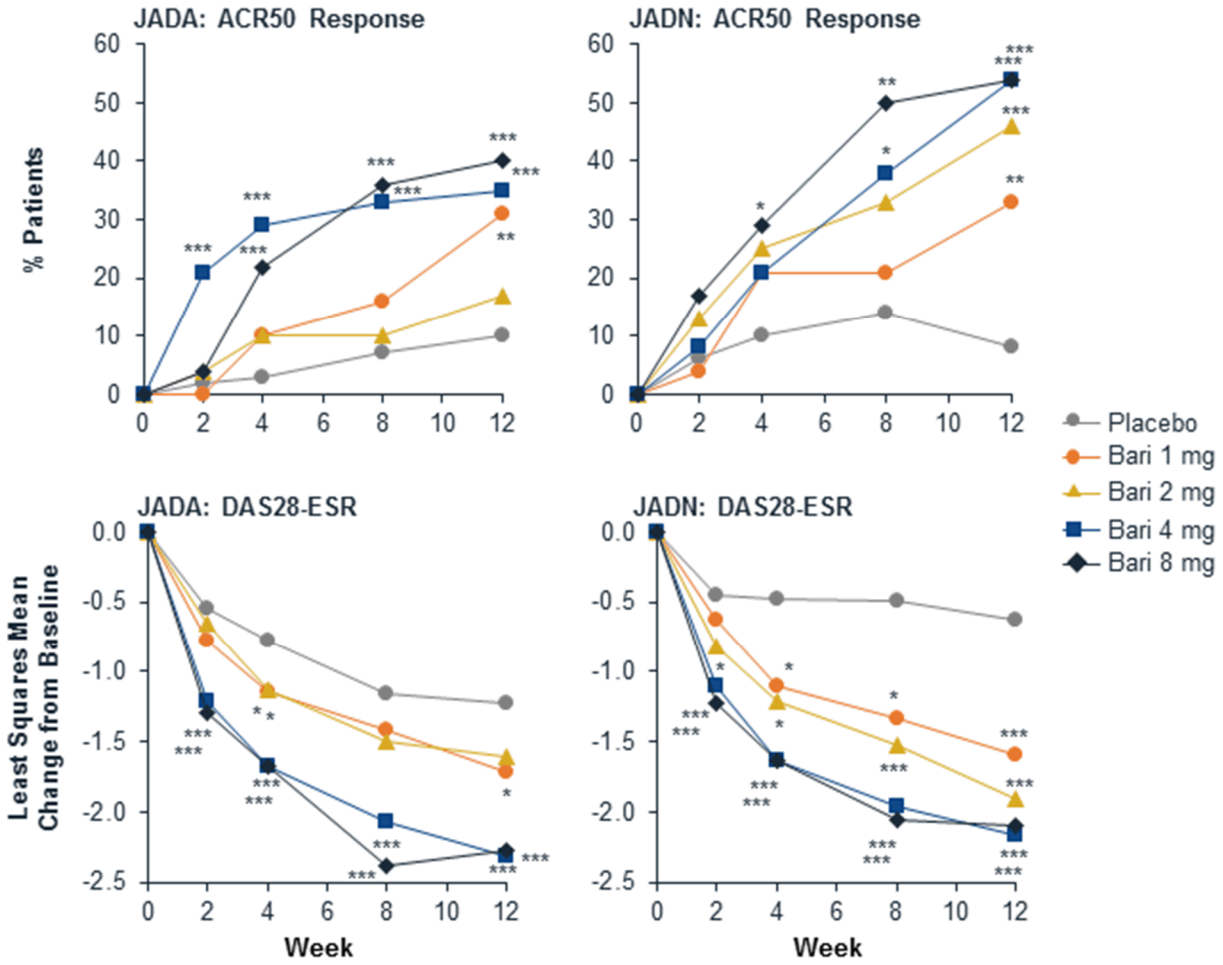
Abbreviations: n = number of patients with indicated event; N = number of patients in group; Pbo = placebo; SAE = serious adverse event; TEAE = treatment emergent adverse event.
Baricitinib dose versus placebo: *p≤0.05; **p≤0.01.
Data are from Weeks 0 – 12.
[a] g/dL in JADA and mmol/L in JADN.

Table 13: Onset of Statistical Separation for Composite Endpoints and Components

	JADA	JADN
ACR50	8-mg: Wk 4 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Not observed 1-mg: Wk 12 only	8-mg: Wk 4 ⇒ Wk 12 4-mg: Wk 8 ⇒ Wk 12 2-mg: Wk 12 only 1-mg: Wk 12 only
Change in DAS28-ESR	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 4 1-mg: Wk 4, Wk 12	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 2 ⇒ Wk 12 1-mg: Wk 4 ⇒ Wk 12
Change in CDAI	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Not observed 1-mg: Not observed	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 4 ⇒ Wk 12 1-mg: Wk 4 ⇒ Wk 12
Change in TJC68	8-mg: Wk 4 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 4 1-mg: Not observed	8-mg: Wk 4 ⇒ Wk 12 4-mg: Wk 4 ⇒ Wk 12 2-mg: Wk 8 ⇒ W12 1-mg: Wk 12 only
Change in SJC66	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Not observed 1-mg: Not observed	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 4 ⇒ W12 1-mg: Wk 8 ⇒ Wk 12
Physician's Global Assessment	8-mg: Wk 4 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Not observed 1-mg: Not observed	8-mg: Wk 2 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 2 ⇒ W12 1-mg: Wk 2 ⇒ Wk 12
HAQ-DI	8-mg: Wk 4 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Not observed 1-mg: Wk 2, Wk 12	8-mg: Wk 2 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 2, Wk 4, W12 1-mg: Wk 8 ⇒ Wk 12
Patient's Assessment of Pain	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Not observed 1-mg: Wk 4, Wk 12	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 2 ⇒ Wk 12 1-mg: Wk 4 ⇒ Wk 12
Patient's Global Assessment	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Not observed 1-mg: Wk 4 ⇒ Wk 12	4-mg/8-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 4 ⇒ Wk 12 1-mg: Wk 2 ⇒ Wk 12
hsCRP	8-mg: Wk 2 ⇒ Wk 8 4-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 2 ⇒ Wk 8 1-mg: Wk 2 ⇒ Wk 12	8-mg: Wk 2 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 2 ⇒ Wk 12 1-mg: Wk 4 ⇒ Wk 12
ESR	8-mg: Wk 2, Wk4, Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 2, Wk 4 1-mg: Wk 2, Wk4, Wk 12	8-mg: Wk 2 ⇒ Wk 12 4-mg: Wk 2 ⇒ Wk 12 2-mg: Wk 4 ⇒ Wk 12 1-mg: Wk 2 ⇒ Wk 12

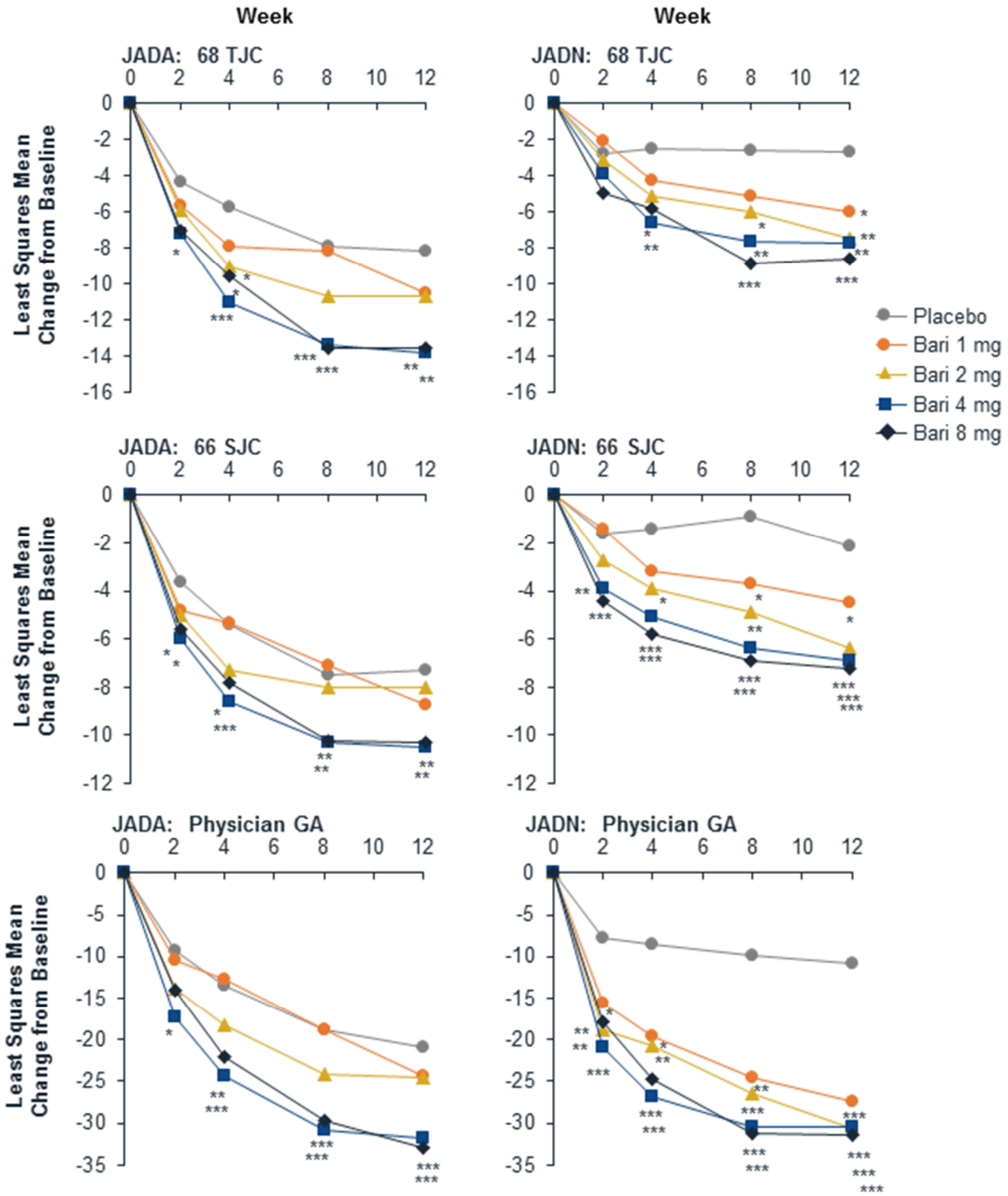
Abbreviations: ACR50 = 50% improvement in American College of Rheumatology criteria; CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score based on the 28 diarthrodial joint count; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire–Disability Index; hsCRP = high-sensitivity C-reactive protein; SJC = swollen joint count; TJC = tender joint count; Wk = week. Placebo was included through Week 12 in Studies JADA and JADN.

Figure 35: ACR50 response rates and change from baseline in DAS28-ESR over time in Studies JADA and JADN



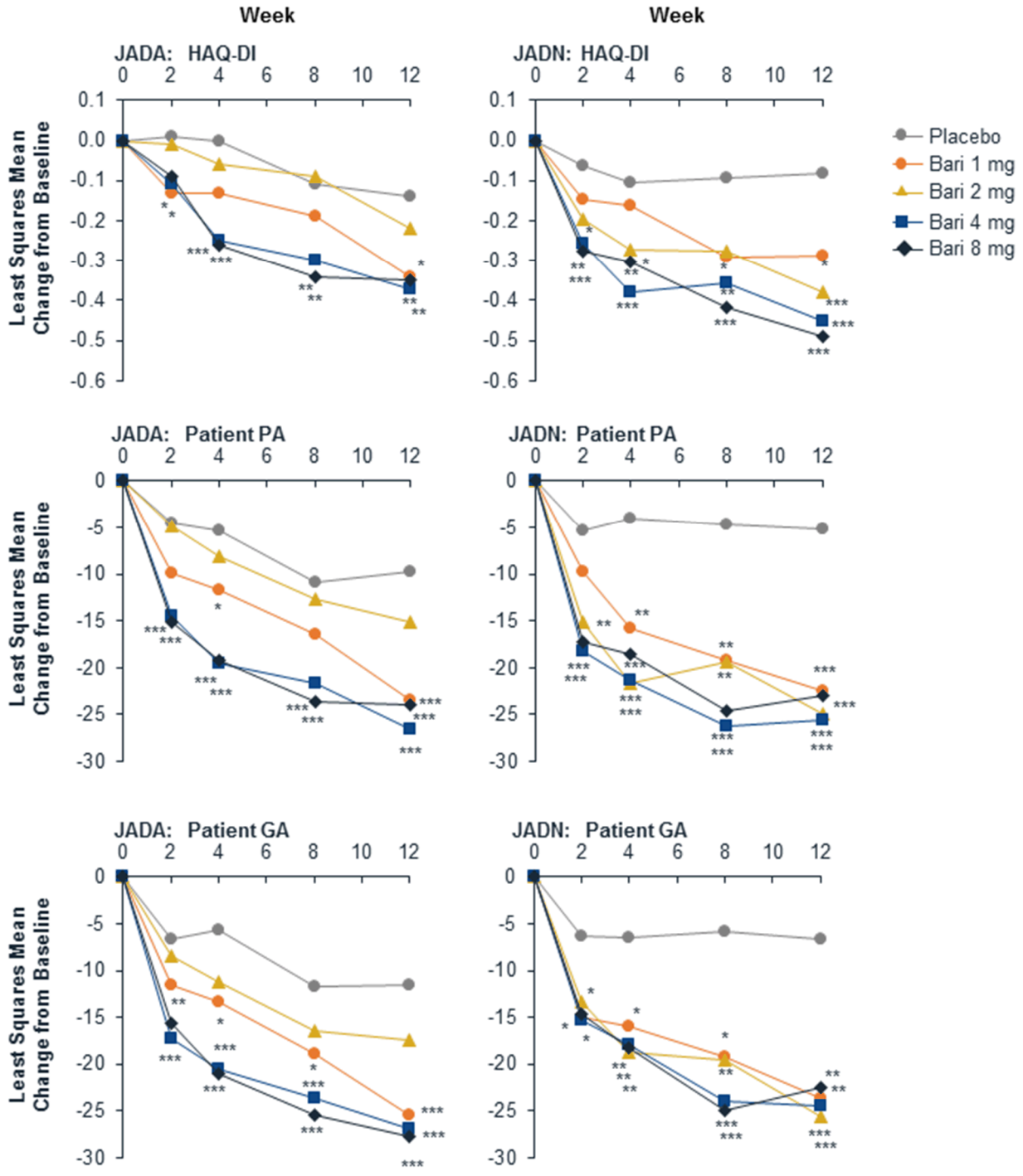
Abbreviations: Δ = change; ACR50 = 50% improvement in American College of Rheumatology criteria; ANCOVA = analysis of covariance; DAS28 = Disease Activity Score based on the 28 diarthrodial joint count; ESR = erythrocyte sedimentation rate; LS = least squares; vs = versus.
*p<=.05, **p<=.01, ***p<=.001 vs placebo.
Imputation methods: observed data for ΔDAS28-ESR. NRI for ACR50.

Figure 36: Physician-Reported Outcomes through Week 12 in Studies JADA and JADN



Abbreviations: Δ = change; ANCOVA = analysis of covariance; GA = global assessment; LS = least squares; SJC = swollen joint count; TJC = tender joint count; vs = versus.
*p<=.05, **p<=.01, ***p<=.001 vs placebo.
All analyses are observed data.

Figure 37: Patient-Reported Outcomes through Week 12 in Studies JADA and JADN.



Abbreviations: Δ = change; ANCOVA = analysis of covariance; GA = global assessment; HAQ-DI = Health Assessment Questionnaire–Disability Index; LS = least squares; PA = pain assessment; vs = versus.
All analyses are observed data.

4.1.2. Phase 2 Exposure Response Analysis

The E-R relationship characterized based on Phase 2 study JADA is included in Section 1.4 (Figure 3). The results from this E-R analysis are consistent with the observed clinical data and support that the choice of 4-mg as the primary dose to be tested in Phase 3; and 2-mg as a second dose that might be suitably effective for some patients. Further evaluation of 1-mg or lower doses would not offer an acceptable probability of achieving treatment goals in many patients.

5. Pivotal Efficacy Studies with Baricitinib

- Baricitinib has shown substantial evidence of efficacy across RA patient populations from DMARD-naïve patients to those with inadequate response to multiple DMARDs.
- In the 3 DMARD-IR studies (JADW, JADX, and JADV), greater than 95% of patients across the studies had prior inadequate response or intolerance to MTX, consistent with the proposed indication.
- Benefit was rapid (within days), consistent across clinically relevant measures, and maintained during long-term treatment.
- The most robust efficacy was seen for the 4-mg dose, which demonstrated significantly improved efficacy against leading injectable and oral standard of care comparators (MTX in JADZ and adalimumab used with background MTX in JADV).
- In a randomized and blinded assessment in the long-term extension study JADY, remaining on the 4-mg dose was superior to 2-mg dose taper for long-term maintenance of efficacy. However, most patients maintained LDA or remission even with dose tapering from 4-mg to 2-mg. The minority of patients who required rescue following taper could recapture LDA/remission with return to 4-mg.
- Final E-R analysis based on combined Phase 2 and 3 data confirmed Phase 2 findings.
- Final E-R subgroup analysis shows that the more refractory bDMARD-IR and 2+cDMARD-IR patients had higher EC50 and EC80 values than the less refractory 1cDMARD-IR patients. It indicates that the more refractory patients (bDMARD-IR and 2+cDMARD-IR) need higher baricitinib concentrations to achieve the same efficacy as the less refractory patients.

5.1. Efficacy Endpoints

The Phase 3 studies employed efficacy endpoints that encompass four key domains of treatment in RA: signs and symptoms, physical function, PROs, and radiographic progression of structural joint damage.

5.1.1. Efficacy Measures

Signs and Symptoms: The primary outcome measure in all studies was the percent of patients who achieved at least a 20% improvement in the ACR response criteria (ACR20).

The ACR50 and ACR70, which assess the percent of patients who achieve at least a 50% and 70% improvement in the ACR criteria, respectively, were included as additional endpoints as these higher levels of improvement may better reflect the expectations of patients, prescribers, and healthcare systems.

Compared to ACR responses, continuous disease activity measures have more sensitivity to discriminate between treatment groups (FDA 2013, Felson 2007) and are more clinically useful as they can reflect the momentary disease state, including low disease activity and remission, which are the clinical treatment targets recommended by current guidelines (Singh 2015, Smolen 2017). These measures include Disease Activity Score based on 28 joint counts (DAS28) and Simplified Disease Activity Index (SDAI), both of which have been validated and are commonly used to assess disease activity. The inclusion of SDAI remission as a key secondary endpoint is

consistent with the 2013 FDA draft guidance on developing drug products for the treatment of RA (FDA 2013).

Physical Function or Disability: Patients' assessment of their physical functioning was measured using the Health Assessment Questionnaire-Disability Index (HAQ-DI). The HAQ-DI is a patient-reported questionnaire that measures disease-associated disability.

Patient-Reported Outcomes: Patients completed daily electronic PRO (ePRO) diaries capturing duration and severity of morning joint stiffness, worst tiredness, and worst joint pain through Week 12 in the cDMARD-IR Studies JADX and JADV. Additionally, all studies collected information on fatigue (FACIT-F), health-related quality of life (SF-36) and work productivity and activity impairment (WPAI-RA) at study visits. These were included because they are recognized symptoms of importance to patients (Taylor 2016).

Structure: Slowing the progression of structural joint damage is the quality that classifies a treatment as disease-modifying. To assess progression of joint damage, the modified Total Sharp Score (mTSS), which is a radiographic measure of structural joint damage in the hands and feet, was included as a key secondary endpoint in JADV and JADZ and an exploratory measure in JADX.

5.1.1.1. Primary Endpoint

The primary endpoint in each study was the percent of patients who achieved ACR20, the most commonly used primary outcome measure in RA registration trials designed to show superiority of active treatment over placebo.

ACR20 is defined as at least 20% improvement in the following ACR Core Set values:

- Number of tender joints (0 to 68)
- Number of swollen joints (0 to 66)
- In at least 3 of the following 5 assessments:
  - Patient's assessment of pain (0 to 100 mm visual analog scale [VAS]))
  - Patient's Global Assessment of Disease Activity (0 to 100 mm VAS)
  - Physician's Global Assessment of Disease Activity (0 to 100 mm VAS)
  - Patient's assessment of physical function as measured by the HAQ-DI
  - Acute phase reactant as measured by hsCRP as a laboratory assessment of systemic inflammation (an alternative, erythrocyte sedimentation rate [ESR], was also collected and incorporated among other secondary objectives)

The ACR50 and ACR70 were also assessed as additional endpoints.

5.1.1.2. Secondary Endpoints

In each Phase 3 study, multiple **key secondary** endpoints were also analyzed using multiplicity-adjusted testing procedures to control the rate of false positive conclusions (see Section 10 for more information regarding the statistical analyses methods).

Simplified Disease Activity Index (SDAI): The SDAI is a tool for measuring disease activity that integrates physical findings, acute phase response, patient self-assessment, and evaluator assessment (Aletaha and Smolen 2005). Disease remission is defined as an SDAI score ≤3.3, and an SDAI score ≤11 indicates low disease activity (LDA). The SDAI score 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
- Patient's Global Assessment of Disease Activity (0 to 10 cm VAS)
- Physician's Global Assessment of Disease Activity (0 to 10 cm VAS)

The percentage of patients achieving remission (SDAI ≤3.3) was a **key secondary** endpoint in each of the Phase 3 studies, with the percentage of patients achieving LDA (≤11) and change from baseline included as additional secondary endpoints.

Clinical Disease Activity Index (CDAI): The CDAI is a tool for measuring disease activity that integrates physical findings, patient self-assessment, and evaluator assessment. CDAI includes all components of SDAI except CRP. Disease remission is defined as a CDAI score ≤2.8, and a CDAI score ≤10 indicates LDA. CDAI was used as an inclusion criterion and the principal outcome measure for the JADY randomized dose taper substudy, as well as additional secondary objective across the completed studies (including change from baseline, LDA, and remission).

Disease Activity Score (DAS28): The DAS28-CRP is a measure that takes into account the number of swollen and tender joints (0-28), CRP, and the Patient's Global Assessment of Disease Activity (Vander Cruyssen et al. 2005). Change from baseline in the DAS28-CRP was a **key secondary** endpoint in the Phase 3 studies. This can also be calculated using ESR (DAS28-ESR), which was included as an additional secondary measure.

Health Assessment Questionnaire-Disability Index (HAQ-DI): A patient-reported questionnaire that measures disease-associated disability. The HAQ-DI consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities (Fries et al. 1980, 1982; Ramey et al. 1996). Scores range from 0-3 with a higher score indicating worse physical function. Change from baseline in the HAQ-DI was a **key secondary** endpoint in the Phase 3 studies.

van der Heijde Modified Total Sharp Score (mTSS): X-rays of the hands/wrists and feet were scored for radiographic progression of structural joint damage as measured using the mTSS (van der Heijde 2000). This methodology quantifies the extent of bone erosions for 44 joints and joint space narrowing for 42 joints with higher scores representing greater damage. Change from baseline in the mTSS was a **key secondary** endpoint in Studies JADV and JADZ and an exploratory endpoint in Study JADX.

ePRO Diary: Patients in Studies JADV and JADX completed a daily electronic diary beginning at the time of randomization through Week 12. The following outcome measures were assessed using data from the diary:

- Duration of Morning Joint Stiffness: a single item that allowed the patients to enter the length of time in minutes that their morning joint stiffness lasted each day.
- Morning Joint Stiffness Severity Numeric Rating Scale (NRS): a single-item, 11-point scale anchored at 0 and 10, with 0 representing "no joint stiffness" and 10 representing "joint stiffness as bad as you can imagine." Patients rated their morning joint stiffness each day by selecting the one number that described their overall level of joint stiffness from the time they woke up.
- Tiredness Severity Numeric Rating Scale (Worst Tiredness NRS): A single-item, 11-point scale anchored at 0 and 10, with 0 representing "no tiredness" and 10 representing "tiredness as bad as you can imagine." Patients rated their tiredness by selecting the one number that described their worst level of tiredness during the past 24 hours.
- Severity of Joint Pain Numeric Rating Scale (Worst Joint Pain NRS): A single-item, 11-point scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine." Patients rated their joint pain by selecting the one number that described their worst level of joint pain in the last 24 hours.

These ePRO diary assessments were **key secondary** endpoints in Studies JADX and JADV.

5.2. JADW (bDMARD-IR)

5.2.1. JADW Study Design

Study JADW was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 24-week study comparing the efficacy of 4-mg and 2-mg doses of baricitinib versus placebo on signs, symptoms, clinical remission, physical function, and additional PROs (Figure 5). Eligible patients had moderately to severely active RA, had an insufficient response to or intolerance to at least 1 prior biologic TNF inhibitor, with no upper limit on the number or nature of prior bDMARDs (bDMARD-IR), and were taking 1-2 stable background cDMARDs (predominantly MTX). Patients were randomly assigned in a 1:1:1 ratio to receive baricitinib 4-mg, baricitinib 2-mg, or placebo, remaining on their stable background cDMARDs ± NSAIDs, analgesics, and corticosteroids (up to 10 mg prednisone daily or equivalent). Patients who did not adequately respond to study drug were eligible for rescue treatment (baricitinib 4-mg) beginning at Week 16.

The primary objective of the study was to determine whether baricitinib 4-mg was superior to placebo in this bDMARD-IR patient population, as assessed by the proportion of patients achieving ACR20 at Week 12. The comparison of 2-mg to placebo (using ACR20 at Week 12) was a **key secondary objective**.

5.2.1.1. JADW Inclusion and Exclusion 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 Classification of Rheumatoid Arthritis (Aletaha et al. 2010)
- Had at least 6 tender joints (of 68 joints examined) and 6 swollen joints (of 66 joints examined)
- Had a CRP measurement greater than or equal to the ULN
- Were receiving stable doses of background cDMARD therapy
- Had been treated at approved doses with at least 1 biologic TNF-α inhibitor (eg, infliximab, certolizumab, golimumab, etanercept, adalimumab) for at least 3 months and in the opinion of the investigator either:
    - Experienced insufficient efficacy or loss of efficacy at a dose and duration that, in accordance with local clinical practice, is considered acceptable to adequately assess clinical response or experienced intolerance of such treatment.

Patients were excluded from participation if they:

- Had received a bDMARD within 4 weeks of study entry
- Had a recent history of infection including active TB or untreated latent TB or other serious infections
- Had certain abnormal laboratory results
- Had comorbidities that unacceptably increased the patient's risk when taking study drug.

5.2.2. JADW Patient Characteristics and Disposition

Baseline characteristics were balanced across treatment arms (Table 14). Patients enrolled in this study had longstanding disease (median of 10.7 years since diagnosis) and high baseline disease activity and disability. Notably, over 50% of enrolled patients had previously received 2 or more bDMARDs, over 25% had received 3 or more, and over 40% had received one or more non-TNF inhibitor bDMARDs.

Patient disposition throughout the study is shown in Figure 38. Approximately 90% of patients in the baricitinib groups completed the study, 97% of whom entered the LTE study JADY.

Table 14: Baseline Demographics and Disease Characteristics in JADW (bDMARD-IR and cDMARD-IR)

	Placebo (N=176)	Baricitinib 2-mg (N=174)	Baricitinib 4-mg (N=177)
Age, years, mean (SD)	56 (11)	55 (11)	56 (11)
Female, n (%)	145 (82)	137 (79)	149 (84)
Duration of RA, years[a], mean (SD)	13 (9)	12 (8)	13 (9)
ACPA positive, n (%)	125 (71)	124 (71)	119 (67)
RF positive, n (%)	130 (74)	128 (74)	128 (72)
Concomitant steroid use, n (%)	116 (66)	92 (53)	96 (54)
Corticosteroid dose, mg/day[b], mean (SD)	6.7 (2.6)	5.9 (2.7)	6.8 (2.6)
Concomitant MTX use, n (%)	143 (81)	141 (81)	150 (85)
MTX dose, mg/week, mean (SD)	16 (5)	16 (5)	17 (11)
Ever used MTX[c], n (%)	168 (96)	167 (96)	170 (96)
# of concomitant cDMARDs, n (%):			
One	160 (91)	156 (90)	151 (85)
Two	16 (9)	15 (9)	24 (14)
# of prior bDMARDs, n (%):			
One	81 (46)	69 (40)	71 (40)
Two	47 (27)	55 (32)	58 (33)
≥ Three	47 (27)	50 (29)	45 (25)
TNFi:			
One	104 (59)	102 (59)	104 (59)
Two	50 (28)	60 (35)	52 (29)
≥ Three	19 (11)	12 (7)	18 (10)
non-TNFi:			
One	37 (21)	45 (26)	43 (24)
Two	15 (9)	14 (8)	14 (8)
≥ Three	10 (6)	11 (6)	10 (6)
Baseline Disease Activity			
Swollen joint count, of 66, mean (SD)	17 (11)	19 (12)	16 (9)
Tender joint count, of 68, mean (SD)	28 (16)	31 (16)	28 (16)
Physician's Global Assessment, 0-100mm VAS, mean (SD)	67 (19)	67 (17)	67 (18)
Patient's Global Assessment, 0-100mm VAS, mean (SD)	66 (19)	67 (19)	66 (22)
Patient's Assessment of Pain, 0-100mm VAS, mean (SD)	65 (19)	62 (22)	66 (23)
HAQ-DI, mean (SD)	1.78 (0.57)	1.71 (0.55)	1.74 (0.59)
hsCRP, mg/L, mean (SD)	21 (25)	20 (22)	20 (25)
ESR, mm/hour, mean (SD)	47 (24)	45 (24)	48 (26)
DAS28-CRP, mean (SD)	5.9 (0.9)	6.0 (0.9)	5.9 (1.0)
DAS28-ESR, mean (SD)	6.6 (0.9)	6.7 (1.0)	6.6 (1.1)
SDAI, mean (SD)	43 (14)	45 (14)	42 (14)
SDAI >26 , n (%)	154 (89)	159 (93)	147 (85)
CDAI, mean (SD)	41 (13)	43 (13)	40 (14)

Abbreviations: ACPA = anti-citrullinated protein antibodies; CDAI = clinical disease activity index; cDMARD = conventional disease-modifying antirheumatic drug; DAS28-CRP = Disease Activity Score in 28 joints c-reactive protein; DAS28-ESR = Disease Activity Score in 28 joints erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; hsCRP = high-sensitivity C-reactive protein; mTSS = modified Total Sharp Score; MTX = methotrexate; N = number of patients; n = number of patients in specified category; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation; SDAI = simplified disease activity index; TNF = tumor necrosis factor; VAS = visual analog scale.

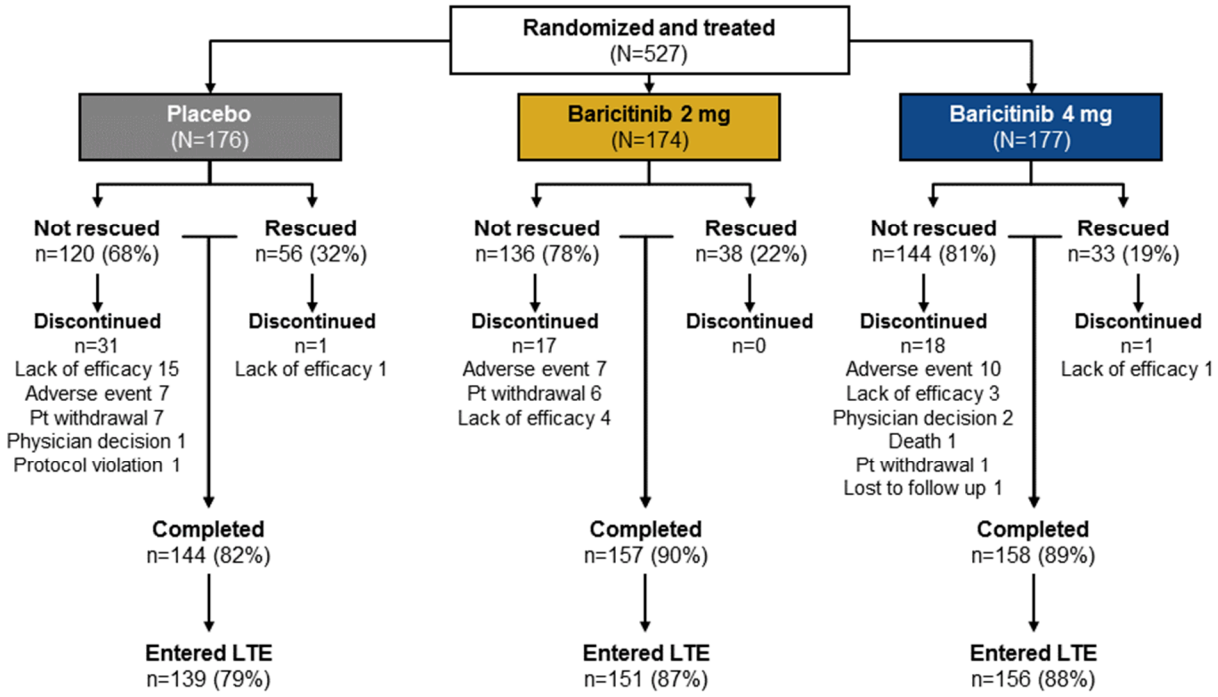
Note: 527 patients were randomized, by region: US & Canada (44%), Europe (30%), Central & South America (10%), Asia (6%), Rest of World (10%) .

a Time from symptom onset.

b Doses are in prednisone equivalent units.

c Includes patients with historical (previous but not currently taking) MTX use and patients with concomitant (currently taking) MTX use.

Figure 38: Patient Disposition in JADW (bDMARD-IR and cDMARD-IR)



Abbreviation: bDMARD-IR = biologic disease-modifying anti-rheumatic drug inadequate responder; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; LTE = long-term extension, Pt = patient.
Indicated treatment is in addition to existing (1-2) background cDMARDs.

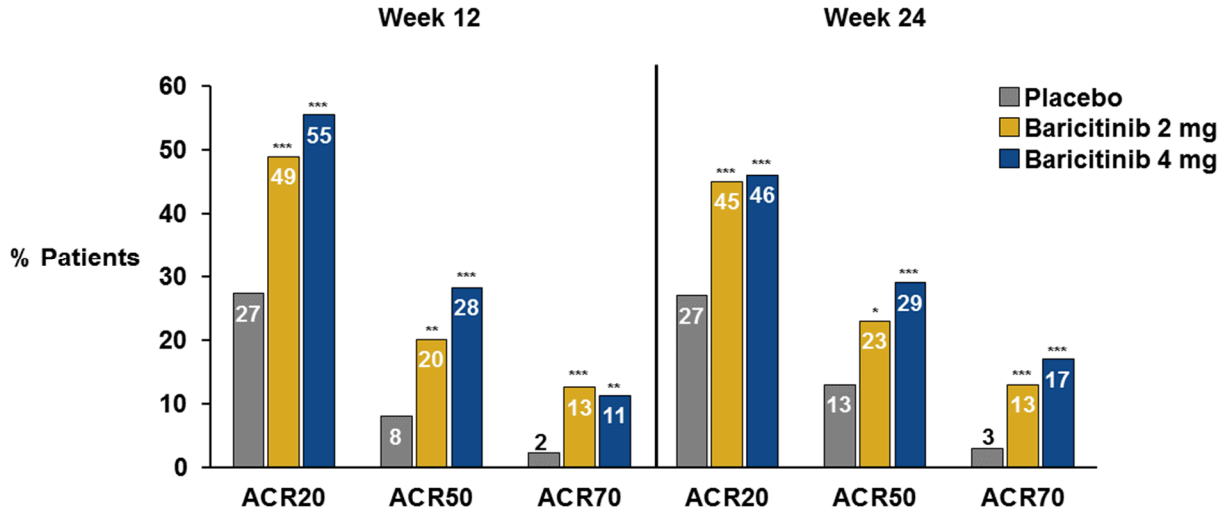
5.2.3. JADW Efficacy Results

5.2.3.1. JADW Primary Endpoint

Study JADW met its primary objective – the ACR20 response rate was significantly higher for baricitinib 4-mg compared to placebo at Week 12 ($p \leq 0.001$). At Week 12, 55% of the 4-mg group achieved an ACR20 response, compared to 27% of the placebo group. The related endpoints of ACR50 ($p \leq 0.001$) and ACR70 ($p=0.002$) were also significant for these comparisons (Figure 39).

The comparison between ACR20 response rate at Week 12 in the placebo and baricitinib 2-mg groups also showed a statistically significant improvement in the baricitinib group ($p \leq 0.001$). These results were similar for ACR50 ($p=0.002$) and ACR70 ($p \leq 0.001$).

Figure 39: Primary Endpoint: ACR Responses in JADW (bDMARD-IR and cDMARD-IR)

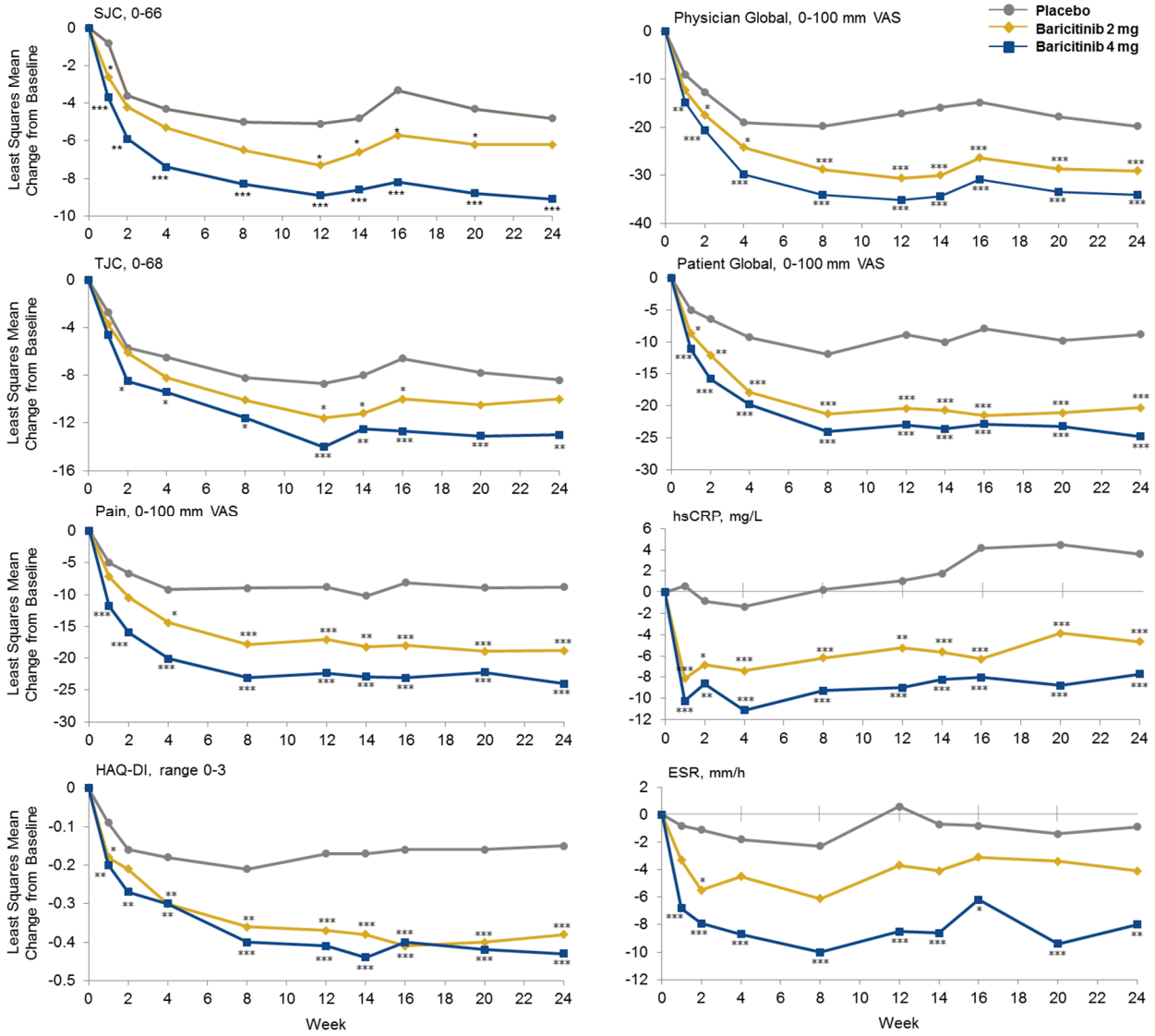


Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; bDMARD-IR = biologic disease-modifying anti-rheumatic drug inadequate responder; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; NRI = non-responder imputation.
*p<=.05, **p<=.01, ***p<=.001 vs placebo.
Indicated treatment is in addition to existing (1-2) background cDMARDs.
Imputation method: NRI.

5.2.3.1.1. JADW ACR Components

The seven components of the ACR were assessed over time. Both dose groups showed a rapid effect compared to placebo, starting from Week 1 (Figure 40). More rapid and larger effects were seen for the 4-mg dose. The 4-mg dose also maintained these effects over time for all ACR components. The 2-mg dose did not show consistent significant separation from placebo for SJC, TJC, or ESR through Week 24.

Figure 40: ACR Components and ESR in JADW (bDMARD-IR and cDMARD-IR)



Abbreviations: ACR = American College of Rheumatology; bDMARD-IR = biologic disease-modifying anti-rheumatic drug inadequate responder; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; HAQ-DI = Health Assessment Questionnaire-Disability Index; ESR = erythrocyte sedimentation rate; hsCRP = high-sensitivity C-reactive protein; mLOCF = modified last observation carried forward; SJC = swollen joint count; TJC = tender joint count.
*p≤0.05, **p≤0.01, ***p≤0.001 versus placebo.
Imputation method: mLOCF.
Indicated treatment is in addition to existing (1-2) background cDMARDs.

5.2.3.2. JADW Key Secondary Endpoint Results

The results of significance testing using multiplicity control for all key objectives are described in Section 1.5.2.1, Table 2.

5.2.3.2.1. JADW SDAI

SDAI remission (SDAI ≤3.3) and low disease activity (SDAI ≤11) were evaluated (Figure 7). At Week 12, neither baricitinib group showed a significant improvement in SDAI ≤3.3 response rate compared to placebo. However, both baricitinib groups showed a significant improvement in

SDAI ≤11 response rate at Week 12 (p≤0.001 for both doses). The 4-mg group showed significant improvement in SDAI ≤3.3 response rate compared to placebo beginning at Week 14 through later timepoints, including Week 24.

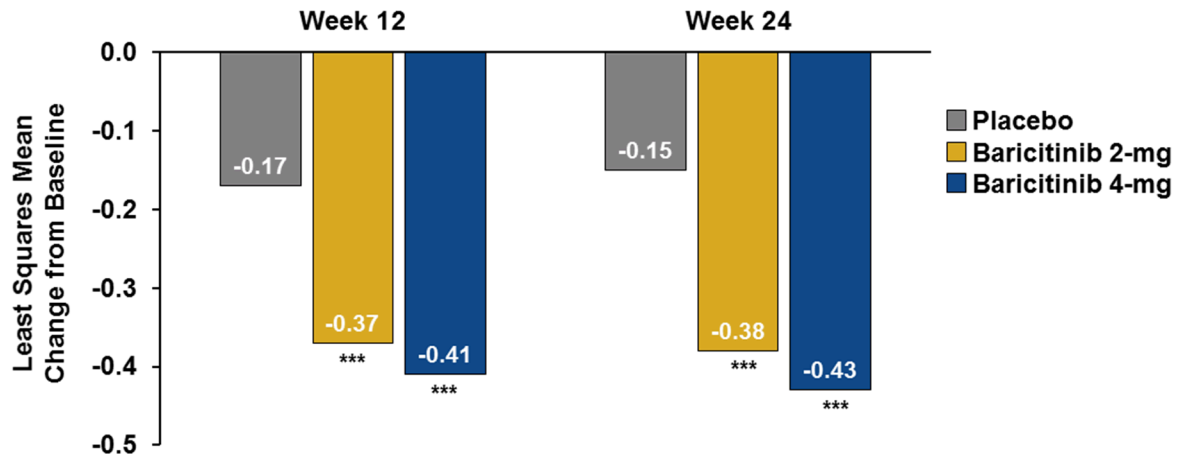
5.2.3.2.2. JADW DAS28-CRP

Compared to placebo, the baricitinib groups showed a statistically significant improvement in DAS28-CRP at Week 12 (p≤0.001 for both dose groups). The statistically significant improvement in the baricitinib groups was observed from Week 1 and was maintained through Week 24 (Figure 6). This was most pronounced for the 4-mg dose: by 4 weeks, 4-mg produced a degree of improvement that was as large as 2-mg ever achieved during the full 6 months. Similar results were observed for other continuous composite measures of disease activity included as additional secondary endpoints (change from baseline in SDAI, CDAI, DAS28-ESR).

5.2.3.2.3. JADW HAQ-DI

The change from baseline in HAQ-DI scores at Weeks 12 and 24 is shown in Figure 41. Compared to placebo, statistically significant improvements in HAQ-DI scores were observed from Week 1 and were maintained through Week 24 for the baricitinib groups (p≤0.001 for both dose groups).

Figure 41: HAQ-DI Change from Baseline to Week 12 and 24 in JADW (bDMARD-IR and cDMARD-IR)



Abbreviations: bDMARD-IR = biologic disease-modifying anti-rheumatic drug inadequate responder; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; HAQ-DI = Health Assessment Questionnaire–Disability Index; LS = least squares
Indicated treatment is in addition to existing (1-2) background cDMARDs.
*p≤0.05, **p≤0.01, ***p≤0.001 versus placebo.
Imputation method: mLOCF.

5.2.4. JADW Efficacy Conclusions

- Baricitinib 4-mg and 2-mg were superior to placebo with respect to improvements in signs and symptoms, LDA rates, physical function, and additional PROs.
- Efficacy was rapid (as early as Week 1) and durable, with beneficial treatment effects compared to placebo sustained through 24 weeks.

- A statistically significant improvement in SDAI remission compared to placebo was not demonstrated at Week 12 for baricitinib 4-mg; however, more than 30% of these patients attained LDA or remission in this highly refractory patient population. For the 4-mg dose, significant improvement in remission vs placebo was observed at later timepoints, starting from Week 14.
- In contrast to the pattern of rapid and durable improvements seen across efficacy measures with baricitinib 4-mg, baricitinib 2-mg demonstrated beneficial treatment effects that appeared later, were smaller in magnitude and were inconsistent in terms of statistical significance.
- Throughout the study the 4-mg dose produced improvements in disease activity that were at least 1.5x as large as the treatment effect of 2-mg over placebo. By 4 weeks, 4-mg produced a degree of improvement that was as large as 2-mg ever achieved during the full 6 months.

5.3. JADX (cDMARD-IR and bDMARD-naïve)

5.3.1. JADX Study Design

Study JADX was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 24-week study comparing the efficacy of 4-mg and 2-mg baricitinib versus placebo on signs, symptoms, clinical remission, physical function, and additional PROs (Figure 5). Eligible patients had moderately to severely active RA, had an insufficient response or intolerance to at least one cDMARD, had not previously been treated with a bDMARD, and were taking 0 to 2 stable background cDMARDs (predominantly MTX). Patients were randomly assigned in a 1:1:1 ratio to receive baricitinib 4-mg, baricitinib 2-mg, or placebo, remaining on their stable background cDMARDs ± NSAIDs, analgesics, and corticosteroids (up to 10 mg prednisone daily or equivalent). Patients who did not adequately respond to study drug were eligible for rescue treatment (baricitinib 4-mg) beginning at Week 16.

The primary objective of the study was to determine whether baricitinib 4-mg was superior to placebo in this cDMARD-IR patient population, as assessed by the proportion of patients achieving ACR20 at Week 12. The comparison of 2-mg to placebo (using ACR20 at Week 12) was a **key secondary objective**.

5.3.1.1. JADX Inclusion and Exclusion 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 Classification of Rheumatoid Arthritis (Aletaha et al. 2010)
- Had at least 6 tender joints (of 68 joints examined) and 6 swollen joints (of 66 joints examined)
- Had an hsCRP measurement ≥1.2 times the upper limit of normal
- Had an insufficient response or were intolerant to at least one prior cDMARD (cDMARD-IR).

Patients were excluded from participation if they:

- Had previously received a bDMARD
- Had a recent history of infection including active TB, untreated latent TB, or other serious infections
- Had specific abnormal laboratory results
- Had comorbidities that put patients at unacceptable risk when taking investigational product.

5.3.2. JADX Patient Characteristics and Disposition

The treatment groups were balanced in regards to baseline demographics, with similar mean values reported in each category (Table 15). These cDMARD-IR patients were generally younger, with shorter RA disease duration, compared with patients in JADW, who had already failed at least one bDMARD. Approximately 25% of patients were taking multiple concomitant cDMARDs, while 6–8% were on no concomitant DMARD treatment. Over 40% had a prior inadequate response or intolerance to only one cDMARD (Table 15).

Approximately 90% of patients in the baricitinib groups completed the study, 95% of whom entered the LTE study JADY (Figure 42).

Table 15: Baseline Demographics and Disease Characteristics in JADX (cDMARD-IR and bDMARD-naïve)

	Placebo (N=228)	Baricitinib 2-mg (N=229)	Baricitinib 4-mg (N=227)
Age, years, mean (SD)	51.4 (12.5)	52.2 (12.3)	51.8 (12.1)
Female, n (%)	189 (82.9)	184 (80.3)	187 (82.4)
Duration of RA, years[a], mean (SD)	7.2 (7.5)	7.6 (7.6)	7.7 (7.9)
ACPA positive, n (%)	172 (75.4)	169 (73.8)	163 (71.8)
RF positive, n (%)	171 (75.0)	177 (77.3)	173 (76.2)
≥ 1 Joint erosion, n (%)	170 (74.9)	163 (71.2)	169 (75.4)
mTSS, Sharp units, mean (SD)	19 (31.4)	26 (40.3)	24 (40.0)
Bone joint erosion score, mean (SD)	12 (19.0)	16 (23.5)	15 (23.0)
Joint space narrowing score, mean (SD)	7 (13.6)	10 (18.4)	9 (18.1)
Concomitant steroid use, n (%)	114 (50.0)	117 (51.1)	115 (50.7)
Corticosteroid dose, mg/day[b], mean (SD)	5.9 (2.6)	6.5 (2.5)	6.2 (2.4)
Concomitant MTX use, n (%)	167 (73%)	170 (74)	171 (75)
MTX dose, mg/week, mean (SD)	16 (4.8)	16.4 (4.7)	16.1 (5.0)
Ever used MTX[c], n (%)	207 (91)	207 (90)	211 (93)
# of prior cDMARDs, n (%):			
None	1 (0.4)	3 (1.3)	1 (0.4)
One	96 (42.1)	104 (45.4)	98 (43.2)
Two	81 (35.5)	61 (26.6)	68 (30.0)
≥ Three	50 (21.9)	61 (26.6)	60 (26.4)
# of concomitant cDMARDs, n (%):			
None	17 (7.5)	18 (7.9)	13 (5.7)
One	150 (65.8)	145 (63.3)	151 (66.5)
Two	55 (24.1)	58 (25.3)	57 (25.1)
Baseline Disease Activity			
Swollen joint count, of 66, mean (SD)	13.1 (7.2)	13.6 (8.7)	13.5 (6.9)
Tender joint count, of 68, mean (SD)	24.3 (15.0)	23.5 (14.1)	24.3 (14.0)
Physician's Global Assessment, 0-100mm VAS, mean (SD)	62.2 (16.8)	64.4 (17.0)	64.0 (18.4)
Patient's Global Assessment, 0-100mm VAS, mean (SD)	60.4 (21.4)	61.6 (20.2)	60.1 (21.7)
Patient's Assessment of Pain, 0-100mm VAS, mean (SD)	57.1 (23.1)	59.5 (21.2)	57.3 (21.9)
HAQ-DI, mean (SD)	1.50 (0.60)	1.51 (0.62)	1.55 (0.60)
hsCRP, mg/L, mean (SD)	17.7 (20.4)	18.2 (21.5)	14.2 (14.5)
ESR, mm/hour, mean (SD)	43.5 (25.1)	44.4 (22.7)	40.9 (24.1)
DAS28-CRP, mean (SD)	5.53 (0.91)	5.57 (0.96)	5.55 (0.87)
DAS28-ESR, mean (SD)	6.19 (1.00)	6.28 (0.99)	6.20 (0.91)
SDAI, mean (SD)	37.2 (11.9)	38.3 (13.4)	37.6 (11.8)
SDAI >26 , n (%)	180 (80.4)	181 (80.4)	188 (83.9)
CDAI, mean (SD)	35.5 (11.7)	36.5 (13.1)	36.2 (11.5)

Abbreviations: ACPA = anti-citrullinated protein antibodies; CDAI = clinical disease activity index; cDMARD = conventional disease-modifying antirheumatic drug; DAS28-CRP = Disease Activity Score in 28 joints c-reactive protein; DAS28-ESR = Disease Activity Score in 28 joints erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; hsCRP = high-sensitivity C-reactive protein; mTSS = modified Total Sharp Score; MTX = methotrexate; N = number of patients; n = number of patients in specified category; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation; SDAI = simplified disease activity index; TNF = tumor necrosis factor; VAS = visual analog scale.

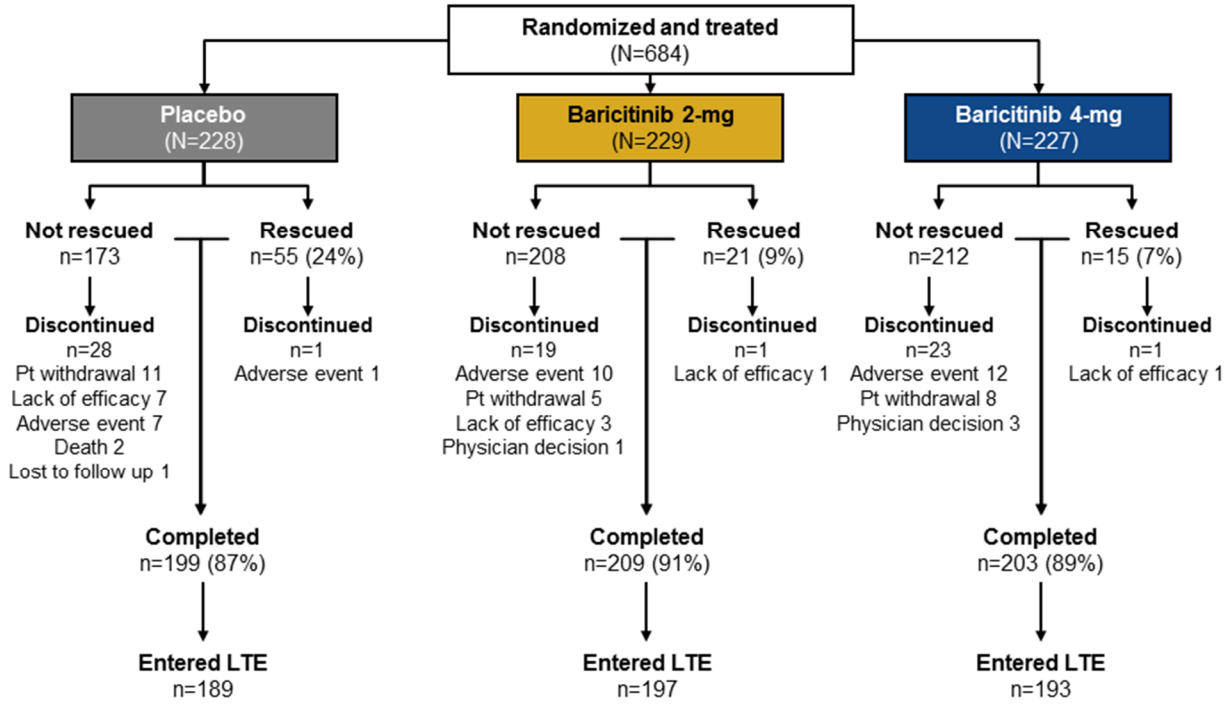
Note: 684 patients were randomized; by region: Central and South America (12.6%), US & Canada (29.8%), Eastern Europe (15.6%), Western Europe (10.8%), Asia (17.5%), Rest of World (13.6%).

a Time from symptom onset.

b Doses are in prednisone equivalent units.

c Includes patients with historical (previous but not currently taking) MTX use and patients with concomitant (currently taking) MTX use.

Figure 42: Patient Disposition in JADX (cDMARD-IR and bDMARD-naïve)



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; cDMARD-IR = conventional disease-modifying antirheumatic drug inadequate responder; LTE = long-term extension; Pt = patient.
Indicated treatment is in addition to existing (0-2) background cDMARDs.

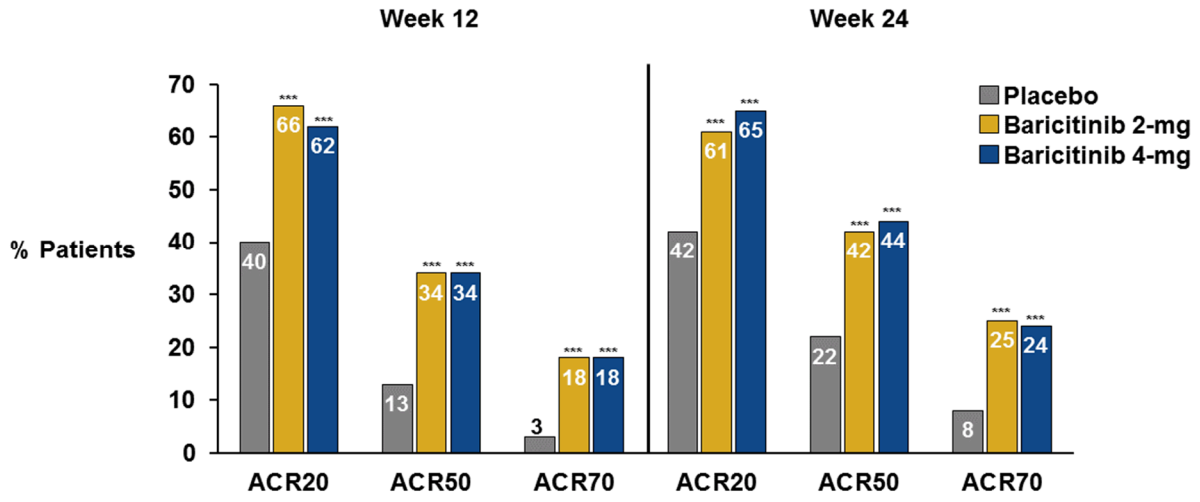
5.3.3. JADX Efficacy Results

5.3.3.1. JADX Primary Endpoint Results

Study JADX met its primary objective – the ACR20 response rate was significantly higher for baricitinib 4-mg compared to placebo at Week 12 ($p \leq 0.001$). At Week 12, 62% of the 4-mg group achieved an ACR20 response, compared to 40% of the placebo group. The related endpoints of ACR50 ($p \leq 0.001$) and ACR70 ($p \leq 0.001$) were also significant for these comparisons (Figure 43).

The comparison between ACR20 response rate at Week 12 in the placebo and baricitinib 2-mg groups also showed a statistically significant improvement in the baricitinib group ($p \leq 0.001$). These results were similar for ACR50 ($p \leq 0.001$) and ACR70 ($p \leq 0.001$).

Figure 43: Primary Endpoint: ACR Responses in JADX (cDMARD-IR and bDMARD-naïve)



Abbreviations: ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD-IR = conventional disease-modifying antirheumatic drug inadequate responder; NRI = non-responder imputation.
*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo.
Indicated treatment is in addition to existing (0-2) background cDMARDs.
Imputation method: NRI.

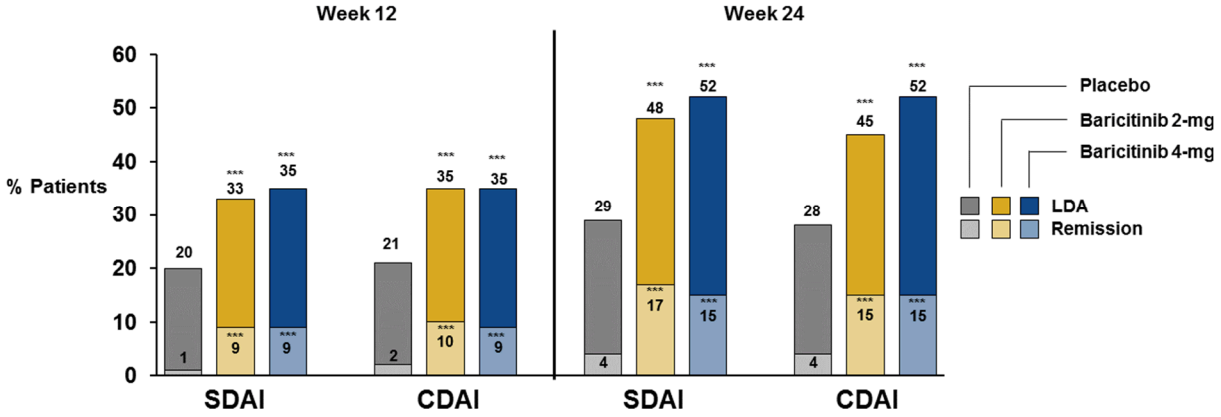
5.3.3.2. JADX Key Secondary Endpoint Results

The results of significance testing using multiplicity control for all key objectives are described in Section 1.5.2.1, Table 3.

5.3.3.2.1. JADX SDAI

SDAI ≤3.3 (remission) and ≤11 (LDA) response rates at Weeks 12 and 24 are shown in Figure 44. At Week 12, both baricitinib groups showed a statistically significant improvement in SDAI ≤3.3 and ≤11 response rates compared to placebo (p≤0.001 for all comparisons).

Figure 44: SDAI and CDAI Response Rates in JADX (cDMARD-IR and bDMARD-naïve)



Abbreviations: CDAI = Clinical Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD-IR = conventional disease-modifying antirheumatic drug inadequate responder; NRI = non-responder imputation; SDAI = Simplified Disease Activity Index.
P-value vs. Placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001.
Total height of each bar = SDAI ≤ 11, CDAI ≤ 10. Lower (paler) portion of each bar = SDAI ≤ 3.3, CDAI ≤ 2.8
Indicated treatment is in addition to existing (0-2) background cDMARDs.
Imputation method: NRI.

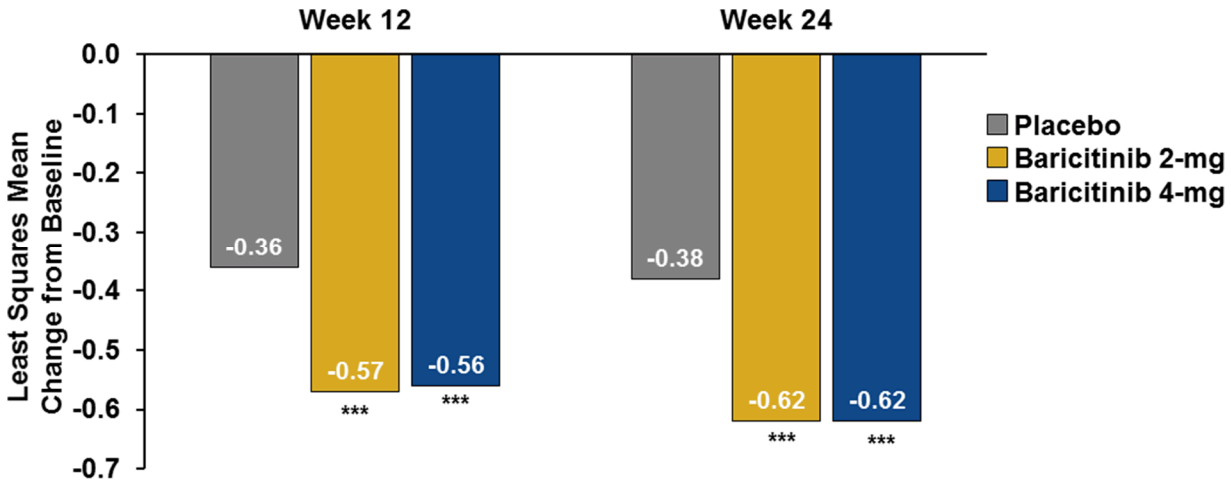
5.3.3.2.2. JADX DAS28-CRP

The change from baseline in DAS28-CRP through Week 24 is shown in Figure 8. Compared to placebo, a statistically significant improvement in mean DAS28-CRP was observed at Week 12 for both baricitinib groups ($p \leq 0.001$ for both). The statistically significant improvement was observed from Week 1 for the baricitinib groups and was maintained through Week 24. Similar results were observed for other continuous composite measures of disease activity included as additional secondary endpoints (change from baseline in SDAI, CDAI, DAS28-ESR). A dose-response was observed (Figure 8), but was less pronounced than in the more highly refractory JADW population (Figure 6).

5.3.3.2.3. JADX HAQ-DI

The change from baseline in HAQ-DI scores at Weeks 12 and 24 is shown in Figure 45. Compared to placebo, statistically significant improvements in HAQ-DI scores were observed at Week 12 for the baricitinib groups ($p \leq 0.001$ for both).

Figure 45: HAQ-DI Change from Baseline at Week 12 and 24 in JADX (cDMARD-IR and bDMARD-naïve)

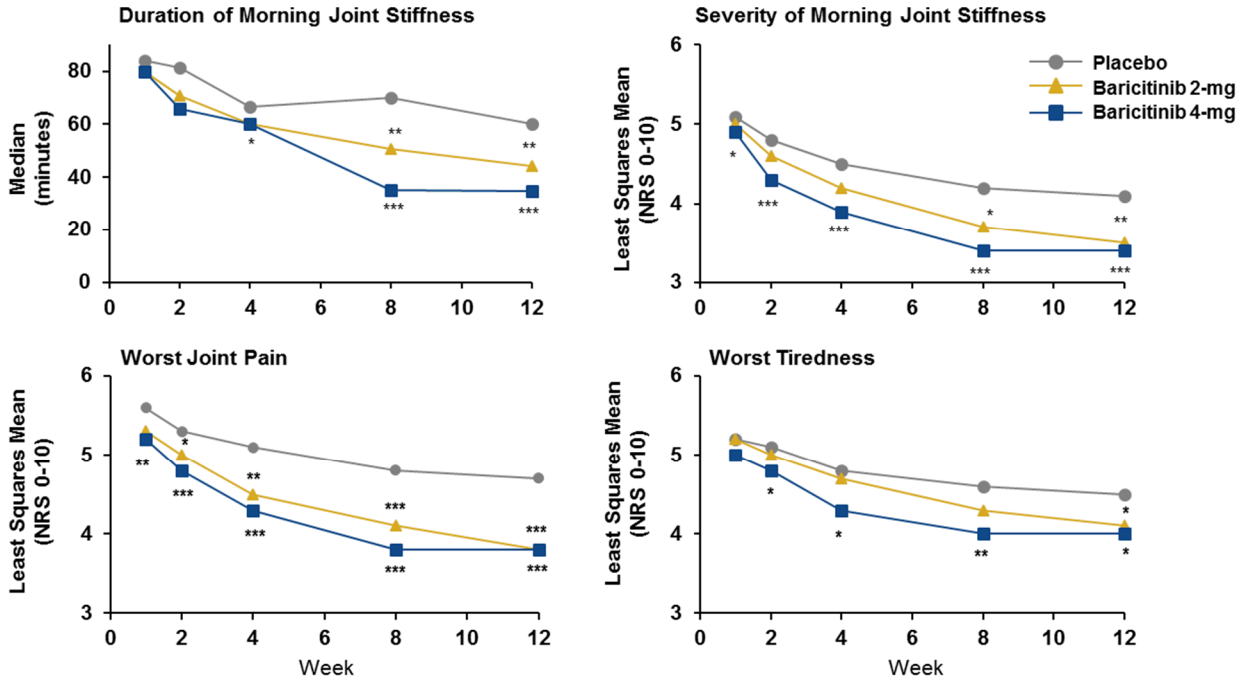


Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; cDMARD-IR = conventional disease-modifying antirheumatic drug inadequate responder; HAQ-DI = Health Assessment Questionnaire-Disability Index; mLOCF = modified last observation carried forward.
*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ vs placebo.
Indicated treatment is in addition to existing (0-2) background cDMARDs.
Imputation method: mLOCF.

5.3.3.2.4. JADX Electronic Daily Diary PROs

Duration of Morning Joint Stiffness, Severity of Morning Joint Stiffness NRS, Worst Tiredness NRS, and Worst Joint Pain NRS through Week 12 are shown in Figure 46. Significant improvements for 4-mg compared to placebo were observed for all measures from Week 4 to 12; 2-mg was also significant for all measures at the 12-week timepoint.

Figure 46: Electronic Daily Diary PROs through Week 12 in JADX (cDMARD-IR and bDMARD-naïve)

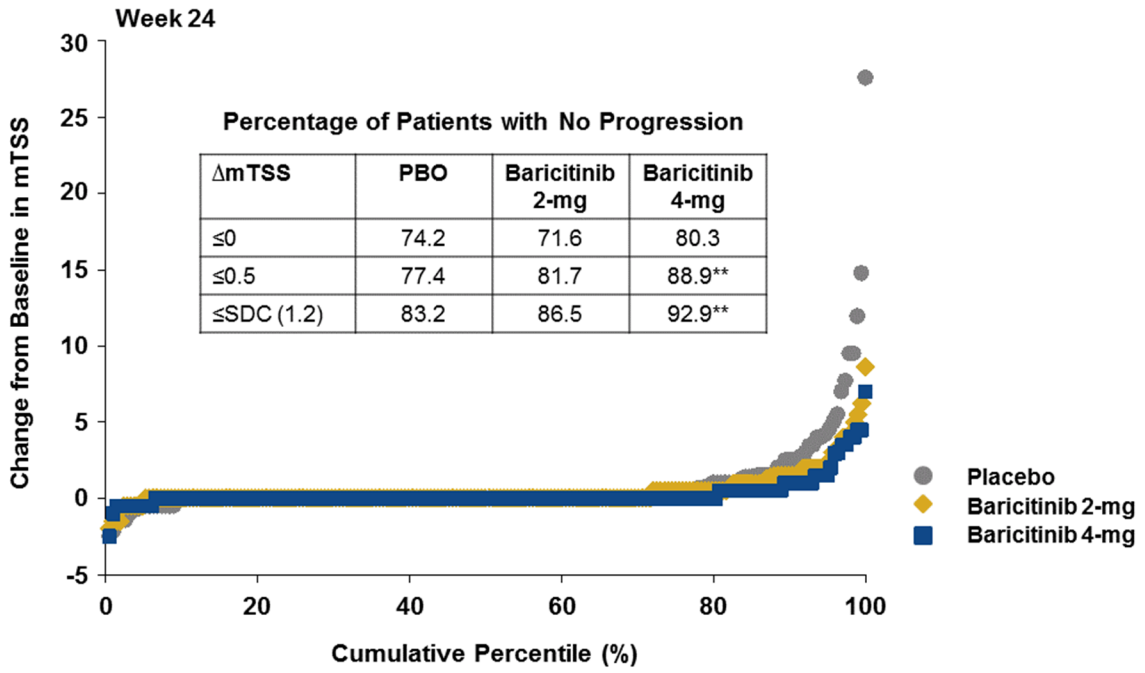


Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; cDMARD-IR = conventional disease-modifying antirheumatic drug inadequate responder; LOCF = last observation carried forward; NRS = numeric rating scale.
*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo
Indicated treatment is in addition to existing (0-2) background cDMARDs.
Imputation method: LOCF.

5.3.3.2.5. JADX mTSS

Compared to placebo, a statistically significant decrease in radiographic progression of joint damage based on mTSS was observed at Week 24 for the baricitinib groups (p=0.043 for 2-mg and p=0.004 for 4-mg) (Figure 9). The comparison of 4-mg to placebo remained statistically significant in analyses using all observed data as randomized. A cumulative probability plot and proportions of patients with progression across commonly-used thresholds is provided (Figure 47).

Figure 47: JADX (cDMARD-IR and bDMARD-naïve) mTSS Probability Plot



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; cDMARD-IR = conventional disease-modifying antirheumatic drug inadequate responder; mTSS = modified Total Sharp Score; PBO = placebo; SDC = smallest detectable change.
**p≤0.01 versus placebo.
Each point on the cumulative probability plot represents an individual patient
Indicated treatment is in addition to existing (0-2) background cDMARDs.
Imputation method: LE.

5.3.4. JADX Efficacy Conclusions

- Baricitinib 4-mg and 2-mg were superior to placebo with respect to improvements in signs and symptoms, LDA and remission rates, physical function, and additional PROs.
- Efficacy was rapid (as early as Week 1) and durable, with beneficial treatment effects compared to placebo sustained through 24 weeks.
- Baricitinib statistically significantly inhibited radiographic progression of structural joint damage compared to placebo at 24 weeks. The largest and most consistent treatment effect was seen for the 4-mg dose.
- Overall, Study JADX showed that baricitinib 2-mg and 4-mg provide efficacy for cDMARD-IR patients. A dose-response was seen for inhibition of radiographic progression. Additionally, a dose-response was seen across continuous composite disease activity scores and time to onset of benefit; this dose-response was less marked than in the highly refractory bDMARD-IR JADW patient group.

5.4. JADZ (DMARD-Naïve)

5.4.1. JADZ Study Design

Study JADZ was a Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group, 52-week study that compared the efficacy of baricitinib 4-mg

monotherapy or baricitinib 4-mg + MTX to MTX monotherapy on signs and symptoms, clinical remission, physical function, additional PROs, and radiographic progression of structural joint damage (Figure 10). Eligible patients had moderately to severely active RA, previously had no or limited treatment with MTX, and were naive to other cDMARDs or bDMARDs. Patients were randomly assigned in a 4:3:4 ratio to receive MTX monotherapy, baricitinib 4-mg monotherapy, or the combination. Once-weekly oral MTX was escalated to a maintenance dose: 10 mg x 4 weeks → 15 mg × 4 weeks → 20 mg. A lower dose of MTX was available where clinically indicated (12.5 mg maintenance). Patients continued any stable background NSAIDs, analgesics, and corticosteroids (up to 10 mg prednisone daily or equivalent). Those who did not adequately respond to study drug were eligible for rescue treatment (baricitinib 4-mg + MTX) beginning at Week 24, after the assessment of the primary and key secondary endpoints (see below).

The primary objective of the study was to determine whether baricitinib 4-mg monotherapy was noninferior to MTX monotherapy, as assessed by the proportion of patients who achieved ACR20 at Week 24. Week 24 was used for the key efficacy assessments in this study to allow MTX, which does not have a rapid onset of action, to achieve optimal efficacy. Comparisons for superiority of baricitinib 4-mg monotherapy and baricitinib 4-mg + MTX to MTX monotherapy (using ACR20 at Week 24) were **key secondary objectives**.

5.4.1.1. JADZ Inclusion and Exclusion 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 (Aletaha et al. 2010)
- Were rheumatoid factor or anti-CCP antibody positive
- 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 an hsCRP measurement ≥1.2× the ULN (3.6 mg/L)
- Had no or limited (3 or fewer doses) previous treatment with MTX.

Patients were excluded from participation if they:

- Had previously received a DMARD (other than ≤3 doses of MTX)
- Had a recent history of infection including active TB, untreated latent TB, or other serious infections
- Had specific abnormal laboratory results
- Had comorbidities that put patients at unacceptable risk when taking study drug.

5.4.2. JADZ Patient Characteristics and Disposition

JADZ enrolled DMARD-naïve patients with a mean age of approximately 50 years (Table 16). The median duration of RA was approximately 2 months, reflecting a patient population with predominantly recent-onset disease.

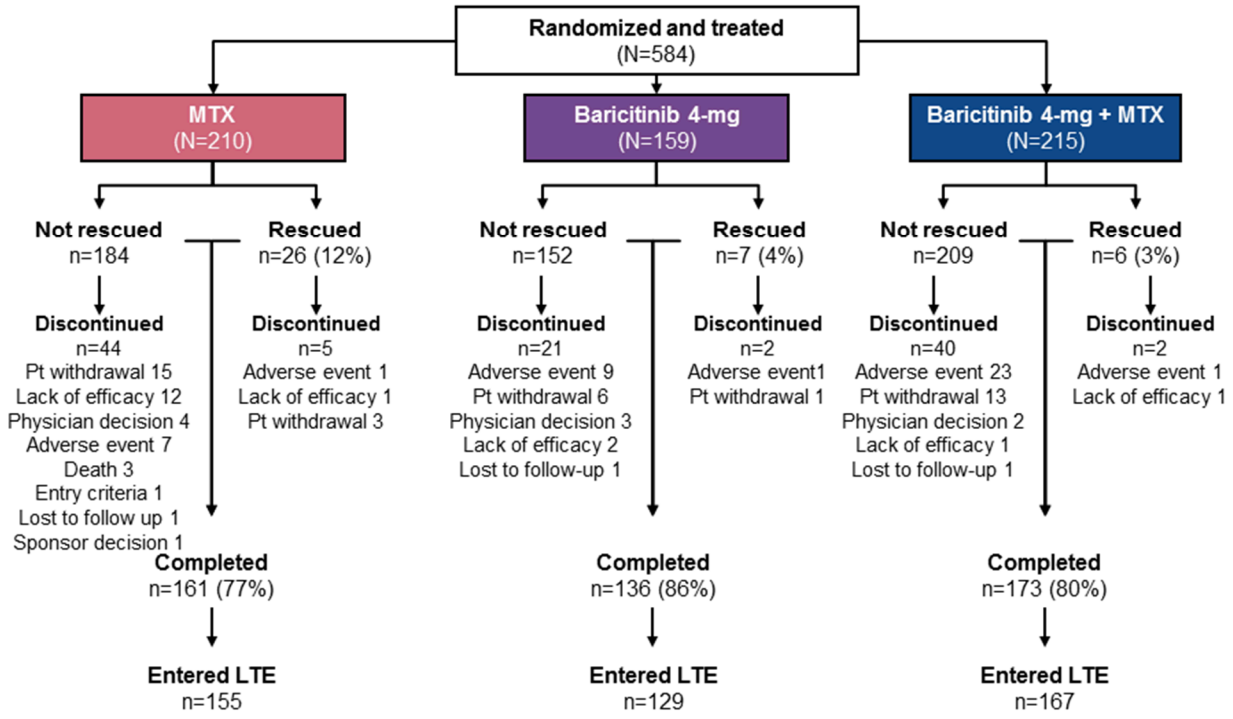
Patient disposition throughout the study is shown in Figure 48. Approximately 83% of patients in the baricitinib groups completed the study, 96% of whom entered the LTE study JADY.

Table 16: Baseline Demographics and Disease Characteristics in JADZ (DMARD-Naïve)

	MTX (N=210)	Baricitinib 4-mg (N=159)	Baricitinib 4-mg + MTX (N=215)
Age, years, mean (SD)	50.5 (13.4)	50.9 (13.0)	48.5 (13.5)
Female, n (%)	148 (70)	121 (76)	156 (73)
Duration of RA, years[a], mean (SD)	2.4 (4.5)	3.0 (5.9)	2.5 (3.7)
ACPA positive, n (%)	193 (92)	142 (89)	192 (89)
RF positive, n (%)	203 (97)	155 (97)	204 (95)
≥ 1 Joint erosion, n (%)	138 (66)	105 (66)	137 (64)
mTSS, Sharp units, mean (SD)	11.82 (22)	13.32 (27)	11.39 (20)
Bone joint erosion score, mean (SD)	7.89 (12)	8.72 (16)	7.45 (12)
Joint space narrowing score, mean (SD)	3.93 (10)	4.61 (12)	3.95 (10)
Concomitant steroid use, n (%)	76 (36)	47 (30)	83 (39)
Corticosteroid dose, mg/day[b], mean (SD)	6.7 (2.5)	6.1 (2.6)	6.5 (2.4)
Ever used MTX[c], n (%)	15 (7)	12 (8)	17 (8)
Baseline Disease Activity			
Swollen joint count, of 66, mean (SD)	16.4 (10.6)	16.1 (9.2)	16.3 (9.5)
Tender joint count, of 68, mean (SD)	26.5 (14.8)	26.4 (14.1)	27.7 (14.5)
Physician's Global Assessment, 0-100mm VAS, mean (SD)	66.7 (17.1)	68.1 (17.0)	66.4 (16.9)
Patient's Global Assessment, 0-100mm VAS, mean (SD)	65.6 (23.8)	65.0 (22.1)	63.1 (23.6)
Patient's Assessment of Pain, 0-100mm VAS, mean (SD)	65.2 (24.1)	64.1 (21.6)	62.6 (22.6)
HAQ-DI, mean (SD)	1.67 (0.66)	1.64 (0.73)	1.58 (0.66)
hsCRP, mg/L, mean (SD)	22.3 (21.8)	23.8 (26.2)	24.3 (29.4)
ESR, mm/hour, mean (SD)	54.3 (28.5)	50.8 (26.8)	49.4 (25.8)
DAS28-CRP, mean (SD)	5.86 (1.00)	5.90 (0.98)	5.91 (0.93)
DAS28-ESR, mean (SD)	6.60 (0.99)	6.57 (1.07)	6.59 (0.96)
SDAI, mean (SD)	41.7 (13.9)	42.6 (14.0)	42.8 (13.4)
SDAI >26 , n (%)	177 (86.3)	141 (89.8)	196 (92.0)
CDAI, mean (SD)	39.4 (13.2)	40.3 (13.4)	40.4 (12.8)

Abbreviations: ACPA = anti-citrullinated protein antibodies; CDAI = clinical disease activity index; cDMARD = conventional disease-modifying antirheumatic drug; DAS28-CRP = Disease Activity Score in 28 joints c-reactive protein; DAS28-ESR = Disease Activity Score in 28 joints erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; hsCRP = high-sensitivity C-reactive protein; mTSS = modified Total Sharp Score; MTX = methotrexate; N = number of patients; n = number of patients in specified category; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation; SDAI = simplified disease activity index; TNF = tumor necrosis factor; VAS = visual analog scale.
Note: 584 patients were randomized; by region: Central and South America (28.9%), US & Canada (20.7%), Rest of World (18.8%), Japan (17.8%), Europe (13.7%).
a Time from symptom onset.
b Doses are in prednisone equivalent units.
c Includes patients with historical (previous but not currently taking) MTX use and patients with concomitant (currently taking) MTX use.

Figure 48: Patient Disposition in JADZ (DMARD-Naïve)



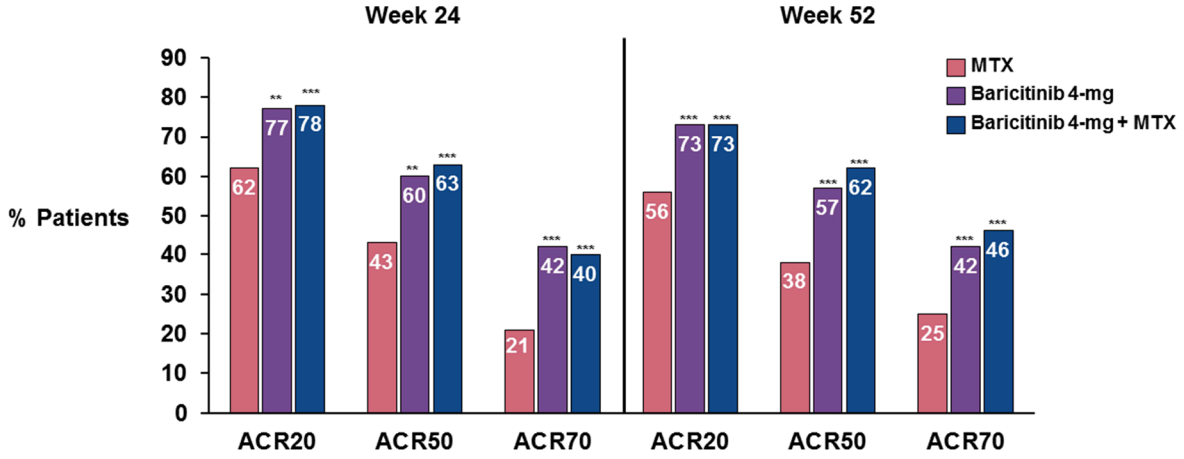
Abbreviation: DMARD = disease-modifying antirheumatic drug; LTE = long-term extension; MTX = methotrexate; Pt = patient.
Treatment did not include a background cDMARD

5.4.3. JADZ Efficacy Results

5.4.3.1. JADZ Primary Endpoint Results

Study JADZ achieved the primary objective of showing that baricitinib monotherapy was noninferior to MTX monotherapy with respect to ACR20 response rates at Week 24 (Figure 49). Furthermore, baricitinib monotherapy ($p=0.003$) and combination therapy ($p\leq0.001$) provided significantly higher ACR20 response rates than MTX monotherapy at Week 24. Baricitinib monotherapy and combination therapy also provided significantly higher response rates than MTX alone for ACR50 ($p=0.002$ and $p\leq0.001$, respectively) and ACR70 ($p\leq0.001$ for both).

Figure 49: Primary Endpoint: ACR Responses in JADZ (DMARD-Naïve)



Abbreviations: 20/50/70% improvement in American College of Rheumatology criteria; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; NRI = non-responder imputation.
*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo.
Treatment did not include a background cDMARD.
Imputation method: NRI.

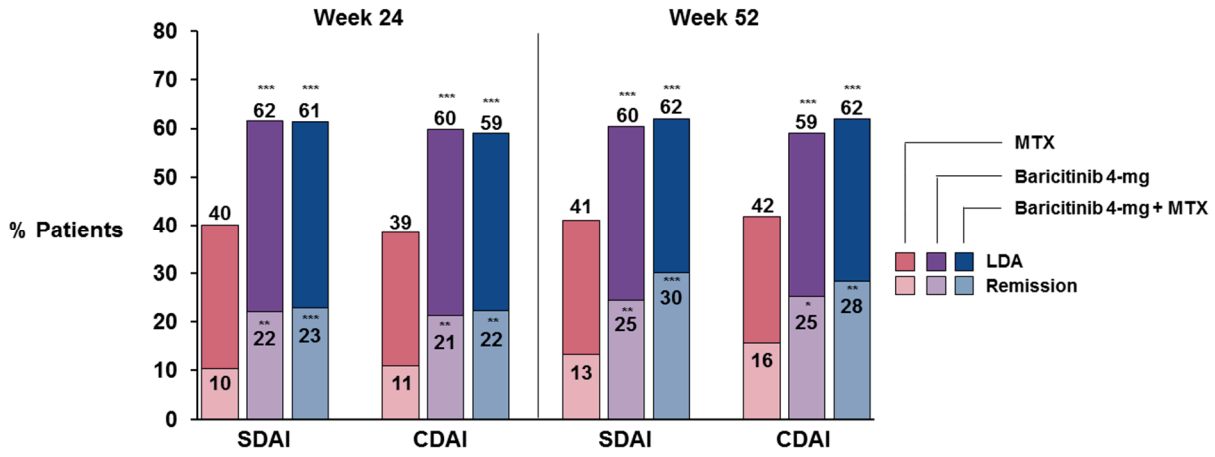
5.4.3.2. JADZ Key Secondary Endpoint Results

The results of significance testing using multiplicity control for all key objectives are described in Section 1.5.2.1, Table 4.

5.4.3.2.1. JADZ SDAI

SDAI response rates at Weeks 24 and 52 are shown in Figure 50. Compared to MTX monotherapy, statistically significant improvements in SDAI ≤3.3 (remission) response rates were observed at Week 24 for the baricitinib monotherapy (p=0.003) and baricitinib + MTX (p≤0.001) groups.

Figure 50: SDAI and CDAI Response Rates in JADZ (DMARD-Naïve)

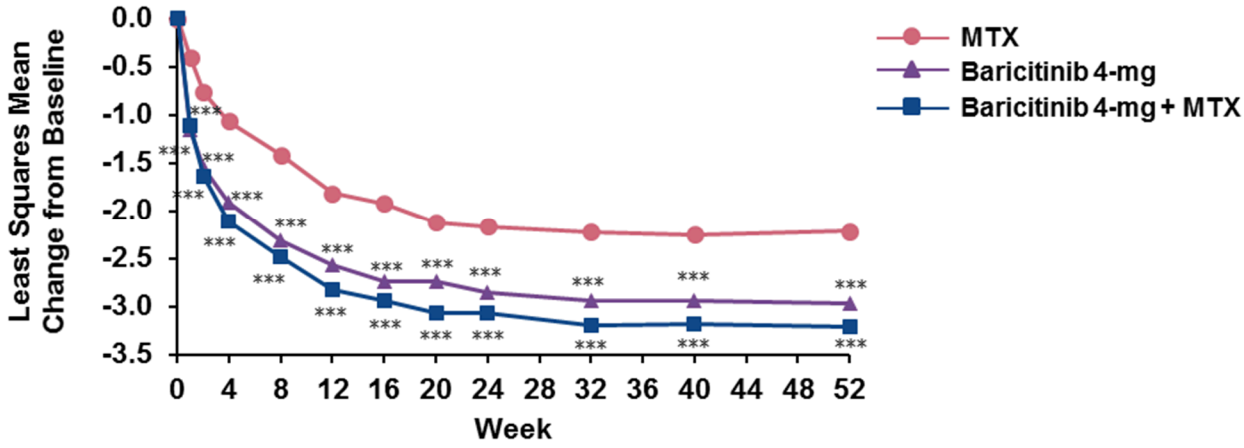


Abbreviations: CDAI = clinical disease activity index; DMARD = disease-modifying antirheumatic drug; LDA = low disease activity; MTX = methotrexate; NRI = non-responder imputation; SDAI = simplified disease activity index.
*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo.
Treatment did not include a background cDMARD.
Imputation method: NRI.

5.4.3.2.2. JADZ DAS28-CRP

The change from baseline in DAS28-CRP through Week 52 is shown in Figure 51. Compared to MTX monotherapy, statistically significant improvements in DAS28-CRP were observed at Week 24 for the baricitinib monotherapy and baricitinib + MTX groups ($p \leq 0.001$ for both). The statistically significant improvement was observed from Week 1 and was maintained through Week 52 for the baricitinib monotherapy and baricitinib + MTX groups. Similar results were observed for other continuous composite measures of disease activity included as additional secondary endpoints (change from baseline in SDAI, CDAI, DAS28-ESR).

Figure 51: DAS28-CRP Change from Baseline through Week 52 in JADZ (DMARD-Naïve)

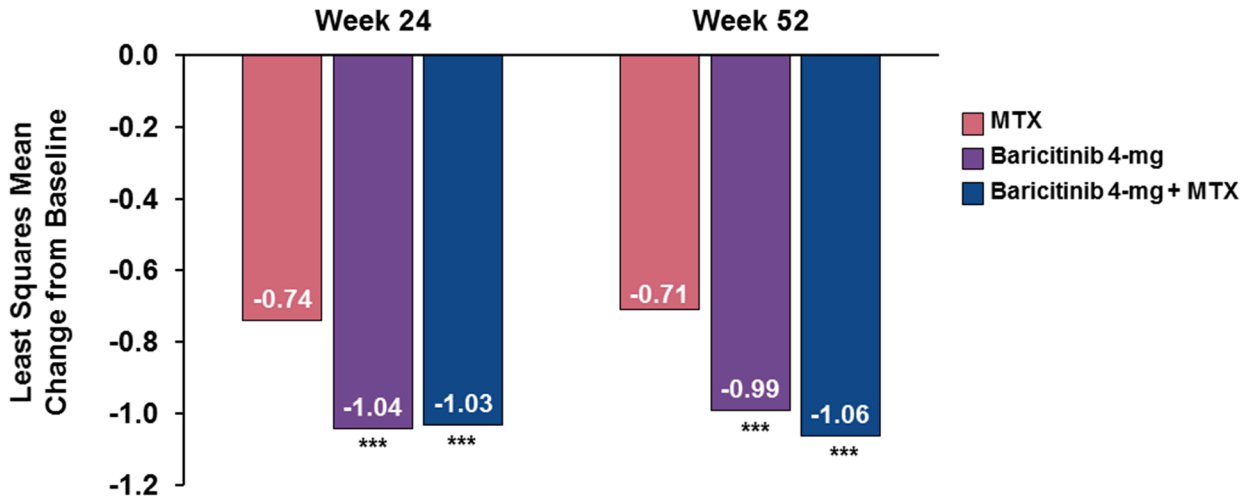


Abbreviations: DAS28 = Disease Activity Score 28 joints; DMARD = disease-modifying anti-rheumatic drug; CRP = C-reactive protein; mLOCF = modified last observation carried forward.
*p≤0.05, **p≤0.01, ***p≤0.001 vs MTX.
Treatment did not include a background cDMARD.
Imputation method: mLOCF.

5.4.3.2.3. JADZ HAQ-DI

The change from baseline in HAQ-DI scores at Weeks 24 and 52 is shown in Figure 52. Compared to MTX monotherapy, statistically significant improvements in HAQ-DI scores were observed at Week 24 for the baricitinib monotherapy and baricitinib + MTX groups ($p \leq 0.001$ for both).

Figure 52: HAQ-DI Change from Baseline to Week 24 in JADZ (DMARD-Naïve)

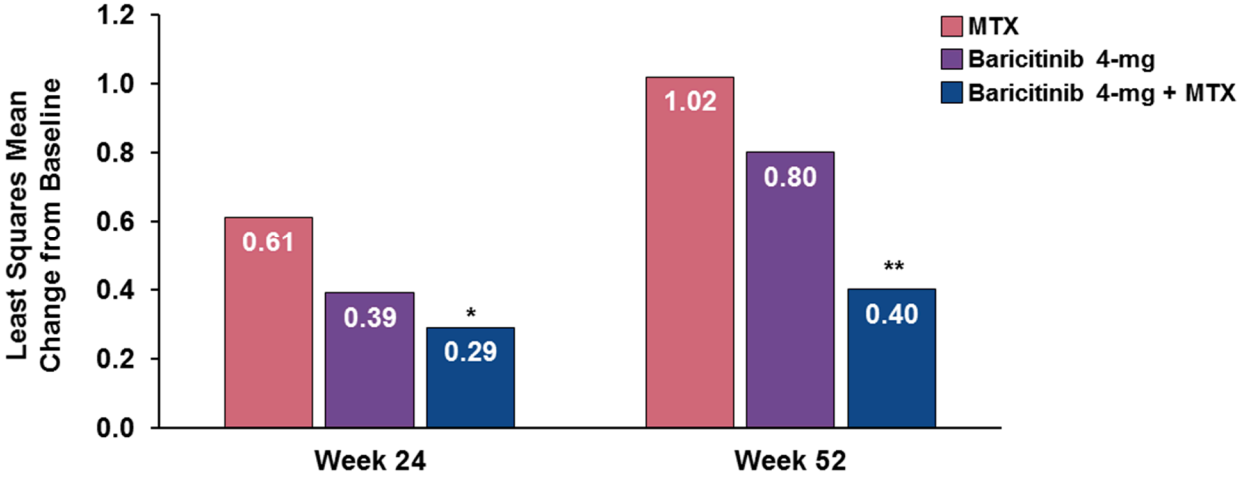


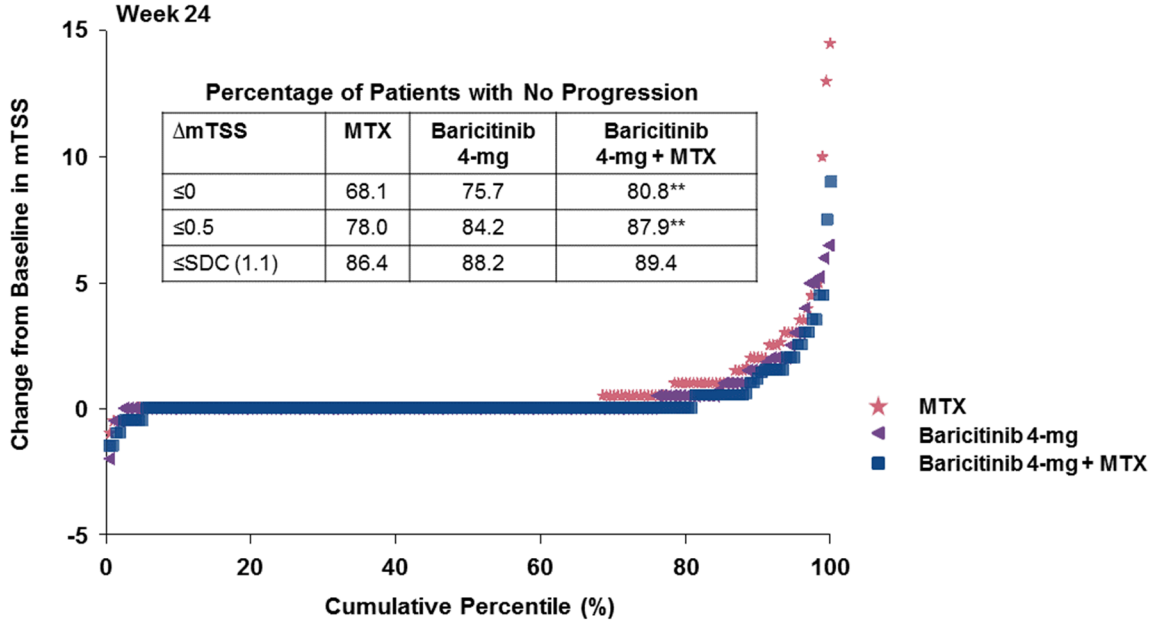
Abbreviations: DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; mLOCF = modified last observation carried forward; MTX = methotrexate.
*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 vs MTX.
Treatment did not include a background cDMARD.
Imputation method: mLOCF.

5.4.3.2.4. JADZ mTSS

Radiographic progression of structural joint damage was reduced in the baricitinib groups versus MTX, an effect that was statistically significant for the combination of baricitinib plus MTX (p=0.026) (Figure 53). The comparison of baricitinib 4-mg + MTX to MTX monotherapy remained statistically significant in analyses using all observed data as randomized. A cumulative probability plot and proportions of patients with progression across commonly-used thresholds is provided in Figure 53.

Figure 53: JADZ (DMARD-naïve) Change from Baseline in mTSS and Cumulative Probability Plot





Percentage of Patients with No Progression

ΔmTSS	MTX	Baricitinib 4-mg	Baricitinib 4-mg + MTX
≤0	68.1	75.7	80.8**
≤0.5	78.0	84.2	87.9**
≤SDC (1.1)	86.4	88.2	89.4

Abbreviations: DMARD = disease-modifying anti-rheumatic drug; LE = linear extrapolation; mTSS = modified Total Sharp Score; MTX = methotrexate; SDC = smallest detectable change.
P-value vs. MTX: * $p \leq 0.05$; ** $p \leq 0.01$.
Each point on the cumulative probability plot represents an individual patient.
Treatment did not include a background cDMARD.
Imputation method: LE.

5.4.4. Efficacy Conclusions from JADZ

- Response rates for MTX monotherapy were consistent with previously published study data and clinical expectations (Breedveld et al. 2006; Jones 2010; Lee et al. 2014).

- Baricitinib 4-mg, used alone or in combination with MTX, was superior to MTX monotherapy with respect to improvements in signs and symptoms, LDA and remission rates, physical function, and additional PROs.
- Efficacy was rapid (as early as Week 1) and durable, with beneficial treatment effects compared to MTX sustained through 52 weeks.
- Radiographic progression of structural joint damage was reduced in the baricitinib groups versus MTX, an effect that was statistically significant for the combination of baricitinib + MTX.
- The inclusion of both a baricitinib monotherapy and baricitinib + MTX combination arm demonstrated that the treatment effects observed for baricitinib monotherapy and the combination of baricitinib + MTX appeared highly comparable in magnitude across many domains of efficacy, including, in particular, for measures of how patients feel and function.

5.5. JADV (cDMARD-IR, bDMARD-naïve)

5.5.1. JADV Study Design

Study JADV was a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo- and active comparator-controlled, 52-week study that compared the efficacy of baricitinib 4-mg to placebo and to adalimumab 40 mg Q2W on signs and symptoms, clinical remission, physical function and additional PROs, and radiographic progression of structural joint damage (Figure 11). Eligible patients had moderately to severely active RA, an inadequate response to established MTX therapy, had not previously been treated with a biologic DMARD, and were taking a stable dose of background MTX ± 1 other cDMARD. Patients were randomly assigned in a 3:3:2 ratio to receive placebo, baricitinib 4-mg, or adalimumab, remaining on their stable background cDMARDs ± NSAIDs, analgesics, and corticosteroids (up to 10 mg prednisone daily or equivalent). Patients who did not adequately respond to study drug were eligible for rescue treatment (baricitinib 4-mg) beginning at Week 16. Non-rescued patients in the placebo group were switched to baricitinib 4-mg at Week 24.

The primary objective of the study was to assess superiority of baricitinib versus placebo, as assessed by the proportion of patients who achieved ACR20 at Week 12. The comparison of baricitinib to adalimumab for noninferiority and superiority (using ACR20 at Week 12) was a **key secondary objective**.

5.5.1.1. JADV Inclusion and Exclusion 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 Classification of Rheumatoid Arthritis (Aletaha et al. 2010)
- Had at least 6 tender joints (of 68 joints examined) and 6 swollen joints (of 66 joints examined)
- Had at least 3 joint erosions on radiographs of hands and feet (or 1-2 erosions if RF or ACPA positive)

- Had an hsCRP measurement of at least 6 mg/L (2× ULN)
- Had an inadequate response to MTX and were receiving stable doses of background MTX.

Patients were excluded from participation if they:

- Had previously received a bDMARD
- Had a recent history of infection including active TB or untreated latent TB or other serious infections
- Had certain abnormal laboratory results
- Had comorbidities that unacceptably increased the patient's risk when taking study drug.

5.5.2. JADV Patient Characteristics and Disposition

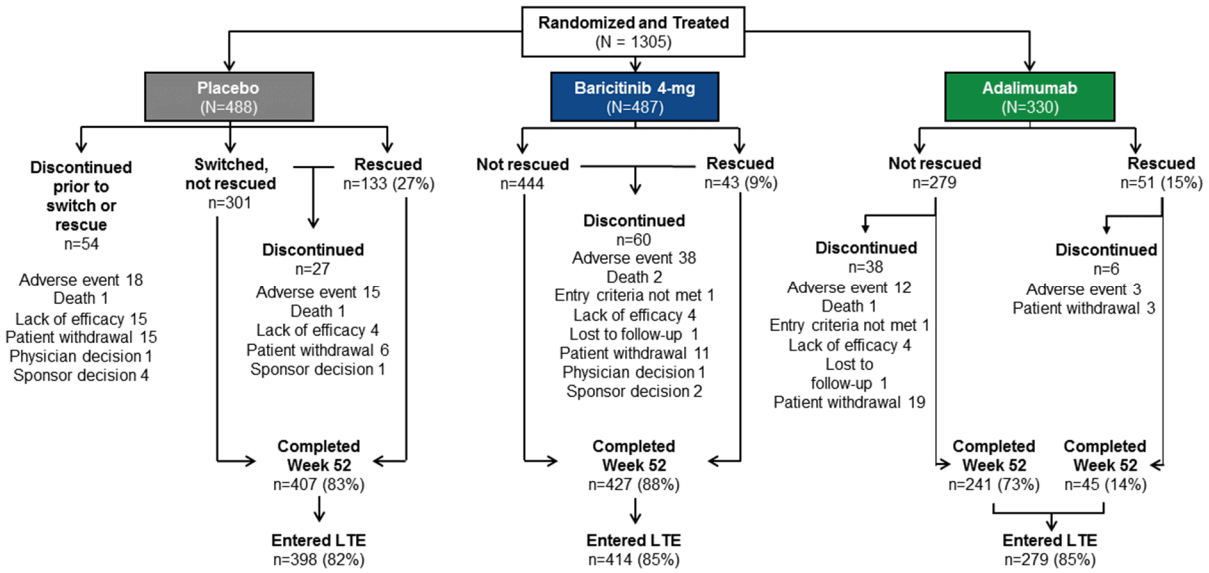
The mean age of patients in Study JADV was approximately 53 years, with a median RA duration of 7.7 years, reflecting a patient population with well-established disease (Table 17). Nearly half of the patients had previously been treated with only one cDMARD. Approximately 90% of patients in the baricitinib group completed the study, 97% of whom entered the LTE study JADY (Figure 54).

Table 17: Baseline Demographics and Disease Characteristics in JADV (cDMARD-IR and bDMARD-naïve)

	Placebo (N=488)	Baricitinib 4-mg (N=487)	Adalimumab (N=330)
Age, years, mean (SD)	53.4 (11.8)	53.5 (12.2)	52.9 (12.3)
Female, n (%)	382 (78.3)	375 (77.0)	251 (76.1)
Duration of RA, years[a], mean (SD)	10.4 (8.7)	10.3 (8.8)	9.6 (8.5)
ACPA positive, n (%)	424 (86.9)	427 (87.7)	295 (89.4)
RF positive, n (%)	451 (92.4)	439 (90.1)	301 (91.2)
≥ 3 Joint erosions, n (%)	371 (76.5)	371 (76.3)	245 (74.9)
mTSS, Sharp units, mean (SD)	45.1 (50.2)	42.5 (50.1)	44.4 (51.0)
Bone joint erosion score, mean (SD)	26.8 (28.6)	25.1 (28.3)	26.4 (28.7)
Joint space narrowing score, mean (SD)	18.2 (23.3)	17.3 (23.2)	18.0 (23.8)
Concomitant steroid use, n (%)	290 (59.4)	275 (56.5)	201 (60.9)
Corticosteroid dose, mg/day[b], mean (SD)	6.0 (2.5)	5.9 (2.6)	6.0 (2.4)
Concomitant MTX use, n (%)	487 (99.8)	487 (100)	330 (100)
MTX dose, mg/week, mean (SD)	14.8 (4.8)	14.9 (4.6)	14.6 (4.4)
Ever used MTX[c], n (%)	487 (99.8)	487 (100)	330 (100)
# of prior cDMARDs, n (%):			
One	204 (41.8)	243 (49.9)	153 (46.4)
Two	169 (34.6)	138 (28.3)	105 (31.8)
≥ Three	114 (23.4)	106 (21.8)	72 (21.8)
# of concomitant cDMARDs, n (%):			
One	398 (81.6)	413 (84.8)	277 (83.9)
Two	89 (18.2)	74 (15.0)	53 (16.1)
Baseline Disease Activity			
Swollen joint count, of 66, mean (SD)	15.5 (9.4)	15.0 (8.2)	15.4 (9.1)
Tender joint count, of 68, mean (SD)	23.3 (13.5)	23.4 (13.0)	23.4 (13.7)
Physician's Global Assessment, 0-100mm VAS, mean (SD)	64.2 (17.1)	65.7 (16.9)	65.3 (16.6)
Patient's Global Assessment, 0-100mm VAS, mean (SD)	60.9 (22.7)	63.1 (21.2)	63.7 (21.2)
Patient's Assessment of Pain, 0-100mm VAS, mean (SD)	59.5 (22.6)	61.8 (21.8)	61.0 (22.7)
HAQ-DI, mean (SD)	1.55 (0.67)	1.57 (0.68)	1.59 (0.70)
hsCRP, mg/L, mean (SD)	19.7 (21.0)	22.2 (22.9)	21.8 (20.8)
ESR, mm/hour, mean (SD)	49.2 (26.1)	49.3 (25.8)	48.4 (25.6)
DAS28-CRP, mean (SD)	5.7 (1.0)	5.8 (0.9)	5.8 (0.9)
DAS28-ESR, mean (SD)	6.4 (1.0)	6.5 (0.9)	6.4 (1.0)
SDAI, mean (SD)	39.5 (13.3)	40.3 (12.7)	40.1 (13.4)
SDAI >26 , n (%)	411 (84.9)	429 (89.0)	278 (85.3)
CDAI, mean (SD)	37.6 (12.8)	38.1 (12.0)	38.0 (13.0)

Abbreviations: ACPA = anti-citrullinated protein antibodies; CDAI = clinical disease activity index; cDMARD = conventional disease-modifying antirheumatic drug; DAS28-CRP = Disease Activity Score in 28 joints c-reactive protein; DAS28-ESR = Disease Activity Score in 28 joints erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; hsCRP = high-sensitivity C-reactive protein; mTSS = modified Total Sharp Score; MTX = methotrexate; N = number of patients; n = number of patients in specified category; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation; SDAI = simplified disease activity index; VAS = visual analog scale.
Note: 1305 patients were randomized; by region: Central and South America (29.1%), Japan (19.1%), Eastern Europe (17.6%), Asia ex-Japan (9.9%), US & Canada (8%), Western Europe (6%), Rest of World (10.3%).
a Time from symptom onset.
b Doses are in prednisone equivalent units.
c Includes patients with historical (previous but not currently taking) MTX use and patients with concomitant (currently taking) MTX use.

Figure 54: Patient Disposition in JADV (cDMARD-IR and bDMARD-naïve)



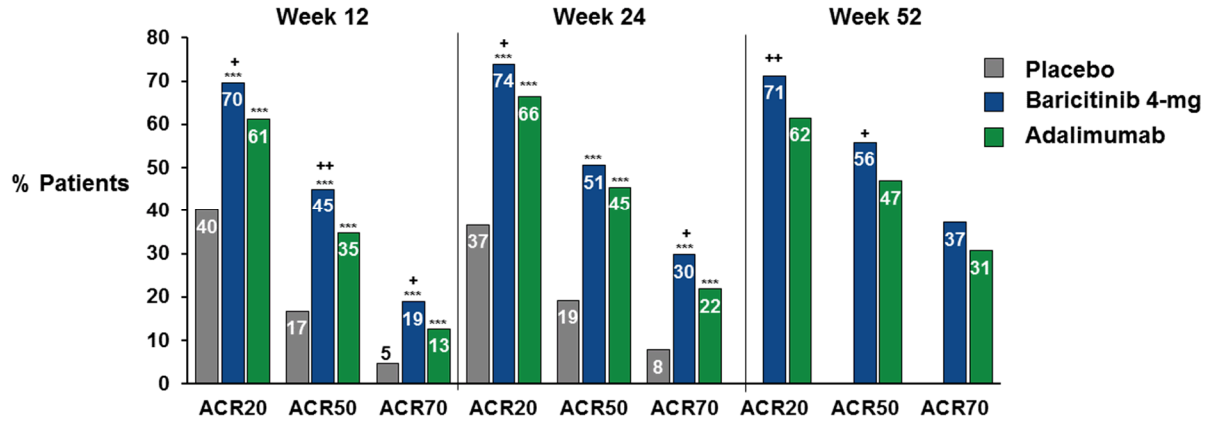
Abbreviation: LTE = long-term extension
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDsa Two patients were randomized and never treated.

5.5.3. JADV Efficacy Results

5.5.3.1. JADV Primary Endpoint Results

Study JADV met its primary objective – the ACR20 response rate was significantly higher for baricitinib 4-mg compared to placebo at Week 12 (Figure 55). The ACR20 response rate at Week 12 was also significantly higher for baricitinib compared to adalimumab, meeting another key study objective. These results were similar for ACR50 and ACR70, where 10% and 6%, respectively, more patients achieved these endpoints compared to adalimumab.

Figure 55: ACR Responses in JADV (cDMARD-IR and bDMARD-naïve)

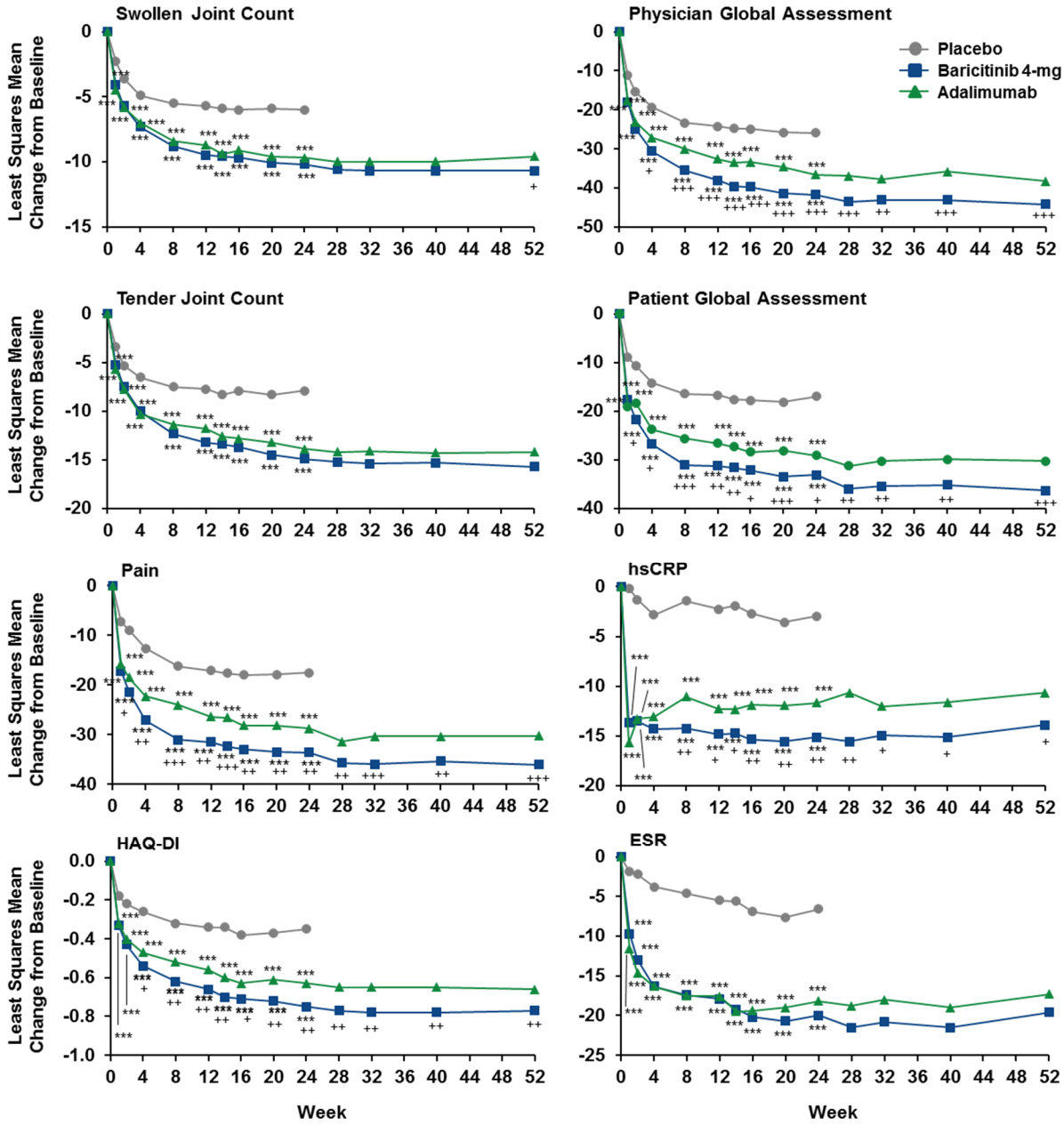


Abbreviations: ACR = American College of Rheumatology; NRI = non-responder imputation
P-value vs. placebo: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001
P-value vs. Adalimumab: $^{+}$ p ≤ 0.05; $^{++}$ p ≤ 0.01; $^{+++}$ p ≤ 0.001
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
Imputation method: NRI.

5.5.3.1.1. JADV ACR Components

Rapid and sustained improvements were noted for baricitinib compared to placebo across all composite score components. Improvements were also evident for baricitinib over adalimumab across components including patient and physician global assessments of disease activity, pain, physical function, and an acute phase reactant. These differences also appeared in the early weeks of treatment and were sustained through Week 52 (Figure 56).

Figure 56: ACR Components and ESR in JADV (cDMARD-IR and bDMARD-naïve)



Abbreviations: HAQ-DI=Health Assessment Questionnaire-Disability Index; hsCRP = high-sensitivity C-reactive protein; ESR=erythrocyte sedimentation rate; LS = least squares
*p≤0.05, **p≤0.01, ***p≤0.001 vs placebo.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
Imputation method: mLOCF.

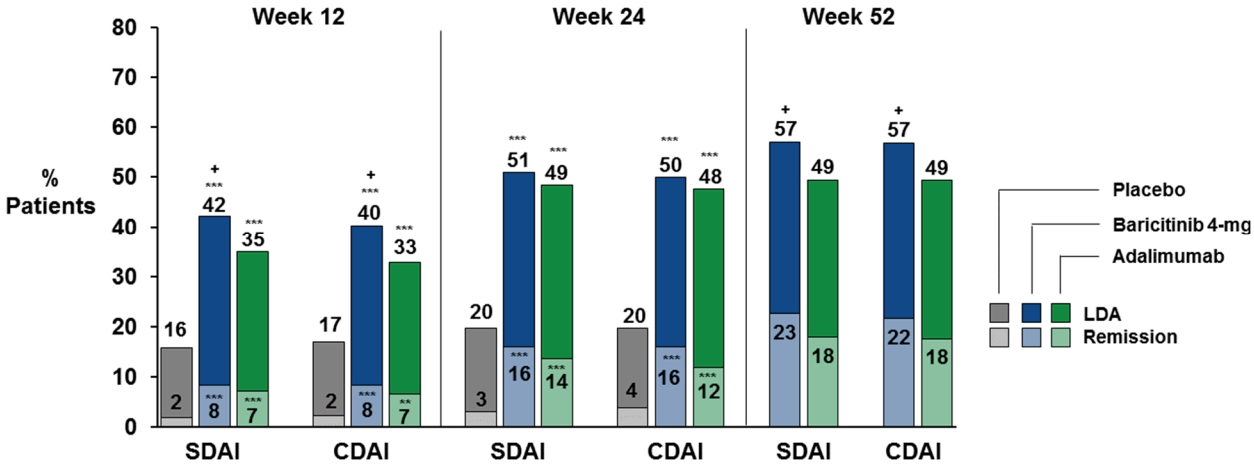
5.5.3.2. JADV Key Secondary Endpoint Results

The results of significance testing using multiplicity control for all key objectives are described in Section 1.5.2.1, Table 5.

5.5.3.2.1. JADV SDAI

Both baricitinib and adalimumab were superior to placebo in increasing the proportion of patients with SDAI ≤3.3 (remission) and ≤11 (LDA) at Week 12 (Figure 57). A higher proportion of patients in the baricitinib 4-mg group achieved LDA compared with the adalimumab group.

Figure 57: SDAI and CDAI Response Rates in JADV (cDMARD-IR and bDMARD-naïve)



Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; CDAI = Clinical Disease Activity Index; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; LDA = low disease activity; NRI = nonresponder imputation; SDAI = Simplified Disease Activity Index.
Total height of each bar = SDAI ≤ 11, CDAI ≤ 10. Lower (paler) portion of each bar = SDAI ≤ 3.3, CDAI ≤ 2.8.
P-value vs. placebo: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001; P-value vs. Adalimumab: $^{+}$p ≤ 0.05; $^{++}$ p ≤ 0.01; $^{+++}$ p ≤ 0.001.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
Imputation method: NRI.

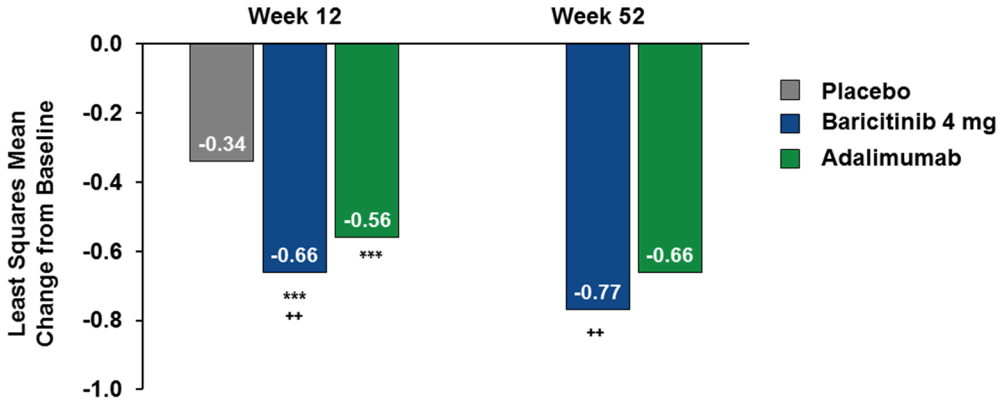
5.5.3.2.2. JADV DAS28-CRP

The DAS28-CRP change from baseline through Week 52 is shown in Figure 12. A statistically significant improvement in DAS28-CRP was observed at Week 12 for the baricitinib group compared to both placebo and adalimumab. Similar results were observed for other continuous composite measures of disease activity included as additional secondary endpoints (change from baseline in SDAI, CDAI, DAS28-ESR).

5.5.3.2.3. JADV HAQ-DI

The HAQ-DI score change from baseline at Week 12 is shown in Figure 58. A statistically significant improvement in HAQ-DI score was observed at Week 12 for the baricitinib group compared to both placebo and adalimumab groups. Baricitinib significantly improved HAQ-DI compared to adalimumab from the initial weeks of treatment, with added improvement sustained through Week 52.

Figure 58: HAQ-DI change from Baseline at Week 12 and 52 in JADV (cDMARD-IR and bDMARD-naïve)



Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; HAQ-DI = Health Assessment Questionnaire-Disability Index; mLOCF = modified last observation carried forward; MTX = methotrexate.
P-value vs. placebo: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001; P-value vs. Adalimumab: $^{+}$p ≤ 0.05; $^{++}$ p ≤ 0.01; $^{+++}$ p ≤ 0.001.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
Imputation method: mLOCF.

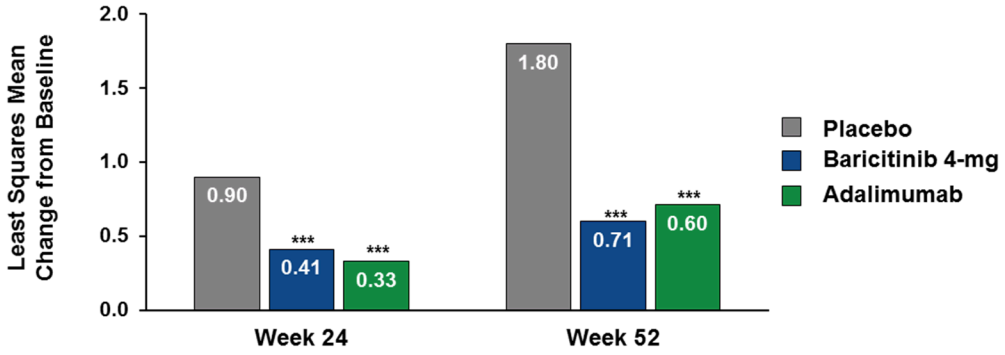
5.5.3.2.4. JADV Electronic Daily Diary PROs

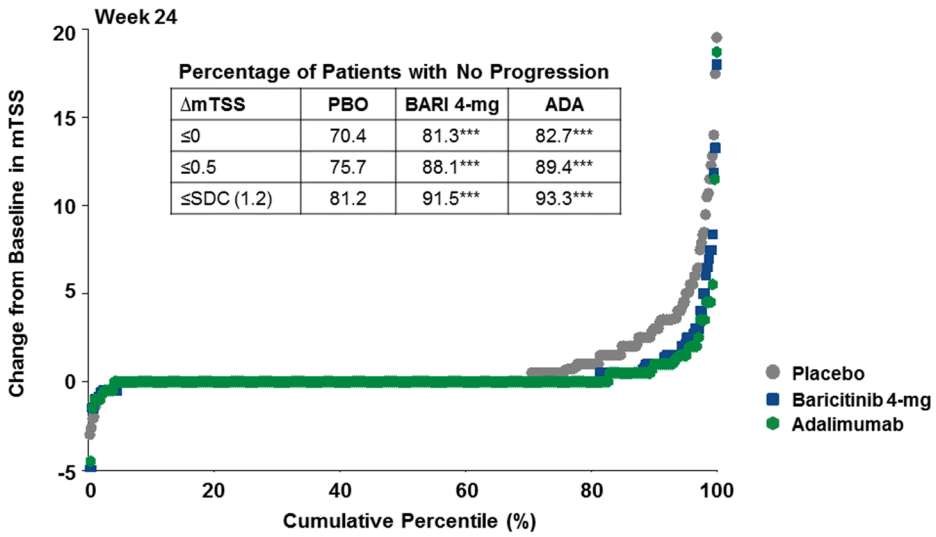
Duration of Morning Joint Stiffness, Severity of Morning Joint Stiffness NRS, Worst Tiredness NRS, and Worst Joint Pain NRS through Week 12 are shown in Figure 13. For each of these RA symptoms, significant improvements were seen for baricitinib vs placebo from Week 1, the first timepoint assessed. Baricitinib also significantly improved each measure compared to adalimumab at the primary Week 12 timepoint.

5.5.3.2.5. JADV mTSS

Baricitinib and adalimumab significantly inhibited radiographic progression of structural joint damage compared to placebo at Week 24 (Figure 59). The comparison of 4-mg to placebo remained statistically significant in analyses using all observed data as randomized. A cumulative probability plot and proportions of patients with progression across commonly-used thresholds is provided in Figure 59.

Figure 59: JADV (cDMARD-IR and bDMARD-naïve) Change from Baseline in mTSS and Cumulative Probability Plot





Abbreviations: Δ mTSS = change from baseline in mTSS; ADA = adalimumab; BARI = baricitinib; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD-IR = conventional disease-modifying anti-rheumatic drug inadequate responder; LE = linear extrapolation; mTSS = modified Total Sharp Score; MTX = methotrexate; PBO = placebo; SDC = smallest detectable change.
P-value vs. placebo: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001.
Each point on the cumulative probability plot represents an individual patient.
Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.
Imputation method: LE.

5.5.4. JADV Efficacy Conclusions

- Baricitinib 4-mg was superior to placebo with respect to improvements in signs and symptoms, LDA and remission rates, physical function, and additional PROs.
- Key secondary comparisons between baricitinib and adalimumab at 12 weeks showed superiority for baricitinib in ACR20 response and improvement in DAS28-CRP.
- Significant improvements were seen with baricitinib compared to adalimumab for all levels of ACR response, all ACR composite components, all other composite disease activity scores, physical function, and all ePRO diary measures.
- Efficacy was rapid (as early as Week 1) and durable, with beneficial treatment effects compared to adalimumab sustained through 52 weeks.
- Baricitinib significantly inhibited radiographic progression of structural joint damage compared to placebo.

- Overall, baricitinib showed statistically significant efficacy compared to placebo and adalimumab on many measures of RA. Adalimumab was used at its approved dose on a background of MTX, a setting in which it is generally considered most efficacious (Smolen et al. 2014), and the efficacy seen for adalimumab was consistent with published adalimumab study data and assumptions used in the design of the study, supporting the generalizability of the results.

5.6. JADY (Extension Study)

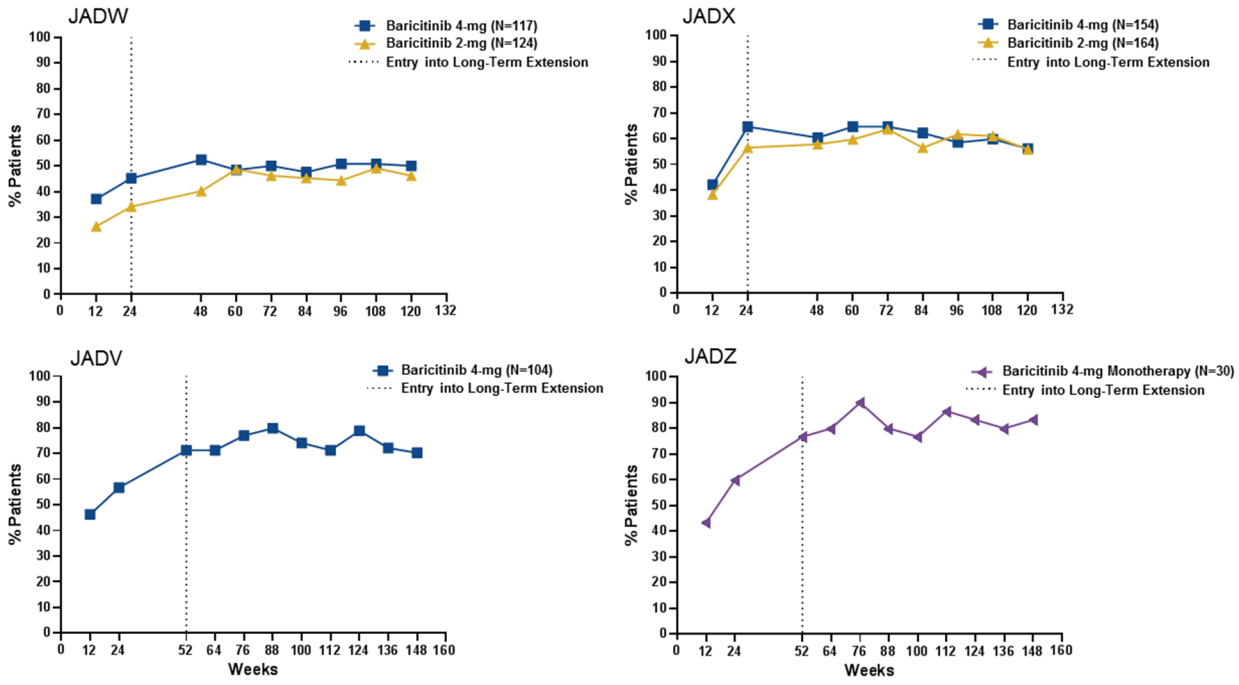
5.6.1. JADY Persistence of Efficacy

As described above, a large majority of patients who completed any of the Phase 3 studies opted to enroll in Study JADY, which presently provides up to an additional 7 years of treatment with baricitinib.

Patients entering JADY received baricitinib while remaining blinded to their original treatment assignment. Patients receiving baricitinib at the completion of their originating study continued on the same dose in JADY. All other patients received baricitinib 4-mg. Rescue treatment (baricitinib 4-mg) was available during JADY. Figure 60 shows categorical response rates at the primary timepoints of the originating studies and through 96 weeks in Study JADY for patients who were originally randomized to baricitinib and were not rescued in an originating study. These patients continued to show sustained efficacy over an additional 96 weeks of treatment following completion of the originating study.

Providing additional supportive evidence of persistent long-term efficacy for baricitinib, retention rates in Study JADY, which commenced enrolling in May 2013, are approximately 80% as of the April 2017 data cutoff.

Figure 60: Proportion of Patients Achieving SDAI <=11 during Originating Studies and an Additional 96 Weeks in JADY



Abbreviations: N = number of patients; SDAI = simplified disease activity index.
Smolen et al. 2017. Data through 01 September 2016.
Imputation method: NRI without considering rescue status.

5.6.2. JADY Dose Taper Study Design

Study JADY incorporated a prospective, blinded, randomized dose taper substudy to determine if patients who achieved sustained LDA or remission with the 4-mg dose could maintain these effects after reduction to the 2-mg dose. The substudy was designed to inform the potential use of baricitinib in accordance with contemporary guidelines (to induce sustained control without delay, then consider attempting taper contingent on maintenance of targets) (Singh 2015; Smolen 2017).

Patients must have met the following criteria to be randomized into the study:

- have received at least 15 months of treatment with baricitinib 4-mg
- have not received rescue therapy in the originating study or Study JADY
- have achieved a sustained (at least 3 months) low disease activity level (defined as CDAI score ≤10 [LDA or remission] for patients originating in Studies JADW, JADX, JADV)

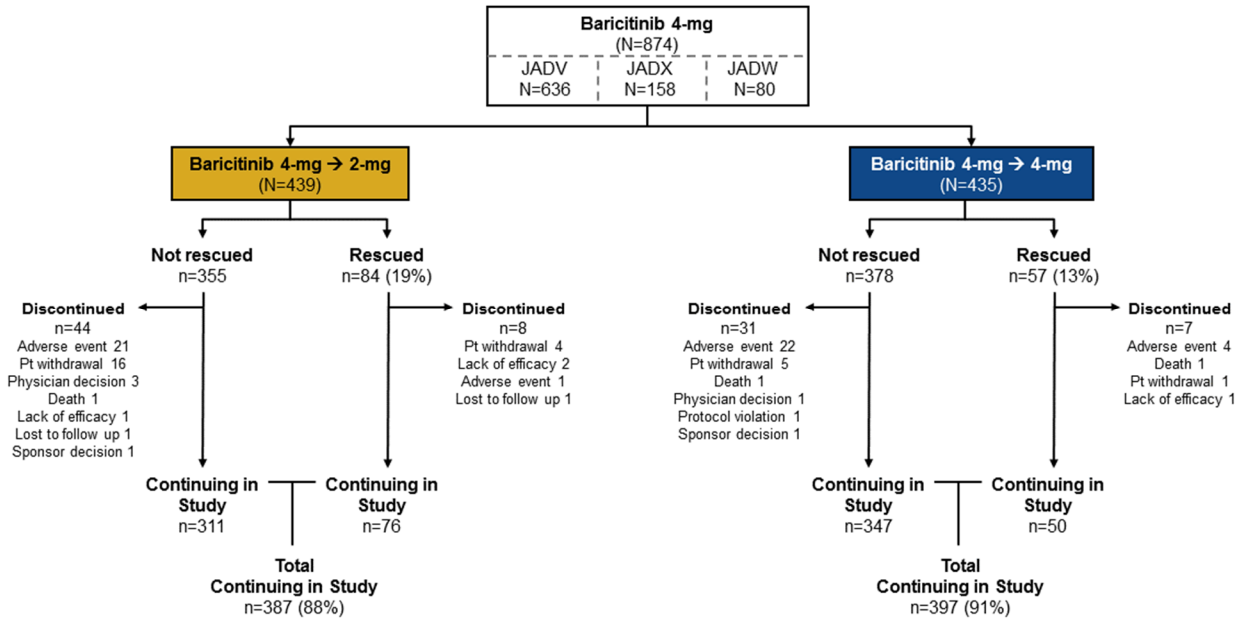
Patients meeting these criteria were blindly randomized 1:1 to either continue 4-mg (4-mg→4-mg) or taper to 2-mg (4-mg→2-mg) without revealing if or when this randomization occurred. Patients who subsequently lost control could be rescued back to 4-mg at the investigator's discretion (Figure 14).

Results are presented here for patients from Studies JADW, JADX, and JADV, but not from JADZ, as JADZ patients required a distinct criterion (sustained remission) to be eligible for randomization.

5.6.3. JADY Dose Taper Patient Characteristics and Disposition

As of April 2017, 874 patients receiving baricitinib 4-mg had been randomized in the dose taper substudy from Studies JADW, JADX, and JADV. The proportion of patients who were subsequently rescued was higher for the dose taper group as compared to the group who remained on 4-mg (Figure 61).

Figure 61: Dose Taper Patient Disposition in Study JADY



Abbreviations: Pt = patient.
For JADW: Indicated treatment is in addition to existing (1-2) background cDMARDs.
For JADX: Indicated treatment is in addition to existing (0-2) background cDMARDs.
For JADV: Indicated treatment is in addition to existing (MTX plus 0-1 other) background cDMARDs.

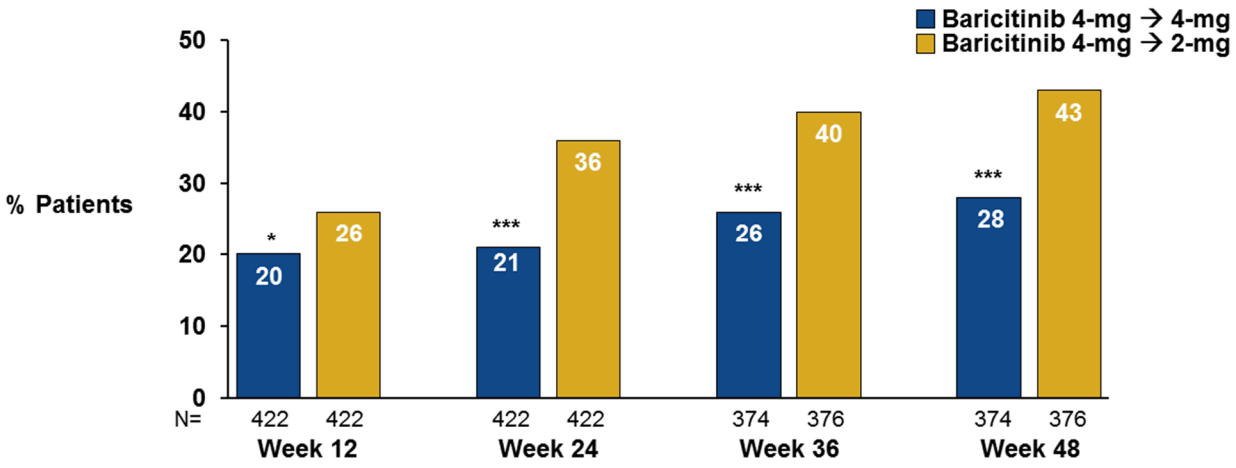
5.6.4. JADY Dose Taper Results

For categorical measures of disease state using CDAI, the proportion of patients who maintained CDAI LDA or remission was statistically significantly higher for baricitinib 4-mg→4-mg compared to 4-mg→2-mg (Figure 15). Analyses based on individual patients' loss of their pre-randomization LDA or remission state (Figure 62), time to relapse (Figure 63), and changes in continuous measures of disease activity (

Table 18) supported these findings.

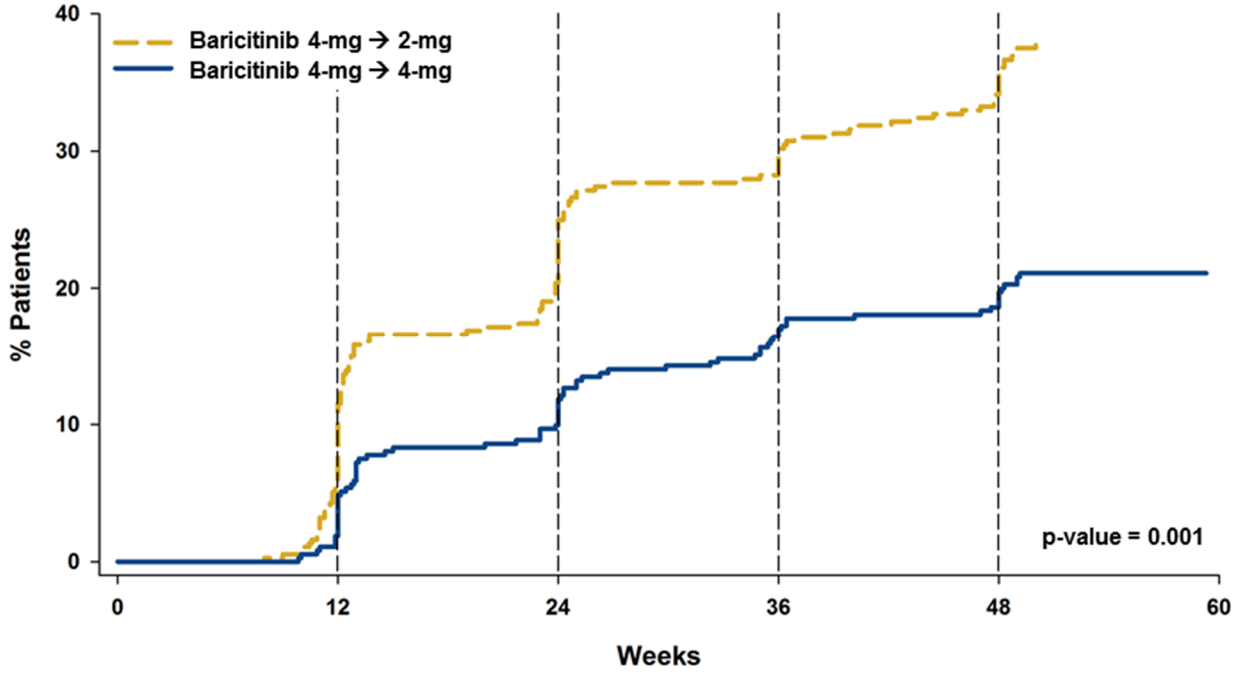
Among patients who did lose response after dose taper and required rescue, at a timepoint 24 weeks post-rescue, observed data showed that two-thirds of these patients recaptured their prior level of disease control, and of the remainder, two-thirds did so during the ongoing follow-up.

Figure 62: Proportion of Patients with Loss of their Individual Pre-randomization State (CDAI), DMARD-IR Studies (JADW, JADX, JADV)



Abbreviation: CDAI = Clinical Disease Activity Index; DMARD-IR = disease-modifying anti-rheumatic drugs; NRI=non-responder imputation.
Baricitinib 4-mg → 4-mg versus 4-mg → 2-mg: *p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001.
Imputation method: NRI.
Includes patients from Studies JADV, JADX, and JADW Continuing in JADY.
a Week 12 and 24 includes patients who had been randomized 24 weeks prior to the datacut.
b Week 36 and 48 inclues patients who had been randomized 48 weeks prior to the datacut.

Figure 63: Kaplan–Meier plot for time to loss of dose taper eligibility criteria (CDAI≤10); patients from Studies JADV, JADX, and JADW continuing in JADY



Abbreviations: CDAI = clinical disease activity index.
The p-value is from the Wilcoxon test.

Table 18: Dose Taper Results for Continuous Efficacy Measures, DMARD-IR Studies (JADW, JADX, JADV)

	Weeks after Dose Taper							
	12		24		36		48	
	4-mg→ 2-mg (N=422[a])	4-mg→ 4-mg (N=422[a])	4-mg→ 2-mg (N=422[a])	4-mg→ 4-mg (N=422[a])	4-mg→ 2-mg (N=376[b])	4-mg→ 4-mg (N=374[b])	4-mg→ 2-mg (N=376[b])	4-mg→ 4-mg (N=374[b])
ΔCDAI	1.75	0.61***	2.48	0.70***	2.34	1.08**	2.70	1.18***
ΔSDAI	1.99	0.71***	2.68	0.84***	2.60	1.17***	2.96	1.31***
ΔDAS28-CRP	0.31	0.09***	0.39	0.10***	0.43	0.15***	0.44	0.17***
ΔDAS28-ESR	0.29	0.09***	0.35	0.10***	0.40	0.17***	0.42	0.15***
ΔTender joint count	1.0	0.3**	1.3	0.2***	1.4	0.4**	1.5	0.4***
ΔSwollen joint count	0.5	0.1**	0.8	0.1***	0.7	0.3*	0.7	0.2*
ΔHAQ-DI	0.05	0.02	0.06	0.01*	0.08	0.02*	0.08	0.05
ΔPatient's assessment of pain	4.1	1.3*	4.4	1.1**	5.2	2.6*	6.0	3.8
ΔPtGA	3.9	1.4*	4.4	1.8*	4.4	2.4	5.5	3.4
ΔPGA	2.2	0.5*	3.2	1.0**	3.3	1.0*	4.1	1.3**
ΔhsCRP	2.37	0.95	1.89	1.25	2.33	0.77*	2.34	1.25

Abbreviations: Δ = change from baseline of dose taper randomization; CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire–Disability Index; hsCRP = high-sensitivity C-reactive protein; mLOCF = modified last observation carried forward; PGA = Physician's Global Assessment of Disease Activity; PtGA = Patient's Global Assessment of Disease Activity; SDAI = Simplified Disease Activity Index.
*** p≤0.001; ** p≤0.010; * p≤0.05 from a 2-sided t-test for 4-mg→4-mg versus 4-mg→2-mg.
a Week 12 and 24 includes patients who had been randomized 24 weeks prior to the datacut.
b Week 36 and 48 inclues patients who had been randomized 48 weeks prior to the datacut.
Imputation method: mLOCF.

5.7. Exposure Response Relationship and Dosing Recommendation based on Combined Phase 2 and 3 Data

Final E-R analysis was conducted for DAS28-CRP scores with data from all 7 Phase 2 and 3 studies (Phase 2/3 PopPKPD dataset) over a wide dose range of 1-mg to 10-mg. DAS28-CRP scores up to Week 24 were used to describe the time course of changes in DAS28-CRP scores using a population PKPD modeling approach. The objectives of the analyses were to evaluate response rate for the 1-mg dose based on pooled Phase 2 and 3 data and to characterize E-R relationships for different patient subpopulations for commercial dose recommendation.

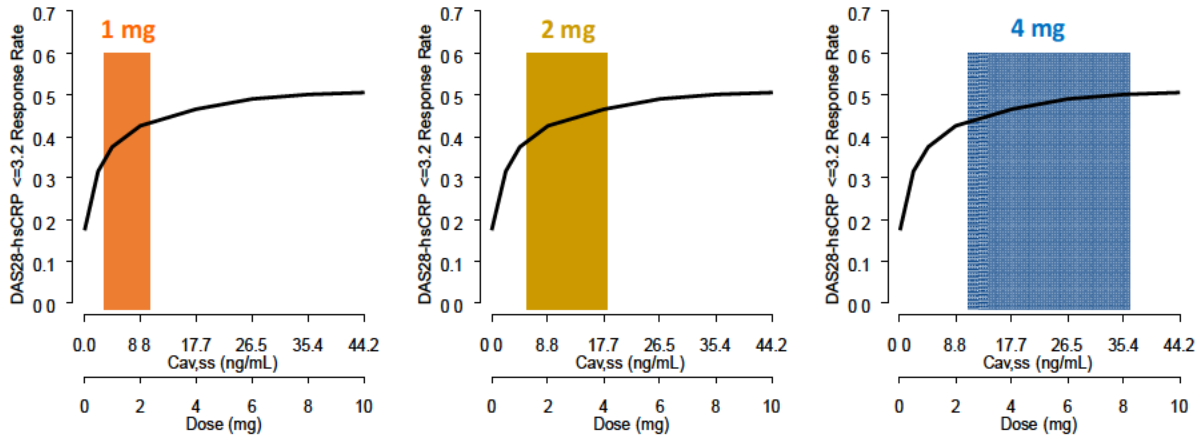
5.7.1. Final Exposure Response Analysis for 1-mg QD Dosing

The E-R modeling results for DAS28-CRP ≤3.2 (summarized from the model-predicted absolute DAS28-CRP scores) at Week 12, are shown in Figure 64 for the cDMARD-IR patients in the pooled Phase 2 and 3 data set. The predicted placebo-adjusted response rates in low disease activity (DAS28-CRP≤3.2) at the 1-, 2-, and 4-mg QD doses were 20%, 25%, and 29%, respectively, indicating that highest efficacy was achieved at 4-mg QD. The 1 mg dose was not evaluated in the Phase 3 studies, but efficacy predicted from the final E-R model indicated

approximately 25% and 45% increase in relative efficacy at 2-mg and 4-mg relative to the 1 mg dose.

The estimated E-R relationship for DAS28-CRP ≤3.2 at Week 12 is consistent with that estimated based on the Phase 2 study JADA (Section 1.4, Figure 3). The final E-R relationship confirmed that the 1-mg exposures reside on the ascending portion of the E-R curve and would not offer an acceptable probability of achieving treatment goals in many patients.

Figure 64: Model-predicted Dose/Exposure-Response Relationship of DAS28-CRP ≤ 3.2 at Week 12 in cDMARD-IR Patients based on Combined Phase 2 and 3 Data



Abbreviations: Cav,ss = daily average concentration at steady state of dosing; cDMARD = conventional disease-modifying antirheumatic drug; CRP = C-reactive protein; DAS28= Disease Activity Score based on the 28 diarthrodial joint count; IR =inadequate responder.
Footnote: Shaded areas indicate the range (5^{th}-95^{th} percentile) of Cav,ss for the corresponding doses.

5.7.2. *Exposure Response Analysis for Patient Subpopulations for Commercial Dose Recommendation*

To further explore the posology suggested based on the dose-response relationship observed in Study JADW and in the 1DMARD-IR versus 2+DMARD-IR subgroup analyses from JADX (Section 1.5.3), E-R analysis was conducted to evaluate if patient subpopulations have potentially different E-R properties. The results were used to support the dose recommendation for each patient subpopulation.

Patients included in this analysis are:

- bDMARD-IR: Phase 3 Study JADW and some patients from Phase 2 Studies JADN and JADC
- cDMARD-IR: Phase 2 Studies JADA, JADN, JADC, and Phase 3 Studies JADX and JADV
    - 1cDMARD-IR: cDMARD-IR patients who failed 1 cDMARD
    - 2+cDMARD-IR: cDMARD-IR patients who failed at least 2 cDMARDs

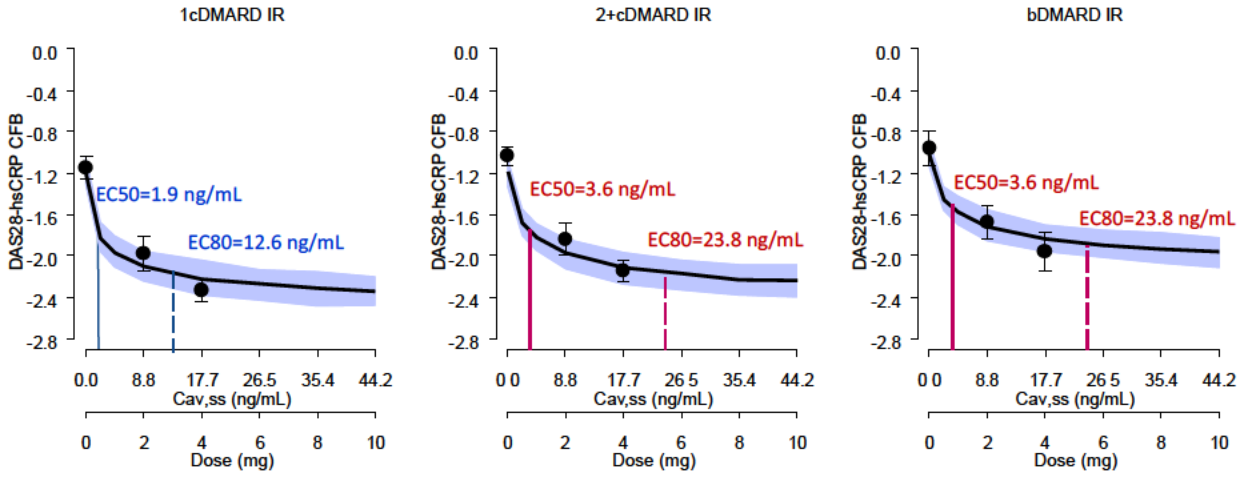
Estimated E-R curves for DAS28-CRP expressed as change from baseline values, along with observed data, are included in Figure 65. Model-predicted and observed data agree with each other well, and the final model passed all qualification standards.

In this E-R analysis, patient subpopulations were identified as significant covariates on the drug effect parameters of Emax (maximum response) and EC50 (Figure 65):

- bDMARD-IR patients had lower Emax compared to cDMARD-IR (including 1cDMARD-IR and 2+cDMARD-IR) patients.
- The more refractory patients, bDMARD-IR and 2+cDMARD-IR, had the same EC50 (and corresponding EC80) values, which were higher than those in the less refractory 1cDMARD-IR patients.

These results indicate that higher drug concentrations are needed for the more refractory patients (bDMARD-IR and 2+cDMARD-IR) to achieve the same efficacy as for the less refractory patients. Specifically, the fact that the EC80 value for the more refractory patients of 23.8 ng/mL is above the 2-mg concentration range (5^{th} - 95^{th} percentile of average concentrations at 2-mg = 5.6 -18.1 ng/mL) suggests that the 2-mg concentrations will not achieve an 80% maximum response in the more refractory patients.

Figure 65: Estimated Dose/Exposure Response Relationship for Change from Baseline Values of DAS28-CRP at Week 12 in the 1cDMARD-IR, 2+cDMARD-IR, and bDMARD-IR Populations



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; Cav,ss = average concentration during a dosing interval at steady state; cDMARD = conventional disease-modifying antirheumatic drug; CFB= change from baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score based on the 28 diarthrodial joint count; EC50 = concentration required to achieve 50% maximum response; EC80 = concentration required to achieve 80% maximum response; IR= inadequate responder.

Note: Solid black lines and badns are model-predicted mean response with corresponding 90% prediction intervals. Circles represent observed data and error bars are 90% confidence intervals.

6. Overview of Safety

- The safety profile of baricitinib 2-mg and 4-mg has been established based on an extensive clinical development program and a RA safety database of 3492 patients with 7860 PYE; nearly a 90% increase in PYE since the initial submission.
- In the placebo-controlled time period, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to AEs were noted more frequently for baricitinib-treated patients compared to placebo and for baricitinib 4-mg patients compared to 2-mg, although differences were small with overlapping confidence intervals. Deaths were reported less frequently for baricitinib-treated patients compared to placebo.
- Mild to moderate treatment-emergent infections, including herpes zoster and upper respiratory tract infections, were commonly reported in baricitinib-treated patients with no increased risk for serious infections. A variety of opportunistic infections were reported by baricitinib treated patients with no dose related differences and incidence rates for individual events reported were within published ranges for RA patients.
- Malignancies were observed in the baricitinib clinical studies. The incidence rate reported for all baricitinib-treated patients and by dose was within the range reported for other RA therapies.
- For positively adjudicated major adverse cardiovascular events (MACE), no differences were observed between baricitinib- and placebo-treated patients in the number, frequency, and incidence rate. With long-term exposure, the MACE incidence rate for all baricitinib treated patients was 0.5, which is within the range reported for RA patients in general and from other registration programs.
- Based on DVT/PE event imbalances noted in the placebo-controlled period, venous thromboembolism (VTE) is an important potential risk for baricitinib and has been included as a warning and precaution in draft labeling. Across all baricitinib exposures and treatment duration, the stable estimate of VTE incidence rate is 0.53 with no difference by dose and within the VTE incidence rate range published for RA patients.
- GI perforations were infrequent with an incidence rate in the low end of the range of published rates in patients with RA (Section 1.6.6).
- Clinical Chemistry:
  - Lipid parameters, such as total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, and triglycerides increased in a dose-related manner and remained stable over continued baricitinib exposure. LDL increases were primarily due to increases in larger LDL particles and decreases in smaller dense LDL particles, generally thought to be more atherogenic.
  - Creatine phosphokinase increased within 1 week of treatment in a dose-related manner and plateaued at 8 to 12 weeks. No clear association was observed with adverse outcomes such as myopathy or rhabdomyolysis.
  - Elevations in serum ALT and AST were common, plateaued at Week 4, were not dose-related, and not associated with drug-induced liver injury (Hy's law criteria).
- Hematological Findings:
  - Declines in hemoglobin were noted during the first 2 weeks of baricitinib treatment, which returned to near baseline values with continued administration. Compared to placebo, baricitinib was not associated with an increased incidence of TEAEs of anemia.
  - Decreases in absolute neutrophil counts were noted during the first month of baricitinib treatment and remained stable over continued treatment. Reductions to $<1.0 \times 10^9$/L were uncommon at 2-mg (0.6%) and 4-mg (0.2%) baricitinib.
  - Increases in lymphocyte counts were noted within the first week of baricitinib treatment, which returned to baseline or below within 12-24 weeks. Decreases to $<0.5 \times 10^9$/L were noted (0.8% at 2-mg and 0.6% at 4-mg), and reductions in lymphocyte counts by increasing Common Terminology

Criteria for Adverse Events (CTCAE) grade were associated with an increased frequency of nonserious infections.
  - Dose-related increases in platelet counts were noted within the first 2 weeks of treatment, which returned toward baseline and remained stable. Increases to >600 x10^9/L were noted for 1.1% of 2-mg and 2.3% of 4-mg baricitinib-treated patients. No association was found between platelet counts and thrombotic events.
- Postmarketing adverse event data from approved countries have revealed no new safety signals.
- An extensive risk management plan evaluating over 13,000 patients in prospective and retrospective observational studies, registries, and post-marketing surveillance studies is planned and already underway in countries where baricitinib is approved.

6.1. Evaluation of Safety

6.1.1. Safety Database

The RA integrated safety analyses (All BARI RA) comprise data from 3492 RA patients who received baricitinib: one Phase 1 drug-drug interaction study with RA patients (Study JADB), three Phase 2, four Phase 3 completed studies, and one ongoing long-term RA extension study. This document focuses on integrated safety data for the RA indication. The overall safety database also included four concluded Phase 2 studies in patients with psoriasis, diabetic nephropathy, atopic dermatitis, and systemic lupus erythematosus and a Phase 3 RA regional study. Safety data from 18 Phase 1 clinical pharmacology studies of non-RA patients have also been assessed.

6.1.1.1. Integration/Pooling of Studies

This integrated safety data analysis focuses on 4 analysis subsets or pools (Table 7). The first is the PC dataset used for evaluation of the placebo-controlled (PC) time periods comparing placebo to 2-mg and 4-mg baricitinib-treated patients in the 4 studies that included placebo, 2-mg and 4-mg treatment groups. An additional placebo-controlled data set (PC 4-mg) includes 6 studies with placebo and baricitinib 4-mg dose groups and allows greater power to detect differences between baricitinib and placebo via a larger PC sample size. This dataset is the focus for the venous thromboembolic event discussion.

The EXTENDED dataset provides longer-term follow-up data for patients treated with 2-mg or 4-mg for dose comparisons over longer treatment duration; however, it does not provide comparison to placebo. The ALL BARI RA dataset provides the most stable estimate of AE incidence rates for baricitinib because it includes all doses and durations of exposure.

To assure valid interpretability for the estimation of effects due to the originally randomized treatments among all treated patients, between-group comparisons were conducted only between randomized groups and were censored after rescue or protocol-defined changes in study drug or dose (except for the ALL BARI RA dataset). Because exposure times differed across groups, exposure-adjusted incidence rates were evaluated (referred to as incidence rates and presented per 100 patient-years), as well as event counts and proportions. For selected safety topics, events were also evaluated for patients from the ALL BARI RA dataset on an " as-treated" basis with events ascribed to the dose the patient was on at the time of the event using the ever exposed population for 2-mg (N=1005, PYE=1275) or 4-mg (N=3107, PYE=6392) baricitinib.

6.1.1.2. Adverse Effects Characteristic of the Disease State and Pharmacological Class

The safety assessment included a particular focus on certain safety topics of interest, presented in Section 6.2.5.

6.1.1.3. Patient Characteristics

Overall, patient characteristics were representative of the proposed indication population. Use of concomitant therapies with known safety profiles, including NSAIDs, corticosteroids, and immunomodulatory DMARDs, was highly prevalent. Many patients had a substantial burden of prior therapeutic immunosuppression, often reflecting individual study eligibility criteria (most notably in the bDMARD-IR study, Study JADW). Baseline characteristics are summarized in Table 14 for JADW, Table 15 for JADX, Table 16 for JADZ, and Table 17 for JADV. The prevalence of comorbid conditions was also consistent with expectations for patients with RA, in some instances varying according to the known epidemiology of the geographic regions studied; these are also noted where relevant (for example, TB; see Section 6.2.5).

6.1.1.4. Disposition and Compliance with Study Drug

From the PC dataset, more placebo-treated patients (12.9%) discontinued study drug compared to baricitinib-treated patients at 2-mg (6.5%) and 4-mg (7.3%). A similar pattern was observed in the PC 4-mg dataset (baricitinib 4-mg: 5.4% and placebo: 10.7%).

Among patients who completed an eligible Phase 2 or Phase 3 study, approximately 90% elected to proceed to the long-term extension study (JADY) with 2656 patients enrolled as of 01 April 2017. In JADY, 297 patients started on 2-mg and 2359 on 4-mg baricitinib. Of the 2656 patients, 21% discontinued. The most common reasons for discontinuation were adverse event (38.5%) and lack of efficacy (22.0%), with discontinuation due to lack of efficacy more common for patients entering on 2-mg (27/297, 9.1%) than 4-mg (96/2359, 4.1%). In total, 0.6% of patients (15/2656) were lost to follow-up during JADY.

Based on individual study data, mean compliance in the baricitinib treatment arms was 98% or higher.

6.1.1.5. Exposure

In the All BARI RA dataset, patient-years of exposure (PYE) to any dose of baricitinib increased 86.5% from 4214 in the initial submission (N = 3464) to 7860 as of 01 April 2017 (N = 3492). From the ALL BARI RA dataset there were 1005 patients who were ever exposed to baricitinib 2-mg (1275 PYE; initially or in dose taper) and 3107 patients who were ever exposed to baricitinib 4-mg (6392 PYE; initially, or after rescue or switching). These denominators will be used for “as-treated” frequencies or incidence rates (note: because some patients were exposed to both 2-mg and 4-mg, the total is more than 3492). For special safety topics that may include events that occurred after baricitinib discontinuation, the time to the observed event is also included in the denominator (up to 7993 patient years) reflecting patient years of observation.

As of 01 April 2017, 2723 patients with RA had been treated with baricitinib for at least 1 year, 2431 for 1.5 years, and 2182 for 2 years, and the maximum duration of exposure to baricitinib in

RA patients exceeded 6 years. The number of patients and overall extent of exposure are adequate to characterize the safety profile of the molecule for regulatory submission.

6.2. Overview of Adverse Events and Deaths

Selected key safety outcomes from the randomized controlled trials and long-term exposure are summarized in Table 19. In the placebo-controlled time period, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to AEs were noted more frequently for patients receiving baricitinib compared to placebo, with higher frequencies for patients treated with 4-mg compared to 2-mg baricitinib. Differences between baricitinib and placebo, and between baricitinib doses, were modest with overlapping confidence intervals.

Table 19: Overview of Adverse Events

	PC Dataset (Weeks 0-16)			PC 4-mg Dataset (Weeks 0-16)		EXTENDED Dataset		All BARI RA Dataset
	PBO (N=551)	**2-mg (N=479)**	**4-mg (N=479)**	**PBO (N = 1070)**	**4-mg (N = 997)**	**2-mg (N=479)**	**4-mg (N=1371)**	**Phases 1-3 (N=3492)**
Deaths, n (%) [incidence rate]	2 (0.4) [1.3]	0	1 (0.2) [0.7]	2 (0.2) [0.6]	1 (0.1) [0.3]	1 (0.2) [0.16]	10 (0.7) [0.34]	28 (0.8) [0.35]
Patients with ≥1 TEAE, n (%) [EAIR]	326 (59.2) [217.4]	294 (61.4) [214.1]	315 (65.8) [228.9]	610 (57.0) [203.0]	635 (63.7) [217.3]	376 (78.5) [60.9]	1218 (88.8) [41.3]	3023 (86.6) [38.5]
Patients with ≥1 SAE, n (%) [EAIR]	22 (4.0) [14.3]	16 (3.3) [11.4]	25 (5.2) [17.7]	41 (3.8) [13.3]	43 (4.3) [14.4]	62 (12.9) [10.1]	271 (19.8) [9.2]	711 (20.4) [8.9]
AEs leading to temporary interruption of study drug, n (%) [EAIR]	39 (7.1) [26.0]	46 (9.6) [33.5]	58 (12.1) [42.1]	78 (7.5) [26.6]	95 (9.8) [33.3]	105 (21.9) [17.0]	379 (28.3) [12.9]	966 (28.7) [12.4]
AEs leading to permanent discontinuation, n (%) [EAIR]	19 (3.4) [12.3]	19 (4.0) [13.5]	25 (5.2) [17.7]	35 (3.3) [11.4]	42 (4.2) [14.1]	39 (8.1) [6.3]	193 (14.1) [6.5]	435 (12.5) [5.4]

Abbreviations: AE = adverse event; EAIR = exposure-adjusted incidence rate; N = number of patients in the safety dataset; n = number of patients in specified category; PYE = patient-years of exposure; PBO = placebo; RA = rheumatoid arthritis; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Percentages are based on the number of patients in each treatment group (N); EAIR is expressed as the number of patients experiencing an AE per 100 patient-years of exposure to treatment and is derived as 100 times the incidence of the event divided by the sum of all patient exposure time (in years for the specific treatment group).

6.2.1. Deaths

Three deaths were reported in the PC dataset, 2 in the placebo group (IR=1.3) and 1 in the 4-mg baricitinib group (IR=0.7). The overall incidence rate for death in the All BARI RA dataset was 0.35. The incidence rate of death for the 2-mg baricitinib-treated patients (0.16) was lower than for 4-mg baricitinib-treated patients (0.34) and overall (0.35); all were lower than the death incidence rates for placebo or 4-mg from the placebo-controlled period On an as-treated basis, the death incidence rate was 0.16 (95% CI; 0.02, 0.57) for 2-mg and 0.39 (95% CI; 0.25, 0.58) for 4-mg. All are within the range of death incidence rates from other RA clinical programs (Figure 18). From Study JADZ, which evaluated MTX monotherapy, baricitinib 4-mg monotherapy, and a combination of MTX plus baricitinib 4-mg, during Week 0 to 52 three deaths were reported and all were in the MTX monotherapy arm (IR=1.76) .

Cumulatively, 28 treatment-emergent deaths were reported from baricitinib-treated patients from the All BARI RA dataset through 01 April 2017 (Table 19). The most frequent causes of death, as reported by the investigator, were myocardial infarction/cardiovascular events (8/28), infections (6/28; including 1 TB), and malignancies (5/28). One death due to pulmonary embolism and no fatal GI perforations were reported . Based on the events reported and published incidence rates from other RA therapies (Figure 18); baricitinib was not associated with an overall increased risk of death or an increased risk of death from a particular clinical condition.

6.2.2. Other Serious Adverse Events

Serious adverse events (SAEs) include those reported by the investigator as life-threatening, requiring inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, or death. From the PC dataset, more patients reported SAEs in the baricitinib 4-mg group (5.2%) compared with 2-mg (3.3%); reports from placebo-treated patients were 4.0%. From the PC 4-mg dataset, the proportions of patients with SAEs were similar between placebo (3.8%) and 4-mg (4.3%). SAE incidence rates from the EXTENDED dataset were similar for the 2-mg (10.1) and 4-mg (9.2) dose groups. Infections were the most frequently reported SAEs (Table 20).

Table 20: Summary of the 10 Most Common Serious Adverse Events in the ALL BARI RA Dataset

	PC Dataset (Weeks 0-16)			PC 4-mg Dataset (Weeks 0-16)		EXTENDED Dataset		All BARI RA Dataset
	PBO (N=551) PYE=154.3 n (%) [EAIR]	**2-mg** (N=479) PYE=140.3 n (%) [EAIR]	**4-mg** (N=479) PYE=141.4 n (%) [EAIR]	**PBO** (N = 1070) PYE=308.1 n (%) [EAIR]	**4-mg** (N = 997) PYE=297.7 n (%) [EAIR]	**2-mg** (N=479) PYE=617.2 n (%) [EAIR]	**4-mg** (N=1371) PYE=2950.8 n (%) [EAIR]	**Phases 1-3** (N=3492) PYE=7993 n (%) [EAIR]
Patients with ≥1 SAE	22 (4.0) [14.3]	16 (3.3) [11.4]	25 (5.2) [17.7]	41 (3.8) [13.3]	43 (4.3) [14.4]	62 (12.9) [10.1]	271 (19.8) [9.2]	711 (20.4) [8.9]
Pneumonia	2 (0.4) [1.3]	2 (0.4) [1.4]	1 (0.2) [0.71]	2 (0.2) [0.65]	1 (0.1) [0.34]	4 (0.8) [0.65]	13 (0.9) [0.44]	46 (1.3) [0.58]
Osteoarthritis	0	1 (0.2) [0.71]	0	0	0	4 (0.8) [0.65]	12 (0.9) [0.41]	33 (0.9) [0.41]
Herpes zoster	1 (0.2) [0.65]	0	1 (0.2) [0.71]	1 (0.1) [0.32]	3 (0.3) [1.0]	1 (0.2) [0.16]	8 (0.6) [0.27]	28 (0.8) [0.35]
Urinary tract infection	0	0	1 (0.2) [0.71]	1 (0.1) [0.32]	1 (0.1) [0.34]	0	9 (0.7) [0.31]	19 (0.5) [0.24]
Fall	2 (0.4) [1.3]	0	1 (0.2) [0.71]	2 (0.2) [0.65]	1 (0.1) [0.34]	0	6 (0.4) [0.20]	18 (0.5) [0.23]
Rheumatoid arthritis	3 (0.5) [1.9]	0	2 (0.4) [1.4]	5 (0.5) [1.6]	2 (0.2) [0.67]	1 (0.2) [0.16]	5 (0.4) [0.17]	16 (0.5) [0.20]
Pulmonary embolism	0	0	2 (0.4) [1.4]	0	2 (0.2) [0.67]	1 (0.2) [0.16]	5 (0.4) [0.17]	16 (0.5) [0.20]
Deep vein thrombosis	0	0	0	0	0	3 (0.6) [0.49]	4 (0.3) [0.14]	15 (0.4) [0.19]
Atrial fibrillation	0	1 (0.2) [0.71]	0	0	0	3 (0.6) [0.49]	5 (0.4) [0.17]	14 (0.4) [0.18]
Intervertebral disc protrusion	0	0	0	0	0	0	2 (0.1) [0.07]	12 (0.3) [0.15]

Abbreviations: EAIR = exposure-adjusted incidence rate; N = number of patients in the safety dataset; n = number of patients in the specified category; PC = placebo-controlled; PYE = patient-years of exposure; PBO = placebo; RA = rheumatoid arthritis; SAE = serious adverse event
Percentages are based on the number of patients in each treatment group (N); EAIR is expressed as the number of patients experiencing an AE per 100 patient-years of exposure to treatment and is derived as 100 times the incidence of the event divided by the sum of all patient exposure time (in years for the specific treatment group censored at rescue).

6.2.3. Adverse Events Leading to Permanent Discontinuation or Temporary Interruption of Study Drug

6.2.3.1. Permanent Discontinuation

The proportion of patients with an AE reported as the reason for permanent discontinuation was 4.6% for patients treated with baricitinib 4-mg, 3.5% for 2-mg, and 3.1% for placebo in the PC dataset (Table 19). AEs resulting in more than 1 discontinuation in the PC time period were herpes zoster (2 placebo, 5 baricitinib 4-mg, 5 baricitinib 2-mg) and rheumatoid arthritis (2 placebo, 0 baricitinib 4-mg, 0 baricitinib 2-mg). Of note, discontinuation for events of herpes zoster was required, per protocol, in the randomized controlled Phase 3 studies, but not in the extension study (JADY). The majority of herpes zoster events were mild to moderate in severity (see Section 6.2.5.1.3 for more details). In the EXTENDED dataset, the discontinuation incidence rate for 2-mg (6.32) was similar to 4-mg (6.54), while the ALL BARI RA dataset incidence rate was 5.44.

6.2.3.2. Temporary Interruption of Study Drug

Temporary interruptions of study drug were permitted with no limit on the duration. In the ALL BARI RA dataset, 22% of patients had 1 or more temporary interruptions. Mean interruption duration was 18.7 days with a median of 11.0 days.

From the PC dataset the proportion of patients with an AE as the reason for baricitinib interruption was 12.1% for baricitinib 4-mg, 9.6% for 2-mg, and 7.1% for placebo (Table 19). Adverse events leading to temporary interruption were noted at an incidence rate of 12.91 for baricitinib 4-mg and 17.01 for baricitinib 2-mg from the EXTENDED dataset. The most common reason for interruption was infection, followed by GI disorders and lab abnormalities.

6.2.4. Common Adverse Events

A summary of the 10 most common adverse events in the ALL BARI RA dataset is provided in Table 21. The majority of the commonly reported AEs were anticipated events in the RA population (for example, infections including upper respiratory tract infections) or laboratory abnormalities consistent with the pharmacology of JAK inhibitors (for example, increases in creatine phosphokinase [CPK] and lipids). Of these, Upper respiratory tract infections (including viral upper respiratory tract infections and bronchitis), Herpes zoster, and Increased creatine phosphokinase are considered adverse drug reactions.

Table 21: Summary of the 10 Most Common Treatment-Emergent Adverse Events in the ALL BARI RA Dataset

	PC Dataset (Weeks 0-16)			PC 4-mg Dataset (Weeks 0-16)		EXTENDED Dataset		All BARI RA Dataset
	PBO (N=551) PYE=150.0 n (%) [EAIR]	**2-mg** (N=479) PYE=137.3 n (%) [EAIR]	**4-mg** (N=479) PYE=137.6 n (%) [EAIR]	**PBO** (N = 1070) PYE=300.4 n (%) [EAIR]	**4-mg** (N = 997) PYE=292.2 n (%) [EAIR]	**2-mg** (N=479) PYE=617.2 n (%) [EAIR]	**4-mg** (N=1371) PYE=2950.8 n (%) [EAIR]	**Phases 1-3** (N=3492) PYE=7860.3 n (%) [EAIR]
Patients with ≥1 TEAE	326 (59.2) [217.4]	294 (61.4) [214.1]	315 (65.8) [228.9]	610 (57.0) [203.0]	635 (63.7) [217.3]	376 (78.5) [60.9]	1218 (88.8) [41.3]	3023 (86.6) [38.5]
Viral upper respiratory tract infection	3 (0.5) [2.0]	2 (0.4) [1.5]	1 (0.2) [0.7]	3 (0.3) [1.0]	2 (0.2) [0.7]	47 (9.8) [7.6]	210 (15.3) [7.1]	483 (13.8) [6.1]
Bronchitis	19 (3.4) [12.7]	12 (2.5) [8.7]	14 (2.9) [10.2]	30 (2.8) [10.0]	31 (3.1) [10.6]	32 (6.7) [5.2]	163 (11.9) [5.5]	419 (12.0) [5.3]
Upper respiratory tract infection	25 (4.5) [16.7]	27 (5.6) [19.7]	31 (6.5) [22.5]	39 (3.6) [13.0]	46 (4.6) [15.7]	55 (11.5) [8.9]	164 (12.0) [5.6]	393 (11.3) [5.0]
Urinary tract infection	14 (2.5) [9.3]	17 (3.5) [12.4]	16 (3.3) [11.6]	29 (2.7) [9.7]	34 (3.4) [11.6]	44 (9.2) [7.1]	165 (12.0) [5.6]	362 (10.4) [4.6]
Herpes zoster	2 (0.4) [1.3]	5 (1.0) [3.6]	9 (1.9) [6.5]	4 (0.4) [1.3]	14 (1.4) [4.8]	17 (3.5) [2.8]	91 (6.6) [3.1]	243 (7.0) [3.1]
Back pain	18 (3.3) [12.0]	14 (2.9) [10.2]	7 (1.5) [5.1]	26 (2.4) [8.7]	12 (1.2) [4.1]	30 (6.3) [4.9]	102 (7.4) [3.5]	243 (7.0) [3.1]
Influenza	6 (1.1) [4.0]	6 (1.3) [4.4]	9 (1.9) [6.5]	10 (0.9) [3.3]	18 (1.8) [6.2]	12 (2.5) [1.9]	110 (8.0) [3.7]	225 (6.4) [2.9]
Blood CPK increased	3 (0.5) [2.0]	11 (2.3) [8.0]	24 (5.0) [17.4]	6 (0.6) [2.0]	35 (3.5) [12.0]	24 (5.0) [3.9]	97 (7.1) [3.3]	235 (6.7) [3.0]
Hypertension	6 (1.1) [4.0]	16 (3.3) [11.7]	15 (3.1) [10.9]	17 (1.6) [5.7]	21 (2.1) [7.2]	26 (5.4) [4.2]	93 (6.8) [3.2]	222 (6.4) [2.8]
Headache	22 (4.0) [14.7]	30 (6.3) [21.8]	20 (4.2) [14.5]	32 (3.0) [10.7]	38 (3.8) [13.0]	40 (8.4) [6.5]	89 (6.5) [3.0]	212 (6.1) [2.7]

Abbreviations: CPK=creatine phosphokinase; EAIR = exposure-adjusted incidence rate; N = number of patients in the safety dataset; n = number of patients in the specified category; PBO=placebo; PYE = patient-years of exposure; RA = rheumatoid arthritis; TEAE = treatment-emergent adverse event

Percentages are based on the number of patients in each treatment group (N); EAIR is expressed as the number of patients experiencing an AE per 100 patient-years of exposure to treatment and is derived as 100 times the incidence of the event divided by the sum of all patient exposure time (in years for the specific treatment group censored at rescue).

Ordered by most frequent PT based on baricitinib 4-mg dose in the Lilly Ext BARI 2-mg versus 4-mg RA dataset.

6.2.5. Safety Topics of Special Interest

Adverse events of special interest included infections, malignancies, DVT/PE, lipid effects, MACE, GI perforations, hematologic laboratory abnormalities, renal effects, elevations in CPK, and hepatic effects.

6.2.5.1. Infections

From the PC dataset, infections were reported more commonly by patients treated with 4-mg baricitinib (31.9%) compared to 2-mg (28.8%) and placebo (24.1%; Table 22). The most frequently reported infections from the ALL BARI RA dataset were Upper respiratory tract infections (URTI), viral URTI, Urinary tract infections (UTI), Bronchitis, Pharyngitis, Gastroenteritis, Herpes zoster, Influenza, Sinusitis, and Herpes simplex.

6.2.5.1.1. Serious Infections

Clinically meaningful differences in the incidence of serious infections were not seen between baricitinib and placebo or between baricitinib dose groups during short- or long-term exposure (Table 22). The incidence rate of serious infections for the 2-mg dose (3.2) was similar to that of patients treated with 4-mg (3.1) from the EXTENDED dataset and both are comparable to other RA therapies (Figure 21). From the ALL BARI RA dataset, the incidence rate for serious infection using the as-treated analysis was 2.12 (95% CI: 1.40, 3.08) for 2-mg and 3.05 (95% CI: 2.64, 3.51) for the 4-mg treatment group.

Although these data do not support the recognition of serious infection as an important identified risk or adverse drug reaction for baricitinib, longer observation periods across more patient exposures will serve to better characterize whether infections may be increased based on this mode of action.

6.2.5.1.2. Tuberculosis

No cases of tuberculosis were reported in the PC dataset or PC 4-mg dataset. In the EXTENDED dataset, 7 events were reported by baricitinib 4-mg-treated patients (incidence rate 0.24). In the All BARI RA dataset, a total of 11 cases of clinical tuberculosis (incidence rate 0.14) have been reported and one was fatal (disseminated TB). Since the data cutoff date of 01 April 2017, Lilly has received 1 additional report of tuberculosis. Eleven of the 12 reported cases occurred in patients who lived in endemic regions (Taiwan, South Africa, India, Argentina, South Korea, Russia).

6.2.5.1.3. Herpes Zoster

Herpes zoster infections were reported more frequently with baricitinib compared to placebo in the PC dataset, with a similar incidence rate for 2-mg and 4-mg baricitinib-treated patients in the EXTENDED dataset (Figure 22). Most events were mild or moderate in severity. From the ALL BARI RA dataset, the incidence rate of HZ was 3.3. For the as-treated analysis the incidence rate was 2.67 (95% CI; 1.85, 3.73) for 2-mg and 3.21 (95% CI; 2.78, 3.68) for 4-mg.

Eleven percent of HZ cases (N=258) were reported as SAEs. Review of the cumulative herpes zoster cases identified that 8.5% were multidermatomal herpes zoster (lesion distribution beyond

the primary or adjacent dermatomes) with an incidence rate of 0.28. None of the baricitinib cases had visceral involvement; 4 (0.1%) had motor nerve involvement. 13 patients (0.4%) reported post-herpetic neuralgia.

Current RA treatment guidelines recommend vaccination against herpes zoster before initiating DMARD therapy (Smolen et al 2014; Singh et al 2015). Although vaccination was encouraged before randomization in the baricitinib clinical studies, few patients received herpes zoster vaccination. Out of the patients who reported herpes zoster in the ALL BARI RA dataset for Phase 3 studies, 5 had received herpes zoster vaccination prior to their event (2.2%).

The long-term extension study, JADY, did not require patients to discontinue due to a HZ event. Out of 184 patients with a HZ event from JADY, 7 reported recurrence (3.8%).

To provide context for the ALL BARI RA incidence rate of 3.3, Herpes zoster incidence rates from randomized controlled trials in RA for other therapies had an IR/100PY ranging from 0.98 for rituximab (van Vollenhoven 2010) to 4.0 to 5.4 for tofacitinib (Charles-Schoeman 2014).

6.2.5.1.4. Other Opportunistic Infections (Excluding Tuberculosis and Herpes Zoster)

Opportunistic infections reported for patients receiving baricitinib from the ALL BARI RA dataset include esophageal candidiasis, *Pneumocystis jirovecii* pneumonia, cytomegalovirus infection, histoplasmosis, cryptococcal pneumonia, *Paracoccidioides* infection, and *Aspergillus* infection. Opportunistic infections were infrequent and not different between baricitinib 4-mg (0.1%, incidence rate = 0.4) and placebo (0.1%, incidence rate = 0.4) in the PC 4-mg dataset. There were no events in any treatment arm from the PC dataset. From the EXTENDED dataset no dose-related effects were evident; incidence rates were 0.3 for 2-mg and 0.3 for 4-mg.

For contextualization, rates reported were per individual term, not a combination. The incidence rate of *Pneumocystis jirovecii* pneumonia for the ALL BARI RA dataset was 0.04, which is within the range of rates reported from published studies of other RA therapies: incidence rate of 0.01 (Tocilizumab 2009 FDA Medical Review) to 0.19 (Corrona patients with RA treated with TNFi, Greenberg et al 2010). The incidence rate of esophageal candidiasis for the ALL BARI RA dataset was 0.09, which is within the range of rates from randomized controlled trials for other RA therapies: incidence rate of 0.11 (Tocilizumab 2009 FDA Medical Review) to 0.15 (Certolizumab; Bykerk et al 2015).

Table 22: Summary of Infections

Terms	PC Dataset (Weeks 0-16)			PC 4-mg Dataset (Weeks 0-16)		EXTENDED Dataset		All BARI RA Dataset
	PBO (N=551) PYE=150.0 n (%) [EAIR]	2-mg (N=479) PYE=137.3 n (%) [EAIR]	4-mg (N=479) PYE=137.6 n (%) [EAIR]	PBO N=1070 PYE=300.4 n (%) [EAIR]	4-mg N=997 PYE=292.2 n (%) [EAIR]	2-mg N=479 PYE=617.2 n (%) [EAIR]	4-mg N=1371 PYE=2950.8 n (%) [EAIR]	Phases 1-3 (N=3492) PYE=7860.3 n (%) [EAIR]
Patients with ≥1 TEAE of infection	133 (24.1) [88.7]	138 (28.8) [100.5]	153 (31.9) [111.2]	250 (23.4) [83.2]	296 (29.7) [101.3]	233 (48.6) [37.8]	861 (62.8) [29.2]	2121 (60.7) [27.0]
SAEs of Infection	7 (1.3) [4.7]	5 (1.0) [3.6]	7 (1.5) [5.1]	13 (1.2) [4.3]	11 (1.1) [3.8]	20 (4.2) [3.2]	91 (6.6) [3.1]	208 (6.0) [2.6]
Led to permanent discontinuation from study drug	2 (0.4) [1.3]	6 (1.3) [4.4]	9 (1.9) [6.5]	5 (0.5) [1.7]	16 (1.6) [5.5]	8 (1.7) [1.3]	56 (4.1) [1.9]	120 (3.4) [1.5]
Led to temporary interruption of study drug	20 (3.6) [13.3]	29 (6.1) [21.1]	35 (7.3) [25.4]	42 (3.9) [14.0]	58 (5.8) [19.9]	63 (13.2) [10.2]	237 (17.3) [8.0]	616 (17.6) [7.8]
Patients with ≥1 TEAE herpes zoster	2 (0.4) [1.3]	5 (1.0) [3.6]	9 (1.9) [6.5]	4 (0.4) [1.3]	14 (1.4) [4.8]	17 (3.5) [2.8]	94 (6.9) [3.2]	255 (7.3) [3.2]

Abbreviations: EAIR = exposure-adjusted incidence rate; N = number of patients in the safety dataset; n = number of patients in the specified category; PBO = placebo; PYE = patient-years of exposure; RA = rheumatoid arthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Percentages are based on the number of patients in each treatment group (N); EAIR is expressed as the number of patients experiencing an AE per 100 patient-years of exposure to treatment and is derived as 100 times the incidence of the event divided by the sum of all patient exposure time (in years for the specific treatment group).

6.2.5.2. Malignancies

Malignancy Excluding NMSC

Based on the physiologic role of immune surveillance in the endogenous control of malignancy, malignancy has been a topic of interest for any immunosuppressive therapy (Swann and Smyth 2007). As summarized in Section 2.4, in a battery of in vitro studies, baricitinib was not genotoxic in the chromosomal aberration assay using cultured human lymphocytes. It also did not produce neoplastic changes in 6-month transgenic mouse or 2-year rat carcinogenicity studies; in rats, baricitinib administration was associated with increased survival and decreases in proliferative and neoplastic changes.

During clinical studies, clinically meaningful differences in malignancy incidence rates were not seen between baricitinib and placebo, between baricitinib and active comparators, or between baricitinib dose groups (Table 23). Malignancies (excluding NMSC) were also evaluated on an as-treated based with an incidence rate of 0.78 (95%CI; 0.38, 1.44) for 2-mg and 0.81 (95% CI; 0.61, 1.07) for 4-mg baricitinib treated patients. Additionally, an as-randomized analysis on the extended dataset where data were not censored at rescue or dose change to reduce the bias of switching from 2-mg to 4-mg, shows that the incidence rates by dose are similar (Table 25). The nature of the malignancies seen in the baricitinib population (Table 25) were typical of a RA population, and incidence rates were in keeping with expectations for RA based on the published results of prior observational and interventional clinical studies (Figure 23). For comparison, incidence rates for RA and other RA treatments from observational studies range from 0.36 to 1.77 (Gross et al. 2014; Simon et al. 2009) and from clinical trials range from 0.56 to 1.43 (tofacitinib FDA briefing document 2015; abatacept FDA medical review 2005).

Taken together, the nonclinical and available clinical data do not support the recognition of malignancy as an identified risk for baricitinib. However, given that the observation period is relatively short, malignancies will be evaluated post-approval in multiple observational studies.

Nonmelanoma Skin Cancer (NMSC)

The rate of NMSC was similar to the background rate expected in the target RA population and was consistent over time, although from the EXTENDED dataset more NMSC cases were observed in patients treated with baricitinib 4-mg versus 2-mg (Table 26). The incidence rate from the ALL BARI RA dataset was 0.38 and for the as-treated analysis was 0.55 (95% CI; 0.22, 1.13) for 2-mg and 0.36 (95% CI; 0.23, 0.54) for 4-mg.

In comparison, incidence rates for RA patients from observational studies of other therapies range from 0.12 to 3.60 (Amari et al. 2011; Carmona et al. 2011) and from clinical trials range from 0.17 to 0.69 (Burmester et al. 2009; Simon et al. 2015).

Table 23: Summary of Malignancy Excluding NMSC

	PC Dataset (Weeks 0-16)			PC 4-mg Dataset (Weeks 0-16)		EXTENDED Dataset		All BARI RA Dataset
	PBO N=551 PYE=154.3 n (%) [incidence rate**]**	**2-mg N=479 PYE=140.1 n (%) [**incidence rate**]**	**4-mg N=479 PYE=141.4 n (%) [**incidence rate**]**	**PBO N=1070 PYE=308.1 n (%) [**incidence rate**]**	**4-mg N=997 PYE=297.7 n (%) [**incidence rate**]**	**2-mg N=479 PYE=616.5 n (%) [**incidence rate**]**	**4-mg N=1371 PYE=2948.5 n (%) [**incidence rate**]**	**Phases 1-3 N=3492 PYE=7983.7 n (%) [**incidence rate**]**
Overall	0	1 (0.2) [0.7]	0	0	1 (0.1) [0.3]	3 (0.6) [0.49]	22 (1.6) [0.75]	63 (1.8) [0.79]

Abbreviations: N = number of patients assigned by randomization to this treatment group; PBO = placebo; PYE = patient-years of exposure; RA = rheumatoid arthritis
Percentages are based on the number of patients in each treatment group (N); incidence rate is 100 times the number of patients experiencing the AE divided by the event-specific exposure to treatment (exposure time up to the event for patients with the event and exposure time up to the end of the time period for patients without the event, up to rescue), in years.

Table 24: Summary of Malignancy Excluding NMSC in the EXTENDED Dataset without Regard to Dose Change

	EXTENDED Dataset	
	2-mg N = 479 PYE = 1208.3 n (%) [incidence rate]	**4-mg N = 1371 PYE = 3451.0 n (%)** [incidence rate]
Overall	10 (2.1) [0.83]	27 (2.0) [0.78]

Abbreviations: N = number of patients in the safety dataset; n = number of patients in the specified category; PYE = patient-years of exposure
Percentages are based on the number of patients in each treatment group (N); incidence rate is 100 times the number of patients experiencing the AE divided by the event-specific exposure to treatment (exposure time up to the event for patients with the event and exposure time up to the end of the time period for patients without the event, up to rescue), in years.
As randomized including data after rescue. As randomized without regard to dose change.
Data cutoff as of 01 April 2017.

Table 25: Summary of Malignancy Excluding NMSC by Location in the ALL BARI RA Dataset

Site	All BARI RA N=3492
Breast	14
Lung	7
Lymphoma	6
Prostate	5
Kidney	5
Colon and Rectum	5
Melanoma	4
Pancreas	3
Gynecological	3
Ear Nose Throat	2
Gastric/Oesophageal	2
Skin/soft tissue	2
Thyroid	1
Adrenal	1
Bone/cartilage	1
Gallbladder	1
Bladder	1
Total	63

Abbreviations: N = number of patients.
Includes post study events, location is as assessed by the sponsor.

Table 26: Summary of NMSC

	PC Dataset (Weeks 0-16)			PC 4-mg Dataset (Weeks 0-16)		EXTENDED Dataset		All BARI RA Dataset
	PBO N=551 PYE=154.3 n (%) [incidence rate]	2-mg N=479 PYE=140.1 n (%) [incidence rate]	4-mg N=479 PYE=141.4 n (%) [incidence rate]	PBO N=1070 PYE=308.1 n (%) [incidence rate]	4-mg N=997 PYE=297.7 n (%) [incidence rate]	2-mg N=479 PYE=616.2 n (%) [incidence rate]	4-mg N=1371 PYE=2927.3 n (%) [incidence rate]	Phases 1-3 N=3492 PYE=7948.3 n (%) [incidence rate]
Overall	0	0	1 (0.2) [0.7]	1 (0.1) [0.3]	1 (0.1) [0.3]	2 (0.4) [0.32]	15 (1.1) [0.51]	30 (0.9) [0.38]

Abbreviations: N = number of patients assigned by randomization to this treatment group; n = number of patients with event; PBO = placebo; PYE = patient-years of exposure.
Percentages are based on the number of patients in each treatment group (N); incidence rate is 100 times the number of patients experiencing the AE divided by the event-specific exposure to treatment (exposure time up to the event for patients with the event and exposure time up to the end of the time period for patients without the event, up to rescue), in years.

6.2.5.3. MACE

Because patients with RA are at increased risk for cardiovascular events, MACE is a topic of interest for all RA medicines. During the Phase 3 studies, an independent clinical evaluation committee adjudicated potential MACE (cardiovascular death, myocardial infarction, and stroke) and other cardiovascular events (Table 27).

Differences in MACE rates were not seen between baricitinib and placebo or between baricitinib and active comparators, although few events were reported. The MACE incidence rate from the All BARI RA dataset was 0.5 and from the EXTENDED dataset was 0.2 for baricitinib 2-mg treated patients and 0.5 for baricitinib 4-mg treated patients. The as-treated incidence rate for 2-mg baricitinib was 0.16 (95% CI: 0.02, 0.57) and for 4-mg was 0.56 (95% CI: 0.39, 0.78). For other cardiovascular events, no differences were observed between baricitinib and placebo or between dose groups (Table 27). No association was found between changes in lipids or platelets and MACE.

The incidence rates observed for baricitinib-treated patients were within the range reported from development programs for other RA therapies (Figure 24), including abatacept, tocilizumab, adalimumab and tofacitinib. Observational studies have also reported a range of incidence rates per 100 PYE among RA patients in general of 0.10 to 2.52 (Greenberg et al 2011, Solomon et al 2013), while randomized clinical trials reported a range of 0.35 to 4.37 (Tocilizumab Clinical Review of the Complete Response 2009, Kremer et al 2011).

Due to a limited number of reported events, MACE and other cardiovascular events will be evaluated post-approval in multiple observational studies.

Table 27: Summary of Major Adverse Cardiovascular Events and Other Cardiac Events

	PC Dataset (Weeks 0-16)			PC 4-mg Dataset (Weeks 0-16)		EXTENDED Dataset		All BARI RA Dataset
Terms	**PBO N=404 PYE=117.2 n (%) [EAIR]**	**2-mg N=403 PYE=119.6 n (%) [EAIR]**	**4-mg N=404 PYE=120.3 n (%) [EAIR]**	**PBO N=892 PYE=260.8 n (%) [EAIR]**	**4-mg N=891 PYE=268.0 n (%) [EAIR]**	**2-mg N=479 PYE=617.2 n (%) [EAIR]**	**4-mg N=1340 PYE=2935.3 n (%) [EAIR]**	**N=2973 PYE=7231.5 n (%) [EAIR]**
Patients with ≥1 MACE	2 (0.5) [1.7]	0	2 (0.5) [1.7]	2 (0.2) [0.8]	2 (0.2) [0.7]	1 (0.2) [0.2]	16 (1.2) [0.5]	38 (1.3) [0.5]
Patients with ≥1 other cardiovascular event*	2 (0.5) [1.7]	1 (0.2) [0.8]	2 (0.5) [1.7]	3 (0.3) [1.2]	2 (0.2) [0.7]	6 (1.3) [1.0]	23 (1.7) [0.8]	51 (1.7) [0.7]

Abbreviations: EAIR = exposure-adjusted incidence rate; MACE = major adverse cardiovascular event; N = number of patients in the safety dataset; n = number of patients in the specified category; PBO = placebo; PYE = patient-years of exposure

Percentages are based on the number of patients in each treatment group (N).

MACE and other cardiac events were not adjudicated for the Phases 1 and 2 trials.

*Hospitalization for unstable angina, uncharacterized ischemic event, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock because of myocardial infarction, coronary revascularization procedure.

6.2.5.4. Venous Thromboembolism

An imbalance was noted for venous thromboembolism (VTE; including deep vein thrombosis [DVT] and pulmonary embolism [PE]) from the PC 4-mg dataset where 6 patients (0.6%; IR=1.4 [95% CI; 0.10, 1.43]) treated with baricitinib 4-mg (N=997) reported events (Table 8) and no events were reported by placebo-treated patients (N=1070). Although RA patients are at an increased risk for VTE (Kim 2015), this imbalance was unexpected, including 0 events in placebo. Thus, all data relative to VTE were evaluated further for strength of evidence supporting causality. Based on the imbalance in the placebo-controlled time-period VTE has been classified as an important potential risk meriting a labeled warning and further investigation. VTE has been included as an outcome in long-term prospective and retrospective observational studies.

VTE Event Rates from RA Clinical Program

DVT/PE events were found inconsistently in the baricitinib RA clinical program with events reported from the randomized controlled portion of 2 of 8 studies. Further evaluation for consistency of VTE observations included analysis of patients originally randomized to placebo or active comparator and later switched or rescued to baricitinib (Figure 25). Of the 928 placebo-treated patients who either switched or rescued to baricitinib, 1 reported a DVT in their first 24 weeks of exposure (incidence rate of 0.24; 95% CI: 0.01, 1.36). This DVT was 2 days after a femoral fracture; the patient was treated with aspirin, recovered and continued baricitinib treatment. From the patients randomized to active comparator and later switched to baricitinib (162 on methotrexate and 289 on adalimumab), none reported a DVT or PE in their initial 24 weeks of baricitinib exposure. These findings are inconsistent with the observations from the initial placebo-controlled 24 weeks of baricitinib exposure and are not supportive of an acute risk with initial exposure.

From the All BARI RA dataset, 42 patients reported VTE in the clinical program. Examining data from all DVT/PE events and all patient-years of treatment, the rate of accrual shown in the Kaplan-Meier plot demonstrates an annual incidence ~0.5% (Figure 27). The time to event onset after first dose of baricitinib for these 42 events ranged from 37 to 1658 days. These findings are also not supportive of an acute risk or a temporal relationship with initial baricitinib exposure.

No dose-response relationship was observed in the EXTENDED dataset with incidence rates of 0.49 [95% CI; 0.10, 1.43] for 2-mg and 0.48 (95% CI; 0.26, 0.80) for baricitinib 4-mg patients (Figure 26). Likewise, calculations based on the as-treated analysis within the ALL BARI RA dataset show an incidence rate of 0.39 (95% CI; 0.13, 0.92) for 2-mg and 0.58 (95% CI; 0.41, 0.80) for 4-mg.

The incidence rate for consecutive 24-week time periods for all patients treated with baricitinib was around 0.5 with wider confidence intervals showing variability in the point estimate for any individual 6-month interval. The overall incidence rate of VTE from the largest dataset (ALL BARI RA) over the longest duration of exposure (up to 6 years) was 0.53 with a 95% confidence interval of 0.38 to 0.71 (Figure 26). This is the more stable estimate of the baricitinib VTE

incidence rate (0.53) and along with the incidence rates for each dose, is within the range published for other RA therapies and from observational studies, discussed in detail below.

Event and Patient Characteristics

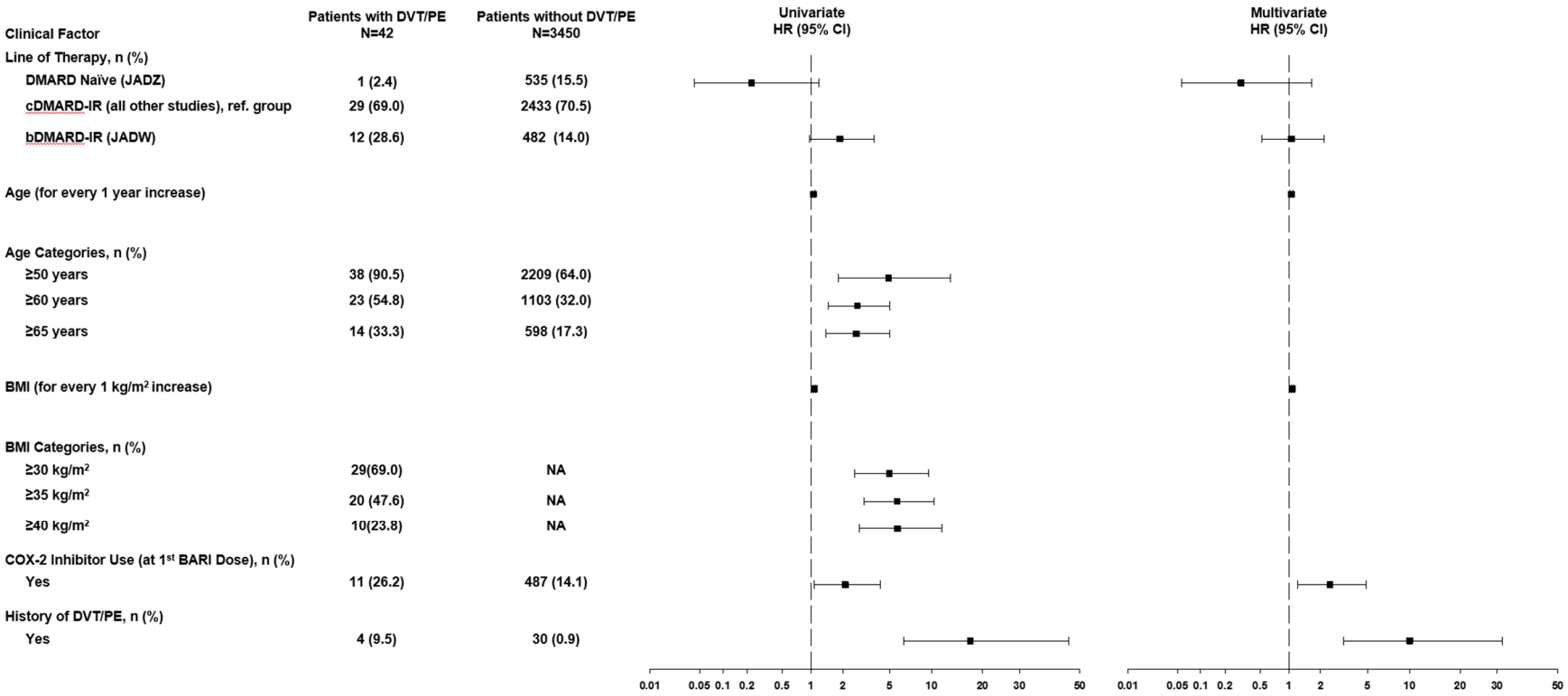
A total of 30 DVTs and 19 PEs were reported by 42 patients in the ALL BARI RA dataset. Twenty-eight patients reported serious adverse events (17 DVTs, 17 PEs) with one PE reported as fatal (incidence rate=0.01). One other fatal PE was reported in Study JADZ for a MTX-treated patient who never received baricitinib (incidence rate=0.6).

Of the 42 baricitinib-treated patients reporting a DVT/PE:

- 28 had exposure to baricitinib after the event, duration ranging from 7 days to 30 months (22 had at least 6 months). Of the 28 re-exposed:
    - 25 were put on continuous anti-coagulation therapy and 3 were not.
    - 2 reported an additional event, 1 and 2 years later with new risk factors (surgery and discontinuation of warfarin).
- For12 patients, the DVT/PE was reported after they had already discontinued baricitinib (days after discontinuation for each event in ascending order: 6, 8, 11, 14, 18, 19, 19, 20, 28, 42, 82, 190).
- 5 patients permanently discontinued (IR=0.06 ALL BARI RA dataset).

From the ALL BARI RA dataset, all 42 patients with an event had one or more risk factors. Risk factors possibly associated with DVT/PE events were evaluated in a single- and multi-variable analysis from the ALL BARI RA dataset comparing the risks between patients with (n = 42) and without events (n = 3450). Factors from the multi-variable analysis associated with an increased risk for DVT/PE in the ALL BARI RA dataset included history of DVT/PE, use of cyclooxygenase-2 (COX-2) inhibitors at time of first baricitinib dose, higher body mass index (BMI), and older age (Figure 66). These are among reported conventional risk factors for VTE for the general population (Wakabayashi 2015). In single-variable analyses, no association was observed between baseline platelet counts and VTE incidence, nor was an association seen between the change from baseline to Week 2 platelet counts and VTE incidence.

Figure 66: Venous thromboembolic risk factor analysis using the multivariable COX regression



Abbreviations: BARI = baricitinib; bDMARD = biologic disease-modifying antirheumatic drug; BMI = body mass index; COX-2 = cyclooxygenase-2; cDMARD = conventional disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; DVT = deep vein thrombosis; IR = inadequate response; N = number of patients in the analysis population; n = number of patients in the specified category; PE = pulmonary embolism.

Contextualizing the Incidence of VTE Observed in the Baricitinib Program

The existing literature through October 2017 suggests that RA patients are at a 2- to 3-fold increased risk of VTE compared to the general population (Matta 2009, Chung 2014). Therefore, the incidence rate of 0 observed in the placebo group was unexpected and is likely inappropriate for contextualizing the overall rate of 0.53 (95% CI 0.38 to 0.71) among baricitinib-treated patients. To better understand the expected incidence of DVT/PE in the RA population and provide context for the findings from baricitinib-treated patients, various sources of information were explored, including clinical studies from approved RA therapies as well as existing literature.

VTE Context from Other Clinical Studies

Finding complete information on counts of serious and non-serious DVT/PE events along with the number of patients and duration of exposure in patient-years is difficult as these data are not included in many publications or summary safety findings. VTE is becoming a more widely recognized risk for the RA population, but limited information is available. Submission data from 3 recently FDA-approved drugs for RA (tocilizumab, tofacitinib, and sarilumab) were located and evaluated for the number of serious PE and DVT events during the controlled periods (Table 28). Publicly available information from these programs was only found for serious events of PE and DVT and when compared with serious events from the baricitinib program, the frequencies in the treatment arms were similar. However, in the tocilizumab and tofacitinib programs, events were also reported in the placebo arms such that the frequencies were not imbalanced compared to placebo. These are indirect comparisons only, as time-periods and numbers of patients were not all the same and patient-years of exposure were not provided.

Table 28: Reported Events of Serious PE and DVT for Recently Approved RA Drugs and Baricitinib

Drug	Treatment Arm	Serious PE	Serious DVT
Tocilizumab (Toci)	PBO+DMARD (N=1170)	1	2
Pooled Ph 3 safety population	Toci 4mg/kg+MTX (N=774)	0	1
0-6 months[a]	Toci 8mg/kg+DMARD (N=1582)	3	0
Tofacitinib (Tofa)	PBO (N=681)	1	1
Ph 3 studies 0-12 months[b]	Tofa 5 bid (N=1216)	2	0
Sarilumab (Sari)	PBO+DMARD (N=661)	0	0
Ph 3 placebo-controlled population	Sari 150mg Q2W+DMARD (N=660)	1	2[c]
("Pool 1") 0-12 months[d]	Sari 200mg Q2W+DMARD (N=661)	0	0[e]
Baricitinib (Bari)	PBO+DMARD (N=1070)	0	0
Placebo-controlled datasets[f]	Bari 2-mg+DMARD (N=479)	0	0
0-6 months	Bari 4-mg+DMARD (N=997)	2	1[g]

a Source: Table 24 of Tocilizumab Medical Review.
b Source: Table 101 of Tofacitinib FDA Clinical Review.
c Including 1 serious event of splenic vein thrombosis.
d Source: Table 26 of Sarilumab Clinical Summary of Safety, obtained through a freedom of information request from the EMA.
e Not including 1 serious event of venous thrombosis limb.
f Data for baricitinib 4-mg and placebo are from the PC 4-mg Dataset. Data for baricitinib 2-mg is from PC dataset.
g Including the event termed as thrombophlebitis in the database.

Exposure adjusted data were recently reported for tofacitinib (Table 29), however it is unclear if this represents all events (serious and non-serious) or only those that were considered serious. Furthermore, the data were limited to the controlled period of observation, for which the mean duration of exposure was about 6 months. There were few VTE events reported and the frequencies were not imbalanced. The DVT and PE incidence rates were lower than expected in an RA population.

Table 29: Number of PE and DVT and Incidence Rates for Tofacitinib in RA

	Placebo-Controlled Cohort (N=5368; PY=4440)			Dose Comparison Cohort (N=5368; PY=4440)	
	Placebo n/N [IR] (95% CI)	Tofa 5-mg BID n/N [IR] (95% CI)	Tofa 10-mg BID n/N [IR] (95% CI)	Tofa 5-mg BID n/N [IR] (95% CI)	Tofa 10-mg BID n/N [IR] (95% CI)
DVT	1/1079 [0.4] (0.0, 2.4)	0/1849 [0] (0.0, 0.9)	0/2024 [0] (0.0, 0.8)	1/1849 [0.1] (0.0, 0.3)	1/2024 [0.1] (0.0, 0.3)
PE	1/1079 [0.4] (0.0, 2.4)	0/1849 [0] (0.0, 0.9)	0/2024 [0] (0.0, 0.8)	2/1849 [0.1] (0.0, 0.4)	3/2024 [0.2] (0.0, 0.4)

Abbreviations: CI = confidence interval; DMARD = disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; PYE = patient-years of exposure; Tofa = tofacitinib.
Source: Mease et al. 2017.

From clinical programs, the most comparable data available were from the sarilumab long-term safety analysis (i.e., "Pool 2" in the sarilumab clinical summary of safety) as it contained exposure-adjusted incidence rates and long-term data for serious PE and DVT. This was a contemporaneous, controlled clinical trial program with similar inclusion/exclusion criteria to the baricitinib program. When evaluating the serious events based on preferred terms, the separate incidence rates for serious PE and DVT were comparable between programs (Table 30).

Table 30: Number of Serious PE and DVT and Incidence Rates for Sarilumab, a Recently Approved RA Drug, and Baricitinib during Extended Treatment Periods

Drug	Patient with Serious PE n [EAIR] (95% CI)	Patients with Serious DVT n [EAIR] (95% CI)
Sarilumab + DMARD[a] PYE = 5845	10[b] [0.17] (0.08, 0.31)	9 [0.15] (0.07, 0.29)
Baricitinib, All BARI RA[c] PYE = 7977 (PE) PYE = 7974 (DVT)	17 [0.21] (0.12, 0.34)	17 [0.21] (0.12, 0.34)

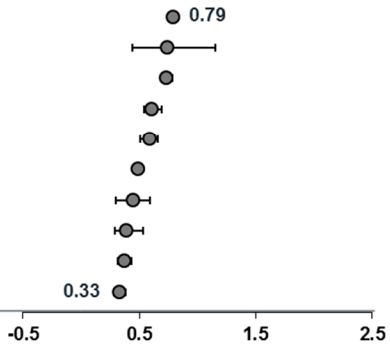
Abbreviations: CI = confidence interval; DMARD = disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; PYE = patient-years of exposure
a Source: Table 27 of Sarilumab Clinical Summary of Safety, obtained through a freedom of information request from the EMA. Calculated EAIR out to 2 decimal places for comparison; was reported for both as 0.2.
b 10 patients with 11 events.
c Events based on PT plus MedDRA embolic and thrombotic event review from the All BARI RA dataset with data cutoff of 01 April 2017, including events on treatment and post-treatment.
Reminder: these are serious events only and so the rates are lower than for all TEAEs presented earlier.

VTE Information from Existing Literature and Observational Studies

The published incidence rate of VTE among RA patients ranges from 0.33 to 0.79 per 100 person-years (Figure 67). The population characteristics and study design have an impact on the rate. For example, Kim et al. (2013) only included serious cases of VTE identified through hospitalization discharge diagnosis codes, whereas other studies identified VTE from a combination of hospitalization and outpatient diagnosis codes. VTE cases from the baricitinib clinical trial program were identified via inpatient and outpatient settings. The overall VTE incidence rate for baricitinib (0.53/100 PYE) fell within the range reported in the literature for RA populations.

Figure 67: Incidence Rates of VTE among RA Patients Reported in Published Observational Studies

References	RA Cohort	Country	Data Source	N	Incidence Rate per 100 PYs (95% CI)
Ogdie 2017	DMARDS	UK	Medical records	31,336	0.79
Bacani 2012	RA	US	Medical records	464	
Eriksson 2017	RA	Sweden	National Register	43,490	
Kim 2013	DMARDS	US	Claims data	22,143	
Holmqvist 2012	RA (prevalent)	Sweden	National register	37,856	
Yusuf 2015	RA	US	Claims data	70,768	
Holmqvist 2012	RA (incident)	Sweden	National register	7904	
Davies 2011	nbDMARDs	UK	Registry (BSRBR)	3673	
Davies 2011	Anti-TNF	UK	Registry (BSRBR)	11,881	
Choi 2013	DMARD	UK	Medical records	9589	0.33



Abbreviations: BSRBR = British Society for Rheumatology Biologics Registers; DMARD = disease-modifying antirheumatic drug; nbDMARD = non-biologic disease-modifying antirheumatic drug; RA = rheumatoid arthritis; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

Incidence rates of VTE in the RA population were estimated using FDA's Sentinel program and the Truven MarketScan databases. Both of these databases are administrative claims datasets with information on patients enrolled in US health plans. In both of these analyses, VTE was defined from hospital diagnosis or an outpatient diagnosis plus anticoagulant dispensing. This approach allows serious and non-serious events to be captured, similar to how events were reported in the baricitinib clinical trial database. Results from 5 Sentinel System data partners, offered through the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program, show the following (Figure 28, Figure 29, and Table 31):

- The incidence rates of VTE varied across patient cohorts treated with different DMARDs and tended to increase with increasing patient age.
- When incidence rates were stratified by age, the incidence rates of VTE in the baricitinib RA cohort were consistent with the rates of VTE observed among patients treated in real-world clinical practice (for example, in the 50–59 year age group, the incidence rate per 100 person-years for baricitinib is 0.57, while for All RA Medications it is 0.90).

These analyses were replicated using a second administrative claims data source, Truven Marketscan (Table 32), and sensitivity analyses were conducted to evaluate the impact of different outcome definitions with varying sensitivity and positive predictive value (PPV) on the

observed incidence rate estimates. Using the most restrictive definition that should have high PPV, i.e., International Classification of Diseases 9 (ICD9) diagnostic codes and anticoagulant dispensing required for all VTE diagnoses, the resulting incidence rate estimates were consistent with those observed in the baricitinib clinical program (Figure 28, Figure 29, and Table 31).

This indirect comparison of data from other clinical studies, the recent sarilumab RA registration program, published tofacitinib data, published RA observational and registry data, and the US Sentinel and Truven claims data demonstrate that the VTE rates observed during the baricitinib RA clinical trial program are within the range expected for RA populations.

Table 31: Crude Incidence of VTE among RA Patients by Age from the Sentinel Database and the Baricitinib RA Clinical Program

	VTE				
	n	%	Events (n)	PY	EAIR (95% CI)
All BARI RA data by Age for Comparison					
All	**3492**	**100**	**42**	**7948.6**	**0.53 (0.38, 0.71)**
18-49	1245	35.7	4	2885.7	0.14 (0.04, 0.35)
50-59	1121	32.1	15	2611	0.57 (0.32, 0.95)
60-64	514	14.7	9	1164.8	0.77 (0.35, 1.47)
65+	612	17.5	14	1287.1	1.09 (0.59, 1.83)
Tofacitinib					
All	**1846**	**100**	**8**	**861.5**	**0.93 (0.40, 1.83)**
18-49	488	26.4	2	215.2	0.93 (0.11, 3.36)
50-59	628	34.0	2	303.0	0.66 (0.08, 2.38)
60-64	338	18.3	2	159.7	1.25 (0.15, 4.52)
65+	392	21.2	2	183.6	1.09 (0.13, 3.94)
All RA Medications					
All	**69,095**	**100**	**719**	**53,786.0**	**1.34 (1.24, 1.44)**
18-49	16,340	23.6	55	11,249.1	0.49 (0.37, 0.63)
50-59	18,151	26.3	127	14,104.2	0.90 (0.75, 1.07)
60-64	9272	13.4	81	6995.8	1.16 (0.93, 1.43)
65+	25,332	36.7	456	21,436.9	2.13 (1.94, 2.33)
cDMARD					
All	**19,001**	**100**	**197**	**13,184.0**	**1.49 (1.30, 1.71)**
18-49	4184	22.0	11	2380.5	0.46 (0.23, 0.83)
50-59	5036	26.5	21	3237.7	0.65 (0.40, 0.99)
60-64	2538	13.4	18	1634.6	1.10 (0.65, 1.74)
65+	7243	38.1	147	5931.1	2.48 (2.10, 2.90)
bDMARD					
All	**19,146**	**100**	**147**	**15,053.0**	**0.98 (0.83, 1.14)**
18-49	5835	30.5	33	4815.7	0.69 (0.48, 0.95)
50-59	6194	32.4	35	5362.1	0.65 (0.46, 0.90)
60-64	2656	13.9	19	2032.5	0.94 (0.56, 1.46)
65+	4461	23.3	60	2842.7	2.11 (1.63, 2.70)

Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CI=confidence interval; EAIR = exposure-adjusted incidence rate; n=number of persons or events in the specified category; PY=person-years; RA=rheumatoid arthritis; VTE=venous thromboembolic events.
Sentinel Database data from 01 January 2011 to 30 October 2016.

Notes: RA patients were identified based on having at least 2 International Classification of Diseases 9 (ICD9) codes for rheumatoid arthritis (714.0, 714.1, 714.2) and at least 1 prescription for a conventional or biologic disease-modifying antirheumatic drug (from cDMARD or bDMARD listed here). VTE was defined based on (a) an inpatient diagnostic code for venous or pulmonary embolism or phlebitis and thrombophlebitis or (b) an outpatient diagnostic code plus a prescription for an anticoagulant (apixaban, dabigatran, dalteparin, edoxaban, enoxaparin, fondaparinux, rivaroxaban, tinzaparin, warfarin) within 31 days of the VTE diagnostic code. Treatment episode-specific incidence rates were based on the first use of a medication in the record and occurrence of a VTE, as defined above, during the days' supply of the medication or the at-risk window, equal to 5 half-lives, immediately following the end of the treatment episode. All patients were required to be

enrolled and have drug coverage for the duration of the observation period. Patients were censored at the end of the study (Oct 2015), disenrollment, or occurrence of the first event. Additionally, for treatment episode-specific incidence rates, patients were censored when they stopped using the medication of interest or initiated treatment with a different medication, whichever came first.

Table 32: Incidence of VTE among Selected Patient Cohorts Diagnosed with RA from the Truven Marketscan Database

Treatment	N	Definition (1) ICD9 + Anticoagulant use			Definition (2) AV: ICD9 + Anticoagulant use; IP and ED: ICD9 only			Definition (3) ICD9 only		
		n	PY	IR	n	PY	IR	n	PY	IR
Any RA Medication										
All ages	205,875	642	245,516	0.68	2576	244,940	1.05	3977	243,396	1.63
18-49	62,394	88	66,175	0.32	328	66,085	0.50	583	65,830	0.89
50-59	68,260	176	86,005	0.52	663	85,841	0.77	1083	85,357	1.27
60-64	33,508	102	38,550	0.70	405	38,466	1.05	609	38,259	1.59
65+	41,623	276	54,786	1.36	1180	54,548	2.16	1702	53,950	3.15
cDMARD										
All ages	71,552	457	58,570	0.78	719	58,452	1.23	1081	58,145	1.86
18-49	19,023	36	12,469	0.29	55	12,463	0.44	101	12,437	0.81
50-59	23,229	93	18,883	0.49	147	18,851	0.78	243	18,770	1.29
60-64	11,899	80	9,750	0.82	121	9,738	1.24	177	9,693	1.83
65+	17,401	248	17,467	1.42	396	17,400	2.28	560	17,245	3.25
bDMARD										
All ages	77,086	548	86,806	0.63	826	86,627	0.95	1334	86,116	1.55
18-49	26,180	103	27,307	0.38	149	27,267	0.55	273	27,153	1.01
50-59	26,696	178	32,116	0.55	251	32,063	0.78	400	31,920	1.24
60-64	11,944	85	13,234	0.64	129	13,201	0.98	215	13,133	1.64
65+	12,266	182	14,149	1.29	297	14,097	2.11	446	13,909	3.21

Abbreviations: AV = ambulatory visit; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; ED = emergency department; IP = inpatient; IR = incidence rate; N = number of patients in group; n = number of events in the specified category; PY = person-years; VTE = venous thromboembolic events.
Data from January 2010 – September 2015.

Notes: RA patients were identified based on having at least 2 ICD9 codes for rheumatoid arthritis (714.0, 714.1, 714.2) and at least 1 prescription for a conventional or biologic disease-modifying antirheumatic drug (from the cDMARDs and bDMARDs listed). VTE was defined as: DEFINITION 1: a diagnostic code plus a prescription for an anticoagulant (apixaban, dabigatran, dalteparin, edoxaban, enoxaparin, fondaparinux, rivaroxaban, tinzaparin, warfarin) within 31 days of the VTE diagnostic code; DEFINITION 2: (a) an inpatient diagnostic code for venous or pulmonary embolism or phlebitis and thrombophlebitis or (b) an outpatient diagnostic code plus a prescription for an anticoagulant (apixaban, dabigatran, dalteparin, edoxaban, enoxaparin, fondaparinux, rivaroxaban, tinzaparin, warfarin) within 31 days of the VTE diagnostic code; DEFINITION 3: a diagnostic code for venous or pulmonary embolism or phlebitis and thrombophlebitis in an inpatient, outpatient or emergency department care setting. Treatment episode-specific incidence rates were based on the first use of a medication in the record and occurrence of a VTE, as defined above, during the days' supply of the medication or the at-risk window equivalent to 5 half-lives immediately following the end of the treatment episode. All patients were required to be enrolled and have drug coverage for the duration of the observation period. Patients were censored at the end of the study (30 September 2015), disenrollment, or occurrence of the first event. Additionally, for treatment episode-specific incidence rates, patients were also censored when they stopped using the medication(s) of interest or initiated treatment with a different medication, whichever came first.

Baricitinib's Mechanism of Action and Potential Thrombosis Risk

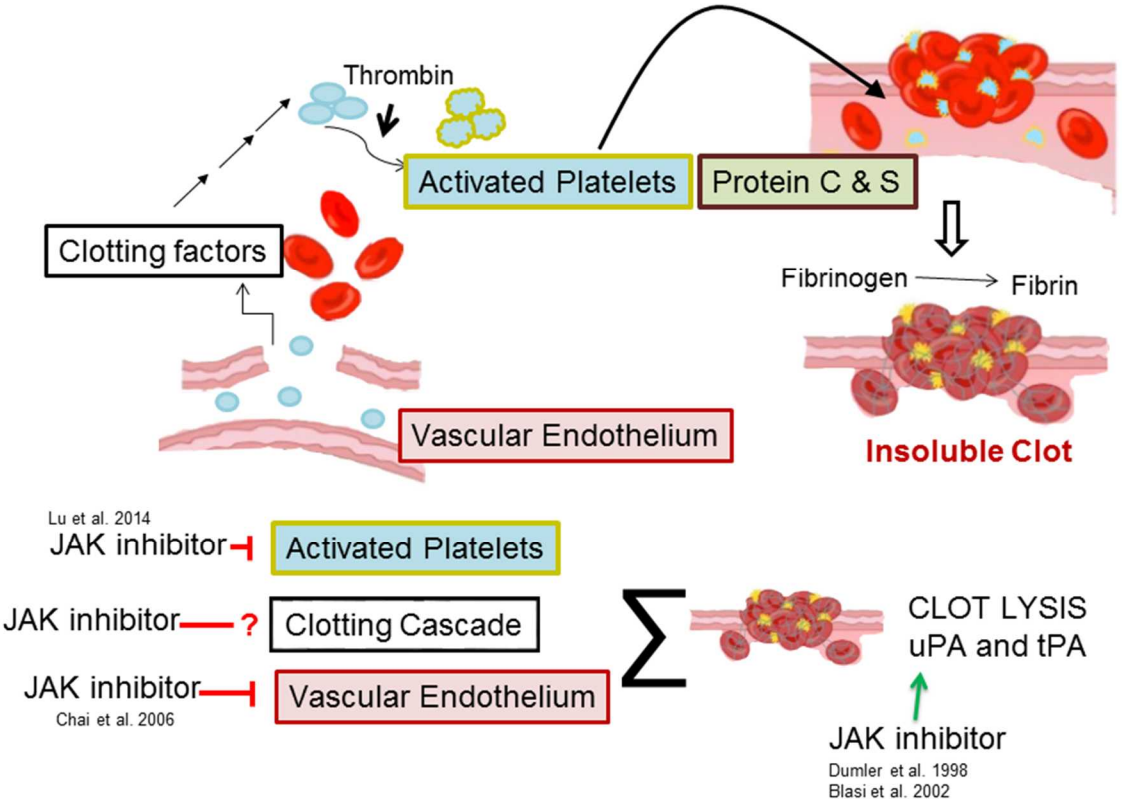
Venous thrombosis is a multi-causal disease that is affected by genetic risk factors coupled with acquired risk factors (Rosendaal 1999). The risk factors broadly include changes in clotting factors that impact the coagulation cascade, changes in antithrombotic mechanisms that impact the vessel wall integrity, and reduced exercise or mobility that impacts stasis (Rosendaal 1999). Thrombus formation and maintenance rely on the presence of activated platelets that serve as initiators of nidus formation (Frenette et al. 2000). The interaction between circulating platelets and components in the damaged endothelium, such as collagen, results in activation of thrombin release and triggering of the clotting cascade (Golebiewska and Poole 2015). The JAK2-STAT3

pathway is involved in collagen-induced platelet activation, and inhibition of JAK2 activity can attenuate platelet activation (Lu et al. 2014). The thrombopoeitin receptor relies on JAK2/Tyk2 activity to protect it from degradation, and JAK2 facilitates its interaction with the ligand thrombopoeitin on the cell surface (Royer et al. 2005). Thrombin-mediated activation of human platelets also relies on JAK2 signaling (Rodriguez-Linares and Watson 1994). Furthermore, vascular smooth muscle cell activation by thrombin also relies on JAK/STAT signaling (Madamanchi et al. 2001). Therefore, inhibition of JAK1 and/or JAK2 signaling by baricitinib may block the early events in thrombus formation and maintenance. Similar results on platelet activation have been observed with TNF-α antagonists, which also converge on JAK/STAT signaling (Manfredi et al. 2016).

Clot lysis relies on local balance of plasminogen activators (uPA and tPA) and inhibitors (PAI-1, PAI-2). The binding of uPA to free PAI-1 in solution generates an uPA/PAI-1 complex that is catalytically inactive and has no signaling activity (Degryse et al 2001). However, when PAI-1 binds to uPA on the cell surface, it induces the internalization of the resulting PAI-1/uPA/uPA receptor (uPAR) complex and inhibits uPA-induced cell migration. Thus, PAI-1 can regulate both pericellular proteolysis and the concentration of uPA and uPAR on the cell surface (Degryse et al 2001). Collectively, clot clearance involves aspects of wound healing and endothelial remodeling which are inhibited by PAI-1. Recently, it has been found that PAI-1 accomplishes these varied functions by binding to the lipoprotein receptor-related protein 1 that leads to activation of the JAK1 pathway (Degryse et al 2004). Collectively, the mechanism of action of a JAK1/JAK2 inhibitor (Figure 68) suggests reduced thrombus formation and maintenance and enhanced clot clearance. Therefore, the mechanism of action of baricitinib does not appear to be causally linked to the VTE events observed in patients.

Measures to assess the potential for thrombosis were evaluated in the toxicology studies at doses up to 300 mg/kg. The duration of exposure to baricitinib ranged from 1 month to 2 years. Endpoints included in the studies were hematology (prothrombin time, activated partial thromboplastin time, platelets) and histological evaluation of blood vessels. There were no baricitinib-related effects observed on coagulation time or thrombus and/or infarcts based on histological evaluations. Baricitinib-related increases in plasma platelet counts occurred in mice and rats. The magnitude of the increases in platelet count were generally minor and were not related to thrombosis or infarcts. Taken together, there were no baricitinib-related findings related to thrombosis reported in nonclinical toxicology studies.

Figure 68: Proposed understanding of the mechanism of action of a JAK1/JAK2 inhibitor and risk factors for thrombosis



Abbreviations: JAK = Janus kinase; tPA and uPA = plasminogen activators.

VTE Conclusion

In summary, an imbalance in VTE events was observed between baricitinib 4-mg and placebo in the 24-week placebo-controlled time period with an overall incidence rate for all baricitinib-treated patients of 0.53/100 patient-years exposure (95% CI: 0.38, 0.71). No dose-response relationship or temporal association was identified, and patients initially treated with placebo (N=928) or active comparator (N=451) who then switched to baricitinib reported a total of 1 event in the first 24 weeks of baricitinib exposure compared to the six events in the placebo-controlled period.

The incidence rate from the overall baricitinib RA development program (0.53) is within the incidence rate range published for RA patients in other clinical trials, observational studies (0.33-0.79) and those found from the Sentinel (0.76 to 3.08) and Truven claims data (0.76 to 2.96) analyses. Mechanistic data along with non-clinical study results for baricitinib are not suggestive of a prothrombotic risk.

Venous thromboembolism has been classified as an important potential risk because the weight of evidence was not sufficient to rule it as drug-related, although it cannot be ruled out. Patients and prescribers will be informed of this potential risk through labeled warnings. Studies are planned or underway to understand and characterize this risk further (Section 6.5).

6.2.6. Clinical Laboratory Observations

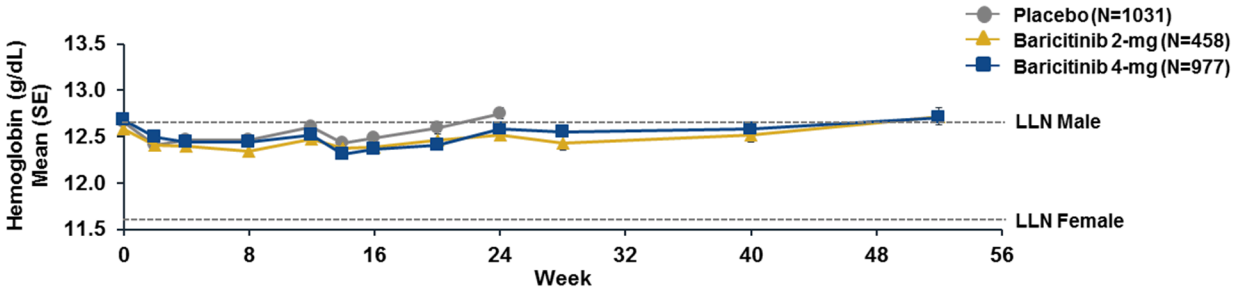
Extensive routine monitoring and evaluation of laboratory analytes were implemented in the baricitinib RA program.

6.2.6.1. Hematology

6.2.6.1.1. Hemoglobin

Initiation of baricitinib treatment was associated with declines in hemoglobin (-0.21, -0.23 and -0.32 g/dL for placebo, baricitinib 2- and 4-mg, respectively) which returned to and subsequently exceeded baseline values with continued administration (Figure 69). Long-term treatment with baricitinib was not associated with an increased incidence of erythropenia-related TEAEs or anemia. Permanent discontinuations of study drug due to AEs of anemia or hemoglobin decreased were infrequent. Frequency of declines in hemoglobin to less than 8.0 g/dL (CTCAE Grade 3) was low at 0.2% of placebo, 0.4% of 2-mg, and 0 of 4-mg treated patients in the PC dataset (Table 9 and Figure 69). There were no Grade 4 changes .

Figure 69: Hemoglobin Laboratory Changes



Abbreviations: LLN = lower limit of normal; N = number of patients; SE = standard error.
Placebo and baricitinib 4-mg data are from the PC 4-mg dataset with extended time and 2-mg data is from the EXTENDED dataset. Data through 01 January 2016 are presented.

6.2.6.1.2. Lymphocytes

In the clinical program, Baricitinib treatment was associated with an increase in circulating absolute lymphocyte count within the first week of treatment, and counts returned to baseline or below within 12 to 24 weeks and remained stable (Figure 70). At Week 16, the within group change from baseline was -0.08, 0.04 and 0.07 x 10^9/L for placebo, baricitinib 2- and 4-mg, respectively. Treatment-emergent lymphocyte count reductions (< 0.5x10^9/L or CTCAE Grade 3) were noted in 0.8% of 2-mg and 0.6% of 4-mg baricitinib-treated patients with no Grade 4 changes (Table 9). Permanent discontinuations due to AEs of lymphopenia were uncommon (0.1%). Worsening of lymphopenia was associated with an increased risk of infection (Table 33).

T-cell, NK cell, and B-Cell lymphocyte subsets were evaluated at multiple timepoints. From the PC 4-mg dataset, a larger proportion of patients had a treatment-emergent abnormal lymphocyte subset cell count up to Week 24 in BARI 4-mg compared to PBO for the following subsets:

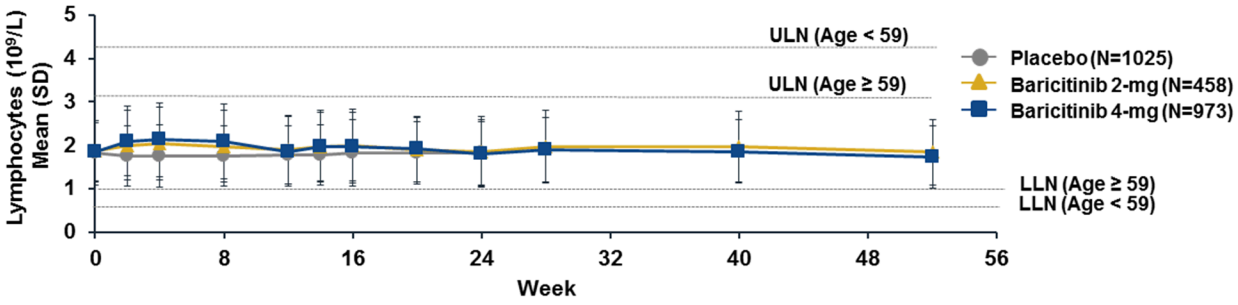
- larger proportion with abnormal high for CD3+ and CD4+ T-cells, NK, and CD19+ B-cell counts

- larger proportion with abnormal low NK cell counts

From the PC dataset, there was no difference in the proportion of patients with a treatment-emergent abnormal low/high lymphocyte subset cell count up to Week 24 between BARI 4-mg and BARI 2-mg.

The observed changes in lymphocytes subsets are consistent with the observed changes for lymphocytes as a whole, and reflect the change in central tendency.

Figure 70: Lymphocyte Laboratory Changes



Abbreviations: LLN = lower limit of normal; N = number of patients; SD = standard deviation; ULN = upper limit of normal.
Placebo and baricitinib 4-mg data are from the PC 4-mg dataset with extended time and 2-mg data is from the EXTENDED dataset. Data through 01 January 2016 are presented.

Table 33: Infection by Worst Lymphopenia CTCAE Grade in PC Dataset

	PBO N = 544			BARI 2-mg N = 477			BARI 4-mg N = 474		
Lymphopenia CTCAE Grade	n-obs	Overall Infection n (%)	Serious Infections n (%)	n-obs	Overall Infection n (%)	Serious Infections n (%)	n-obs	Overall Infections n (%)	Serious Infections n (%)
0 ($\geq$1.1 x10^9/L)	368	111(30.2%)	8 (2.2%)	349	116 (33.2%)	5 (1.4%)	333	122 (36.6%)	6 (1.8%)
1 (<1.1 and $\geq$0.8 x10^9/L)	124	36 (29.0%)	1 (0.8%)	87	29 (33.3%)	1 (1.1%)	102	43 (42.2%)	2 (2.0%)
2 (<0.8 and $\geq$0.5 x10^9/L)	49	10 (20.4%)	0	35	9 (25.7%)	1 (2.9%)	36	18 (50.0%)	2 (5.6%)
3 (<0.5 and $\geq$0.2 x10^9/L)	3	1 (33.3%)	0	6	2 (33.3%)	0	3	0	0
4 (<0.2 x10^9 /L)	0	0	0	0	0	0	0	0	0

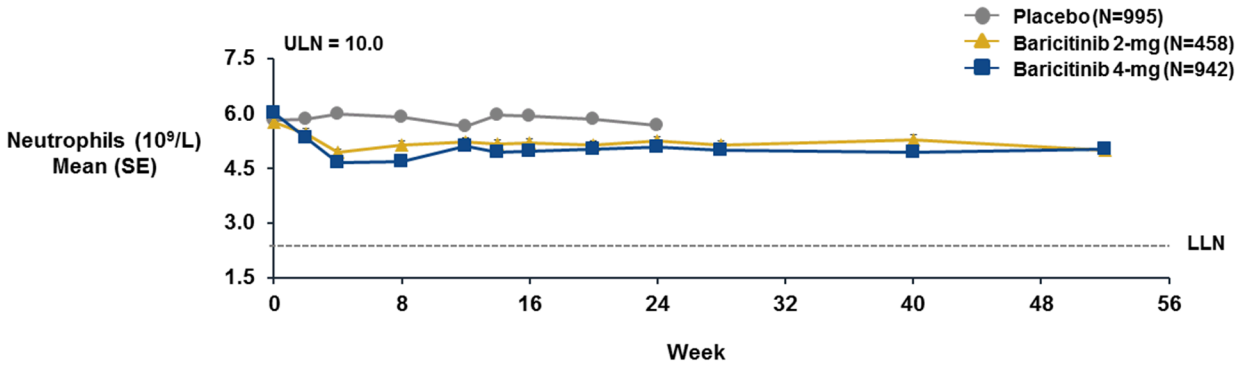
Abbreviations: BARI = baricitinib; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients; n = number of patients in specified category with specified event; n-obs = number of patients in specified category; PBO = placebo.
Percent calculated from n/n-obs*100%.

6.2.6.1.3. Neutrophils

Treatment with baricitinib was associated with a decrease in mean absolute neutrophil count during the first month of treatment that remained stable over time while baricitinib treatment continued (mean change of -0.76 x10^9/L for 2-mg treated patients and -0.94 x10^9/L for 4-mg treated patients, Figure 71). Neutrophil counts largely remained within the normal reference range throughout the duration of treatment with baricitinib. In the PC dataset, neutropenia less than 1 x 10^9/L was uncommon at 0.6% at 2-mg and 0.2% at 4-mg baricitinib (Table 9).

Compared to placebo, a similar proportion of patients receiving baricitinib 4-mg or 2-mg experienced a TEAE of neutropenia or neutrophil count decreased.

Figure 71: Laboratory Changes, Neutrophils



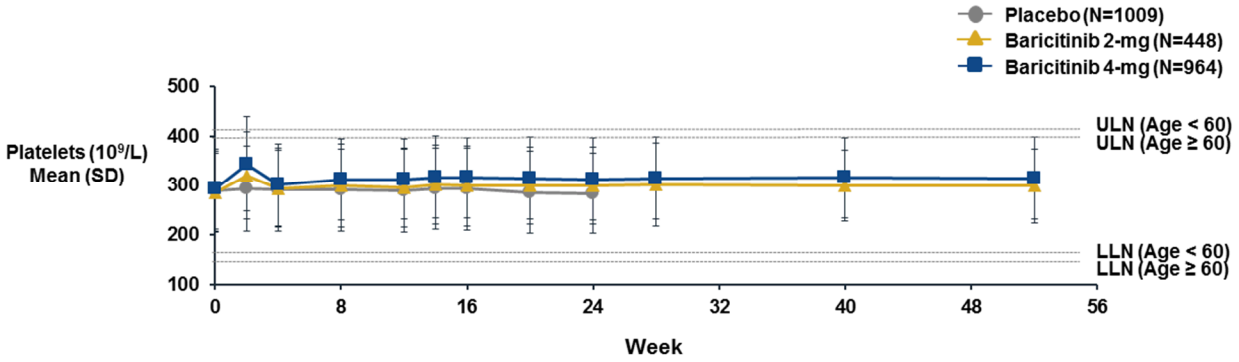
Abbreviations: LLN = lower limit of normal; N = number of patients; SE = standard error; ULN = upper limit of normal.
Placebo and baricitinib 4-mg data are from the PC 4-mg dataset with extended time and 2-mg data is from the EXTENDED dataset. Data through 01 January 2016 are presented.

6.2.6.1.4. Platelets

Treatment with baricitinib was associated with an increase in mean platelet count within the first 2 weeks (51 x10^9/L at 4-mg baricitinib), which then returned towards baseline and remained stable with extended baricitinib exposure (Figure 72). The proportion of patients experiencing a treatment-emergent high platelet count (>600 x10^9/L) was higher in baricitinib 4-mg (2.3%) compared to placebo (1.3%) and 2-mg (1.1%) in the PC dataset (Table 9).

The observations in the RA studies are consistent with an earlier healthy volunteer study (JADE) that showed a transient increase in platelet counts two weeks after initiation of baricitinib. In 6-month rat toxicology studies, treatment with baricitinib resulted in an increase in platelet count that was concomitant with a dose-dependent decrease in spleen weight. It is conceivable that release of mature platelets stored in the spleen is a contributing factor to the observed platelet count increase via reactive/secondary thrombocytosis.

Figure 72: Laboratory Changes, Platelets



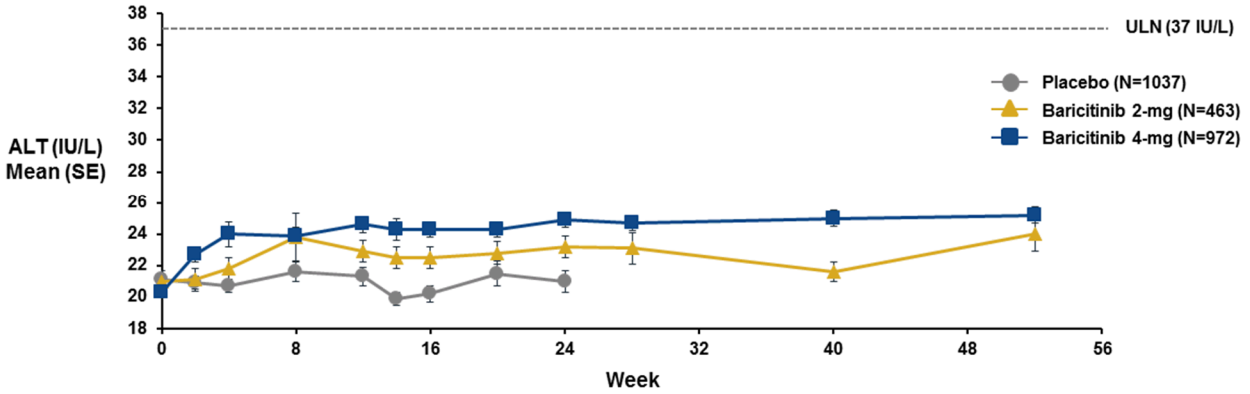
Abbreviations: LLN = lower limit of normal; N = number of patients; SD = standard deviation; ULN = upper limit of normal.
Placebo and baricitinib 4-mg data are from the PC 4-mg dataset with extended time and 2-mg data is from the EXTENDED dataset. Data through 01 January 2016 are presented.

6.2.6.2. Clinical Chemistries

6.2.6.2.1. Aminotransferases and Hepatic Effects

Baricitinib treatment was associated with mean increases of both Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) of approximately 6 U/L that plateaued around Week 4 (Figure 73). Elevations to >3x ULN were noted in less than 2% of baricitinib-treated patients regardless of dose (Table 9). At Week 16, the within-group change from baseline for ALT was 0, 3.2, and 5.3 U/L for placebo, baricitinib 2-, and 4-mg, respectively. Change in AST was consistent with that of ALT. Increases in ALT to >3x ULN in the EXTENDED dataset were noted at a similar frequency for 2-mg (3.3%) and 4-mg (4.5%). All patients with elevations in ALT or AST at least 3x the upper limit of normal (ULN) and total bilirubin at least 2x ULN were examined, including 9 patients with ALT elevations greater than 10x ULN. All cases had a reason other than study treatment or had multiple confounders for these elevations, resulting in no identified cases of drug-induced liver injury. The incidence rate for TEAEs from all hepatic Standard MedDRA Queries (SMQs) in the All BARI RA dataset was 4.4 and in the EXTENDED dataset the incidence rate for 2-mg was 4.2 and for 4-mg was 5.3.

Figure 73: Laboratory Changes, ALT

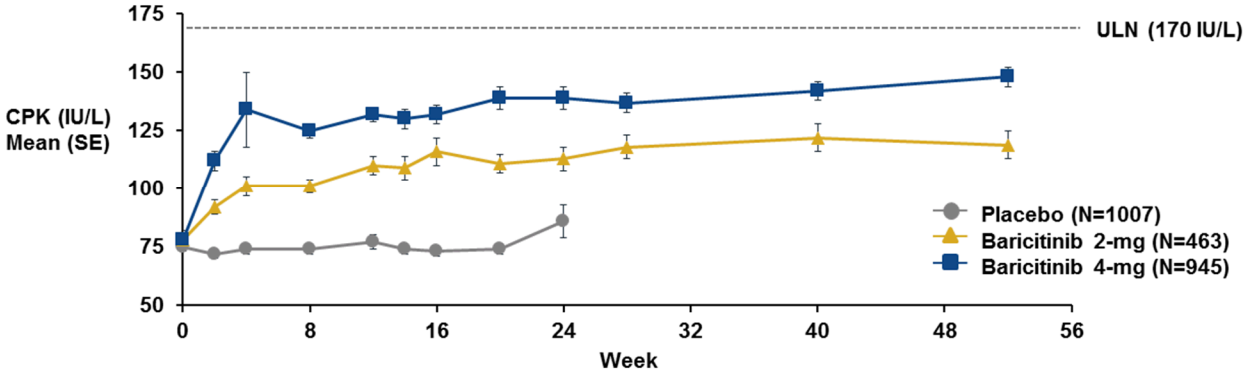


Abbreviations: ALT = alanine aminotransferase; N = number of patients; SE = error; ULN = upper limit of normal.
Placebo and baricitinib 4-mg data are from the PC 4-mg dataset with extended time and 2-mg data is from the EXTENDED dataset. Data through 01 January 2016 are presented.

6.2.6.2.2. Creatine Phosphokinase

Baricitinib treatment was associated with increases in CPK within 1 week of starting baricitinib, plateauing after 8 to 12 weeks and resulting in mean increases of 37 IU/L for 2-mg and 57 IU/L for 4-mg at Week 16 (Figure 74). The frequency of increases to CTCAE grade 3 or greater were 0.6% for placebo, 0.8% for 2-mg and 1.5% for 4-mg (Table 9) , and discontinuations were uncommon at less than 1% . TEAEs related to muscle injury were reported at frequencies of 1-2% for placebo- and baricitinib-treated patients in the placebo-controlled time-period with no rhabdomyolysis. In the EXTENDED dataset, 2 patients reported events of rhabdomyolysis, one with CPK increases associated with exercise and the other due to a fall.

Figure 74: Laboratory Changes, CPK

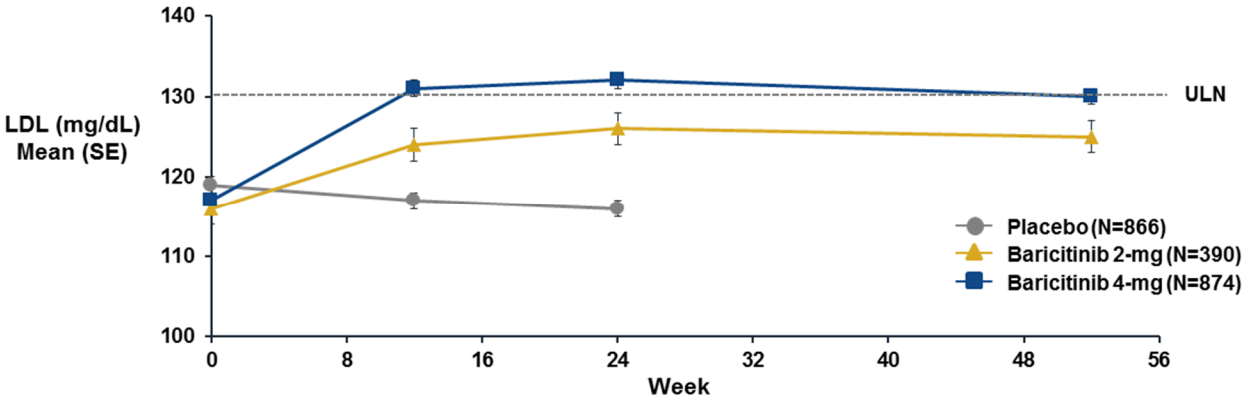


Abbreviations: CPK = creatine phosphokinase; N = number of patients; SE = standard error; ULN = upper limit of normal.
Placebo and baricitinib 4-mg data are from the PC 4-mg dataset with extended time and 2-mg data is from the EXTENDED dataset. Data through 01 January 2016 are presented.

6.2.6.2.3. Serum Lipids

Evaluation of serum lipids showed dose-dependent mean increases for triglycerides and cholesterol within the first 12 weeks that remained stable over continued exposure. Mean increase in LDL cholesterol was 8% for 2-mg and 14% for 4-mg by Week 12 (Figure 75). Increases to $\geq$ 160 mg/dL were noted for 7.8, 11.3 and 13.6 percent of placebo, 2-mg and 4-mg baricitinib-treated patients, respectively (Table 9). The mean LDL/HDL ratio did not change. Treatment-emergent AEs of hypercholesterolemia were commonly reported in a dose-related manner with an incidence rate of 2.35. No association between the lipid changes and MACE was identified; patients who initiated statin therapy had reductions in total cholesterol and LDL-C to baseline levels, although HDL-C remained elevated. The increases noted in LDL were evaluated and determined to be predominantly an increase in larger LDL particles and a decrease in the small dense LDL particles that are generally thought to be more atherogenic.

Figure 75: Laboratory Changes, LDL Cholesterol



Abbreviations: LDL = low-density lipoprotein; N = number of patients; SE = standard error; ULN = upper limit of normal.
Placebo and baricitinib 4-mg data are from the PC 4-mg dataset with extended time and 2-mg data is from the EXTENDED dataset. Data through 01 January 2016 are presented.

6.3. Safety in 2+DMARD-IR Patients

In support of the proposed dosing regimen of baricitinib 4-mg in patients with an inadequate response to 2 or more DMARDs, data were evaluated for key safety parameters from patients in the 4 studies (JADA, JADN, JADX, and JADW) that included placebo, baricitinib 2-mg, and 4-mg who were inadequate responders to 1 DMARD (30% of the treated population) and patients who received ≥2 prior DMARDs (70% of the population).

The safety evaluation of baricitinib 2-mg versus 4-mg in patients with 1 prior DMARD and 2 or more prior DMARDs revealed no unexpected changes to the risk assessment across these sub-populations (Table 34). Few differences were noted in frequency or incidence rate for key safety parameters between those with 2 or more prior DMARDs and 1 prior DMARD. The overall safety profile of baricitinib in the 2 or more prior DMARD inadequate responder subpopulation was consistent with findings from the overall baricitinib-treated population.

Table 34: Key Safety Outcomes: Exposure-Adjusted Incidence Rates and Proportion of Patients Based on Prior Therapy for Studies JADA, JADN, JADX, and JADW

	Weeks 0-16						EXT Period			
	1 prior DMARD			2 or more prior DMARDs			1 prior DMARD		2 or more prior DMARDs	
	PBO	BARI 2-mg	BARI 4-mg	PBO	BARI 2-mg	BARI 4-mg	BARI 2-mg	BARI 4-mg	BARI 2-mg	BARI 4-mg
N [PYE]	172 [45.4]	141 [39.8]	143 [38.5]	378 [104.6]	335 [96.6]	335 [98.8]	141 [175.5]	143 [198.0]	335 [423.0]	335 [444.3]
MTX-IR, n (%)	157 (91.3)	125 (88.7)	128 (89.5)	193 (51.1)	155 (46.3)	154 (46.0)	125 (88.7)	128 (89.5)	155 (46.3)	154 (46.0)
Number of concomitant DMARDs, n (%)										
One	163 (94.8)	133 (94.3)	134 (93.7)	262 (69.3)	226 (67.5)	225 (67.2)	133 (94.3)	134 (93.7)	226 (67.5)	225 (67.2)
Two	0	0	0	101 (26.7)	88 (26.3)	98 (29.3)	0	0	88 (26.3)	98 (29.3)
Three or more	0	0	0	8 (2.1)	12 (3.6)	7 (2.1)	0	0	12 (3.6)	7 (2.1)
Overview of Safety										
Death n, [incidence rate]	0	0	0	2 [1.9]	0	1 [1.0]	1 [0.6]	1 [0.5]	0	2 [0.4]
SAEs n, [incidence rate]	7 [14.9]	5 [12.2]	5 [12.5]	15 [14.0]	11 [11.2]	20 [19.8]	13 [7.2]	20 [9.9]	49 [11.4]	65 [14.4]
TEAEs n, [EAIR]	102 [224.7]	78 [196.1]	81 [210.2]	224 [214.2]	215 [222.5]	233 [235.9]	99 [56.4]	118 [59.6]	274 [64.8]	297 [66.9]
Permanent discontinuation due to AE n, [EAIR]	10 [21.3]	5 [12.2]	7 [17.4]	9 [8.4]	14 [14.2]	18 [17.8]	14 [7.7]	18 [8.9]	25 [5.8]	37 [8.2]
Temporary interruption due to AE n, [EAIR]	15 [33.0]	10 [25.1]	15 [38.9]	24 [23.0]	35 [36.2]	43 [43.5]	24 [13.7]	33 [16.7]	80 [18.9]	84 [18.9]
Serious infection n, [incidence rate]	1 [2.1]	1 [2.5]	2 [5.0]	6 [5.6]	5 [5.1]	6 [6.0]	2 [1.1]	8 [4.0]	18 [4.3]	23 [5.2]
Opportunistic infection excluding TB and herpes zoster	0	0	0	0	0	0	1 [0.6]	1 [0.5]	1 [0.2]	0
DVT/PE n, [incidence rate]	0	0	2 [5.0]	0	0	0	1 [0.6]	4 [2.0]	2 [0.5]	0
MACE n, [incidence rate]	1 [3.4]	0	0	1 [1.1]	0	2 [2.1]	0	0	1 [0.2]	2 [0.5]
Malignancy excluding NMSC n, [incidence rate]	0	0	0	0	1 [1.0]	0	1 [0.6]	4 [2.0]	2 [0.5]	4 [0.9]

	Weeks 0-16						EXT Period			
	1 prior DMARD			2 or more prior DMARDs			1 prior DMARD		2 or more prior DMARDs	
	PBO	BARI 2-mg	BARI 4-mg	PBO	BARI 2-mg	BARI 4-mg	BARI 2-mg	BARI 4-mg	BARI 2-mg	BARI 4-mg
Adverse drug reactions based on core labeling n, [EAIR]										
URI n, [EAIR]	21 [46.3]	13 [32.7]	19 [49.3]	42 [40.2]	64 [66.2]	64 [64.8]	36 [20.5]	39 [19.7]	102 [24.1]	110 [24.8]
Herpes zoster n, [EAIR]	0	0	2 [5.0]	2 [1.9]	5 [5.1]	7 [7.0]	5 [2.9]	8 [4.1]	12 [2.9]	16 [3.6]
Herpes simplex n, [EAIR]	1 [2.2]	0	3 [7.8]	2 [1.9]	4 [4.1]	1 [1.0]	1 [0.6]	4 [2.0]	10 [2.4]	10 [2.3]
Nausea n, [EAIR]	4 [8.8]	3 [7.5]	1 [2.6]	7 [6.7]	9 [9.3]	13 [13.2]	5 [2.8]	3 [1.5]	15 [3.5]	18 [4.1]
ALT increase from normal to ≥3 x ULN n (%)	1 (0.6)	4 (2.9)	1 (0.7)	1 (0.3)	4 (1.2)	5 (1.5)	7 (5.0)	3 (2.1)	5 (1.5)	6 (1.8)
AST increase from normal to ≥3 x ULN n (%)	1 (0.6)	4 (2.9)	2 (1.4)	1 (0.3)	2 (0.6)	3 (0.9)	5 (3.6)	3 (2.1)	3 (0.9)	5 (1.5)
LDL ≥130 mg/dL n (%)	16 (19.0)	16 (16.7)	25 (28.7)	31 (11.6)	73 (27.1)	83 (29.6)	35 (36.5)	41 (47.1)	122 (45.0)	129 (45.6)
CPK >5 x ULN n (%)	1 (0.6)	1 (0.7)	2 (1.4)	2 (0.5)	3 (0.9)	5 (1.5)	2 (1.4)	5 (3.6)	5 (1.5)	9 (2.7)
Triglycerides ≥500 mg/dL, n (%)	2 (1.2)	1 (0.8)	1 (0.8)	2 (0.6)	3 (1.0)	0	1 (0.8)	3 (2.3)	5 (1.6)	1 (0.3)
Neutropenia <1000 cells/mm^3, n (%)	0	2 (1.4)	0	0	1 (0.3)	1 (0.3)	2 (1.4)	0	1 (0.3)	1 (0.3)
Thrombocytosis >600,000 cells/mm^3, n (%)	0	2 (1.4)	3 (2.1)	7 (1.9)	3 (0.9)	8 (2.4)	3 (2.2)	6 (4.3)	5 (1.5)	10 (3.0)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase CPK = creatine phosphokinase; DMARD = disease-modifying antirheumatic drug; DVT = deep vein thrombosis; EAIR = exposure-adjusted incidence rate; IR = inadequate responder; LDL = low density lipoprotein; MACE = major adverse cardiovascular event; MTX = methotrexate; N = number of patients in each subgroup; n = number of patients in the specified category; NMSC = nonmelanoma skin cancer; PBO = placebo; PE = pulmonary embolism; PYE = patient-years of exposure; RA = rheumatoid arthritis; SAE = serious adverse event; TB = tuberculosis; TEAE = treatment emergent adverse event; ULN = upper limit of normal; URI = upper respiratory tract infection.
Data are n, [EAIR] except for safety topics of special interest, which are represented by n, [IR].
Percentages are based on the number of patients by subgroup in each treatment group. Lab percentages are based on number at risk or nonmissing N where applicable.

6.4. Postmarketing Data

No new safety signals were noted from postmarketing data through the resubmission cutoff date (01 April 2017) and through a more recent cutoff date (13 February 2018). Reports received were consistent with the safety profile defined from the RA clinical development program.

Worldwide baricitinib sales data as of 31 January 2018 shows an estimated 12,900 patients exposed to baricitinib. This translates to an estimated 3500 patient-years of therapy.

Adverse event data from spontaneous postmarketing reporting through 13 February 2018 included 1107 AEs in 478 reports. The most frequently reported adverse drug reactions based on the company core safety information were (by MedDRA PT):

- Upper respiratory tract infection (n=41)
- Nausea (n=38)
- Herpes zoster (n=24)
- Herpes simplex (n=16)
- Increased Blood Cholesterol/Hypercholesterolemia (n=9)
- Acne (n=7)
- Creatine phosphokinase increased (n=4)
- Increased Triglycerides (n=3)
- Alanine aminotransferase increased (n=3)
- Low density lipoprotein (LDL) increased (n=2)

Other adverse events reported (events with n≥10) included:

- Drug ineffective (n=35)
- Fatigue (n=31)
- Arthralgia (n=30)
- Headache (n=22)
- Dizziness (n=19)
- Pain in extremity (n=19)
- Pneumonia (n=19)
- Diarrhea (n=18)
- Pyrexia (n=16)
- Rheumatoid arthritis (n=16)
- Cough (n=14)
- Malaise (n=13)
- Alopecia (n=12)
- Vomiting (n=11)
- Weight increased (n=11)
- Dyspnea (n=10)
- Joint swelling (n=10)

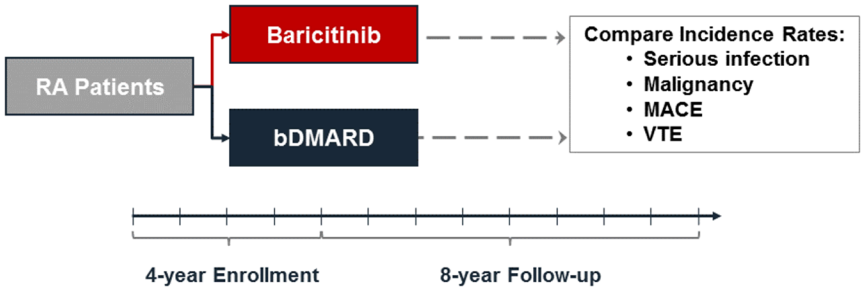
6.5. Risk Management

Lilly has a comprehensive postmarketing pharmacovigilance plan in place that is designed to enhance understanding of the existing safety profile, detect, and characterize any new risks that may emerge as market exposure increases. The safety profile of patients treated with baricitinib will be further characterized through comparative postmarketing observational studies conducted in diverse global regions where baricitinib is approved. All studies will enroll a broad representative population including a control group (except Japan) and collect safety data to evaluate the important potential risks of thrombosis, MACE, serious infection, malignancy, and hepatotoxicity.

1. **Prospective Observational Study:** Lilly will compare the incidence and nature of VTE in a prospective observational study of patients enrolled in the US Consortium of Rheumatology Researchers of North America (Corrona) RA Registry initiating baricitinib (N ~4000) with long-term follow-up versus similar patients treated with bDMARDs or cDMARDs (N ~4000 each) (Figure 76). Venous thromboembolic events will be collected as a targeted AE, with collection of source records. Patients will be actively recruited and observed over a period of 8-12 years for the occurrence of VTE. At the time of full enrollment, the study will have >80% power to detect a 2-fold greater risk of VTE among baricitinib-treated patients compared to those treated with biologics. Comparative analyses will also evaluate the potential risk of MACE, serious infection, and malignancy. The incidence of less commonly anticipated events, such as hepatotoxicity, will be described.
2. **Electronic Healthcare Data Study:** Lilly will conduct a retrospective cohort study to support the general results of the prospective observational study, based on RA patients enrolled in US health plans. The objectives of this study will address the same outcomes as the Corrona RA Registry, accounting for differences in data and covering a similar calendar period. Analyses will parallel those of the Corrona RA Registry, include all eligible RA patients, and account for treatment switching. The occurrence of VTE will be adjudicated using medical records.
3. **Pan-Nordic Health Study:** Using linked healthcare data from national registries in each Nordic country, Lilly will compare the incidence of VTE and other outcomes, as above, among patients with long-term exposure to baricitinib compared to similar patients treated with bDMARDs or cDMARDs. Incident VTE will be collected. Confirmation of VTEs will be explored based on additional clinical information. As in other studies, the incidence of less common outcomes of interest, such as hepatotoxicity, will be described. Exposures during pregnancy to baricitinib and other medications used to treat moderate to severe RA will also be monitored, as will fetal outcomes.
4. **EU Pharmacovigilance Registries:** Lilly will receive information from prospective patient cohorts using baricitinib in European national pharmacovigilance registries.

5. **Japan Postmarketing Safety Study:** Lilly has begun collecting early postmarketing data and will continue through the first ~3000 RA patients treated with baricitinib in routine clinical practice. Patients will be observed for 3 years from the start of baricitinib use. Information on VTE will be collected, along with SAEs reported by healthcare professionals.

Figure 76: Prospective Observational Study



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; MACE = major adverse cardiovascular event; RR = relative risk; VTE = venous thromboembolism

Routine pharmacovigilance activities that will also capture reported cases and aid in further characterization of potential risks and missing information in the postmarketing setting include:

- surveillance of all spontaneous postmarketing reports, serious clinical trial reports, trial-level safety reviews of SAEs and non-serious AEs, and published studies and meeting abstracts
- use of a signal detection tool that utilizes disproportionality testing of spontaneously reported AEs
- surveillance of a large US commercial claims database for significantly elevated drug-event combinations (as specified by the complete list available through the Agency for Healthcare Research and Quality Clinical Classifications Software) evaluated using non-targeted, propensity-score matched analyses

In addition, VTE will be included as an event of special interest for future clinical studies of baricitinib and will be adjudicated by an independent Clinical Endpoint Committee (as implemented for MACE in RA Phase 3 studies to date). The routine pharmacovigilance, data collection from ongoing RA and studies for other indications and postmarketing safety evaluation studies will all serve to better characterize the long term safety profile of baricitinib including the potential risks of serious infections, malignancy, MACE and other events with long latency and those that are uncommon or rare.

7. Conclusions

RA care has advanced greatly in recent decades. With the advent of targeted therapies and treatment strategies, many patients can now avoid the severe progressive joint damage, deformity, disability, and diminished quality of life that formerly prevailed because of widely uncontrolled synovitis. The benefits of achieving sustained remission/LDA and the adverse impact of delayed or suboptimal control on long-term health outcomes are now unequivocally established (Mackey et al. 2015; Smolen et al. 2017).

Although disease control has undoubtedly improved with the approval of new therapies, failure to reach or retain LDA/remission targets remains a major challenge affecting many patients. While a substantial portion of patients fail to reach targets others lose response over time or discontinue because of side effects or tolerability issues (Montag et al. 2011; Singh et al. 2015; Taylor et al. 2016). The proportion of RA patients who are refractory to multiple DMARDs of differing mechanisms continues to grow (Smolen et al. 2017) and chronic opioid analgesic use in US RA patients has advanced rather than receded during the targeted DMARD era (Lee et al. 2017).

Considered in the context of unmet needs and the risks and benefits of available therapies, a favorable benefit-risk can be concluded for baricitinib 4-mg and 2-mg administered once daily for the treatment of patients with moderately to severely active RA. The proposed dosing and administration allows prescribers to utilize baricitinib in a flexible manner based on individual patient characteristics in a way that is supported by data, aligns with practice guidelines, and is responsive to FDA's concerns regarding benefit-risk and dose. Used in this way, once-daily oral baricitinib can represent a valuable addition to the treatment arsenal for US patients with this common and disabling disease, and provides a needed treatment advance for patients who have struggled to manage their moderate to severe rheumatoid arthritis with current therapies.

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9. Appendix 1: Supporting Tables and Figures

Table 35: Baseline Demographics and Disease Characteristics in the 1DMARD-IR and 2+DMARD-IR Subgroups in JADX

	1DMARD-IR (N=298)	2+DMARD-IR (N=381)
Age, years, mean (SD)	52.1 (12.3)	51.5 (12.4)
Female, n (%)	238 (79.9)	318 (83.5)
Duration of RA, years[a], mean (SD)	5.8 (6.4)	8.8 (8.2)
ACPA positive, n (%)	206 (69.1)	294 (77.2)
RF positive, n (%)	221 (74.2)	297 (78.0)
≥ 1 Erosion, n (%)	200 (67.3)	297 (78.6)
mTSS, Sharp units, mean (SD)	16.78 (31.84)	27.50 (41.12)
Erosion Score, mean (SD)	10.79 (19.15)	16.73 (23.75)
Joint space narrowing score, mean (SD)	5.99 (13.96)	10.77 (18.73)
Concomitant steroid use, n (%)	139 (46.6)	204 (53.5)
Corticosteroid dose, mg/day[b], mean (SD)	6.3 (2.4)	6.1 (2.6)
Concomitant MTX use, n (%)	233 (78.2)	275 (72.2)
MTX dose, mg/week, mean (SD)	16.3 (4.8)	16.0 (4.9)
Ever used MTX[c], n (%)	253 (84.9)	372 (97.6)
# of prior cDMARDs, n (%):		
One	298 (100)	0
Two	0	210 (55.1)
≥ Three	0	171 (44.9)
# of concomitant cDMARDs, n (%):		
None	25 (8.4)	18 (4.7)
One	273 (91.6)	173 (45.4)
Two	0	170 (44.6)
Three	0	20 (5.2)
Baseline Disease Activity		
Swollen joint count, of 66, mean (SD)	14.1 (7.6)	12.9 (7.7)
Tender joint count, of 68, mean (SD)	25.1 (13.8)	23.1 (14.6)
Physician's Global Assessment, 0-100mm VAS, mean (SD)	64.1 (17.6)	63.1 (17.4)
Patient's Global Assessment, 0-100mm VAS, mean (SD)	60.8 (21.9)	60.6 (20.5)
Patient's Assessment of Pain, 0-100mm VAS, mean (SD)	58.6 (22.9)	57.4 (21.5)
HAQ-DI, mean (SD)	1.59 (0.59)	1.46 (0.62)
hsCRP, mg/L, mean (SD)	15.0 (17.4)	18.1 (20.4)
ESR, mm/hour, mean (SD)	42.5 (23.1)	43.3 (24.8)
DAS28-CRP, mean (SD)	5.61 (0.90)	5.49 (0.92)
DAS28-ESR, mean (SD)	6.32 (0.98)	6.14 (0.95)
SDAI, mean (SD)	39.00 (12.31)	36.66 (12.45)
SDAI >26 , n (%)	251 (85.7)	293 (78.1)
CDAI, mean (SD)	37.53 (11.93)	34.85 (12.19)

Abbreviations: ACPA = anti-citrullinated protein antibodies; CDAI = clinical disease activity index; cDMARD = conventional disease-modifying antirheumatic drug; DAS28-CRP = Disease Activity Score in 28 joints c-reactive protein; DAS28-ESR = Disease Activity Score in 28 joints erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; hsCRP = high-sensitivity C-reactive protein; mTSS = modified Total Sharp Score; MTX = methotrexate; N = number of patients; n = number of patients in specified category; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation; SDAI = simplified disease activity index; TNF = tumor necrosis factor; VAS = visual analog scale.
a Time from symptom onset.
b Doses are in prednisone equivalent units.
c Includes patients with historical (previous but not currently taking) MTX use and patients with concomitant (currently taking) MTX use.

10. Appendix 2: Baricitinib Efficacy and Safety in Other Indications

In addition to RA, baricitinib is currently in development for atopic dermatitis and systemic lupus erythematosus. A completed 16-week Phase 2 atopic dermatitis study showed significant efficacy versus placebo for baricitinib 4-mg and Phase 3 is currently enrolling; no new safety signals were identified. A 24-week systemic lupus erythematosus Phase 2 study also recently concluded, showing significant efficacy versus placebo for baricitinib 4-mg but not for 2-mg; no new safety signals were identified.

11. Appendix 3: Statistical Analyses Methods

Consistent methods of analysis, including analysis population definitions and methods of imputation for missing data, were used for all four completed Phase 3 studies. Control for multiplicity of hypothesis testing was used in each study to limit the rate of false positive conclusions.

Analysis Population

Efficacy outcomes analyses were conducted across all measures and timepoints using the modified intent-to-treat (mITT) analysis set, defined as all randomized patients who received at least 1 dose of study drug and consistent with International Conference on Harmonisation principles of intention-to-treat. Patients were analyzed according to their randomized treatment, with imputation applied for missing data, data following permanent discontinuation of study drug, or data following rescue. Measures of structural joint damage progression (eg, mTSS) had modified methods applied: they were analyzed in all patients with baseline and at least 1 postbaseline score, and different forms of imputation were applied (see below).

Handling of Missing Data, Premature Discontinuation, and Rescue

Note on rescue: After the primary timepoint for efficacy analyses, non-responding patients were rescued to open-label baricitinib 4-mg, remaining blinded to original treatment assignment. At the first visit where rescue was available, this was automatically executed based on joint counts. Thereafter, rescue could be implemented at investigator discretion based on joint counts. No rescue was available prior to the primary analysis timepoint.

The following imputation methods were used, as appropriate, and in alignment with historical norms for Phase 3 RA clinical trials:

- Non-responder imputation (NRI) for categorical (response/non-response) measures: any rescue or discontinuation from study or study drug (regardless of reason) led to the patient being defined as a non-responder at all subsequent timepoints, thus defining lack of persistence to randomized treatment as treatment failure, a form of effectiveness analysis
- Modified last observation carried forward (mLOCF) for continuous measures: any rescue or discontinuation from study or study drug (regardless of reason) led to use of the value obtained at the point of rescue/discontinuation for all subsequent time points, thus assuming no additional treatment benefit
- Modified baseline observation carried forward (mBOCF) for continuous measures: similar to mLOCF except that discontinuation for an adverse event led to the use of the baseline value for all subsequent time points, thus assuming zero treatment benefit in these cases
- Baseline observation carried forward (BOCF) for continuous measures: rescue or discontinuation from study or study drug (regardless of reason) led to use of the baseline value for all subsequent timepoints, thus assuming zero treatment benefit, a form of effectiveness analysis for continuous data

- Linear extrapolation (LE) for analysis of mTSS (and subcomponents): uses baseline and last available time point prior to rescue or discontinuation from study to project the expected mTSS at the analysis timepoint, thus assuming a constant rate of accumulation of joint damage as that observed while on randomized treatment
- LOCF as randomized for analysis of mTSS: uses baseline and last available timepoint regardless of current treatment assignment, thus attributing all joint damage to the randomized treatment and assuming no additional damage occurs after last measurement obtained
- Primary imputation methods for analysis of data across endpoints were NRI for categorical data, mLOCF for continuous data, and LE for mTSS. mBOCF was used specifically for key secondary continuous endpoints at the primary analysis timepoint.
- Tipping point analyses were conducted as sensitivity analyses of primary and key secondary endpoints using a form of 'missing-not-at-random' imputation: iteratively assign worse outcomes to missing values for patients assigned to baricitinib and better outcomes to those from comparator arms until analyses are no longer statistically significant. Supplemental to these analyses, a 'worst comparison' imputation was performed that assigned the worst possible outcome for missing data in the baricitinib group and the best possible outcome for missing data in the comparator group.

General Analysis Methods

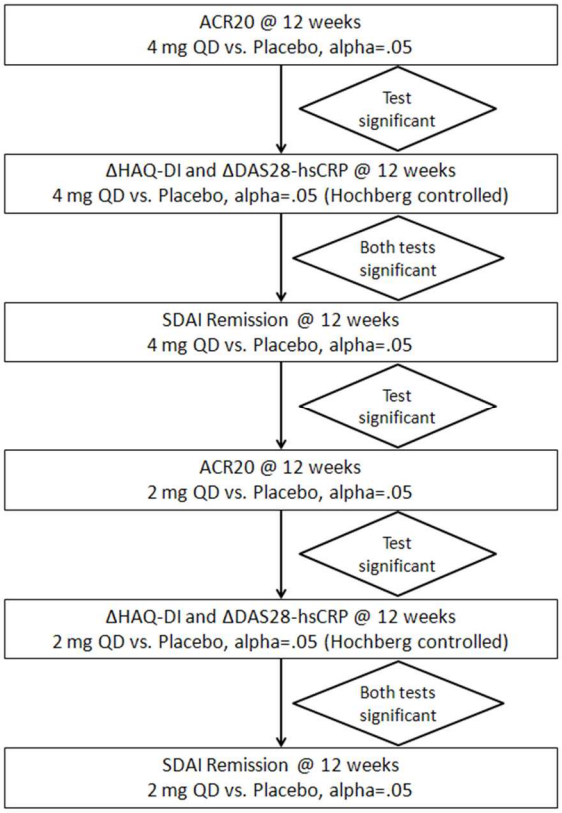
Categorical measures (eg, proportion of patients achieving ACR20, SDAI $\leq$3.3) were analyzed using logistic regression with the randomization stratification factors included in the model and with NRI. Continuous measures (eg, mean change from baseline in HAQ-DI, DAS28-CRP) were analyzed using analysis of covariance (ANCOVA) with baseline value as the covariate and the randomization stratification factors included in the model and with mLOCF imputation (except for primary analysis timepoints for key secondary endpoints, as noted above). Mean change in mTSS was analyzed using the same ANCOVA model with LE as the principal method of imputation. Sensitivity analyses for primary and key secondary endpoints included 1) mixed models for repeated measures (MMRM) for continuous measures, 2) ANCOVA with LOCF as randomized for mTSS, 3) tipping point analyses, and 4) repeat of the primary analysis methods using a per protocol population.

Multiple Testing Procedures

Primary and **key secondary** hypotheses were tested using multiple testing procedures that strongly control the familywise type I error rate (FWER) in order to control the rate of false positive conclusions. Each procedure began with a test of the primary null hypothesis using 2-sided alpha (α) =0.05 (or 1-sided α=0.025 when noninferiority was the primary assessment). Following rejection of the primary null hypothesis, the testing procedures used across the studies, though uniquely applied for each study, fit within the broad framework of stepwise procedures (used primarily in Study JADW [Figure 77]), gatekeeping procedures (used primarily in Study JADX [Figure 78]), or sequentially rejective weighted Bonferroni tests (also commonly referred to as graphical testing approaches, used in Studies JADV [Figure 79] and JADZ [Figure 80]). After rejection of the primary null hypothesis, located at the top of each illustration, arrows

indicate the subsequent test or tests to be conducted, with the indicated fraction or allocation of the type I error rate to be applied to the next test or set of tests. After each subsequent rejection, the procedure proceeded in the same manner by propagating type I error to additional hypothesis tests until no remaining null hypotheses could be rejected with the type I error rate that was allocated to it.

Figure 77: Illustration of the sequential hypothesis testing approach for Study JADW



Abbreviations: Δ = change from baseline; ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-CRP = Disease Activity Score 28 using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; QD = once a day; SDAI = Simplified Disease Activity Index; vs = versus.

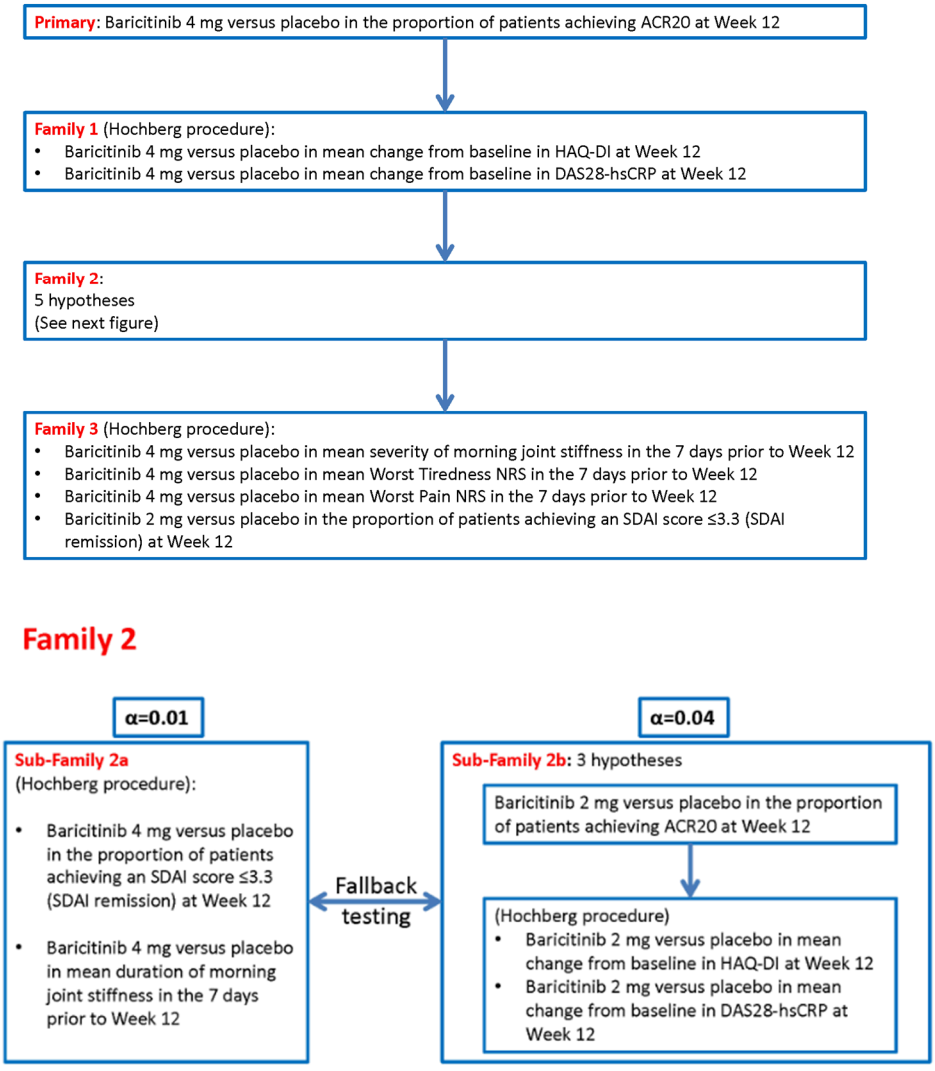
All statistical tests were 2-sided at the alpha level indicated in the figure.

Table 36: Results of Multiplicity-controlled Hypothesis Testing in Study JADW

Realized Step in Procedure	Primary or Key Secondary Endpoint	Type I Error Rate Allocated to Test	Nominal P-value	Result in Significance Testing
1	ACR20, 4-mg vs Placebo	0.05	≤0.001	Significant
2a	DAS28-CRP, 4-mg vs Placebo	0.05	≤0.001	Significant
2b	HAQ-DI, 4-mg vs Placebo	0.05	≤0.001	Significant
3	SDAI remission, 4-mg vs Placebo	0.05	0.140	Not Significant
4	ACR20, 2-mg vs Placebo	0	≤0.001	Untested
5a	DAS28-CRP, 2-mg vs Placebo	0	≤0.001	Untested
5b	HAQ-DI, 2-mg vs Placebo	0	≤0.001	Untested
6	SDAI remission, 2-mg vs Placebo	0	0.723	Untested

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-CRP = Disease Activity Score 28 using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; MJS = Morning Joint Stiffness; SDAI = Simplified Disease Activity Index; vs = versus.

Figure 78: Illustration of the sequential hypothesis testing approach within the overall gatekeeping strategy for Study JADX



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

Table 37: Results of Multiplicity-controlled Hypothesis Testing in Study JADX

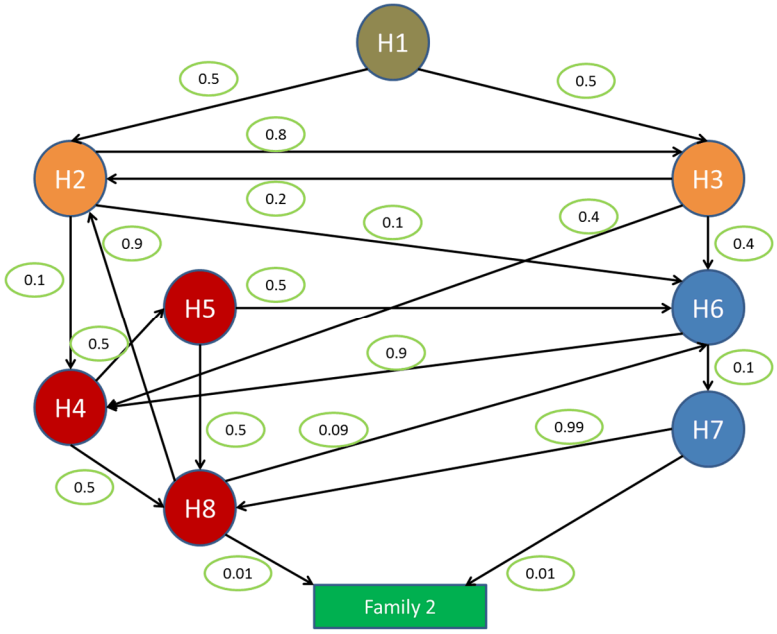
Realized Step in Procedure[a]	Primary or Key Secondary Endpoint	Type I Error Rate Allocated to Test	Nominal P-value	Result in Significance Testing
1	ACR20, 4-mg vs Placebo	0.05	≤0.001	Significant
2a	DAS28-CRP, 4-mg vs Placebo	0.05	≤0.001	Significant
2b	HAQ-DI, 4-mg vs Placebo	0.05	≤0.001	Significant

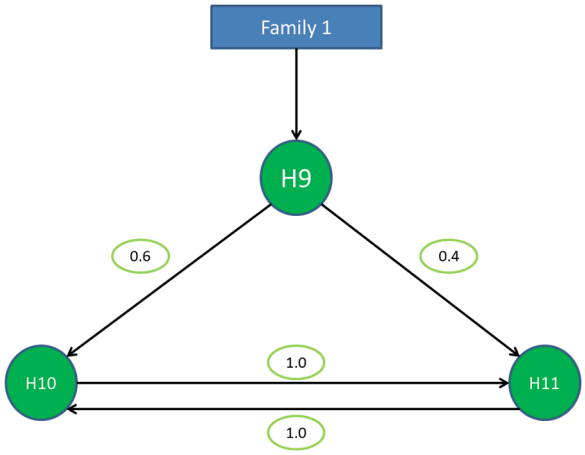
Realized Step in Procedure[a]	Primary or Key Secondary Endpoint	Type I Error Rate Allocated to Test	Nominal P-value	Result in Significance Testing
3	ACR20, 2-mg vs Placebo	0.04	≤0.001	Significant
4a	DAS28-CRP, 2-mg vs Placebo	0.04	≤0.001	Significant
4b	HAQ-DI, 2-mg vs Placebo	0.04	≤0.001	Significant
5a	SDAI remission, 4-mg vs Placebo	0.05	≤0.001	Significant
5b	MJS duration, 4-mg vs Placebo	0.05	≤0.001	Significant
6a	Worst Tiredness, 4-mg vs Placebo	0.05	0.027	Significant
6b	SDAI remission, 2-mg vs Placebo	0.05	≤0.001	Significant
6c	MJS severity, 4-mg vs Placebo	0.05	≤0.001	Significant
6d	Worst Joint Pain, 4-mg vs Placebo	0.05	≤0.001	Significant

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-CRP = Disease Activity Score 28 using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; MJS = Morning Joint Stiffness; SDAI = Simplified Disease Activity Index; vs = versus.

[a] Order of procedure steps not uniquely defined. Representative example shown.

Figure 79: Illustration of the graphical multiple hypothesis testing procedure for Study JADV





H1: ACR20 at 12 weeks, BARI 4-mg vs Placebo

H2: Change from baseline in mTSS at 24 weeks, BARI 4-mg vs Placebo

H3: Change from baseline in HAQ-DI at 12 weeks, BARI 4-mg vs Placebo

H4: Change from baseline in DAS28-CRP at 12 weeks, BARI 4-mg vs Placebo

H5: SDAI remission at 12 weeks, BARI 4-mg vs Placebo

H6: ACR20 at 12 weeks, BARI 4-mg vs Adalimumab

H7: Change from baseline in DAS28-CRP at 12 weeks, BARI 4-mg vs Adalimumab

H8: Duration of Morning Joint Stiffness at 12 weeks, BARI 4-mg vs Placebo

H9: Severity of Morning Joint Stiffness at 12 weeks, BARI 4-mg vs Placebo

H10: Worst Tiredness at 12 weeks, BARI 4-mg vs Placebo

H11: Worst Joint Pain at 12 weeks, BARI 4-mg vs Placebo

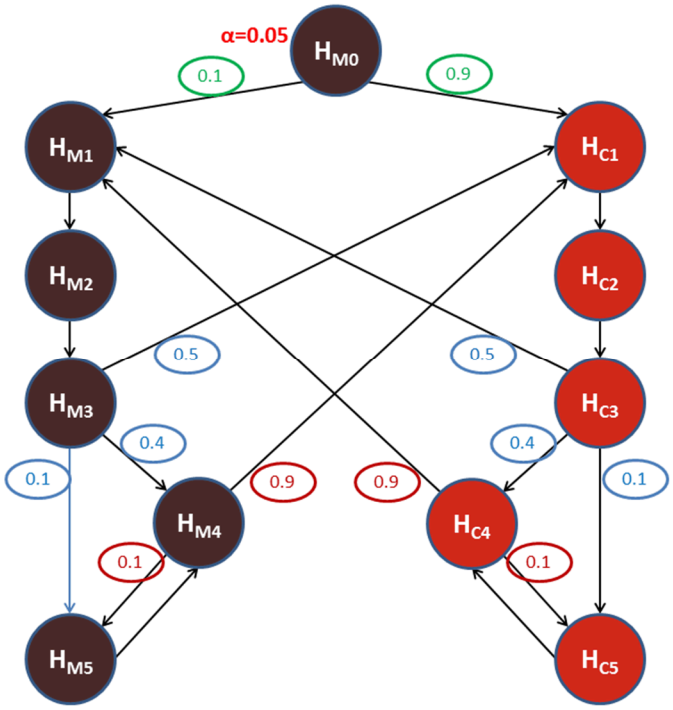
Table 38: Results of Multiplicity-controlled Hypothesis Testing in Study JADV

Realized Step in Procedure[a]	**Primary or Key Secondary Endpoint**	Type I Error Rate Allocated to Test	**Nominal P-value**	**Result in Significance Testing**
1	ACR20, 4-mg vs Placebo	0.05	≤0.001	Significant
2	mTSS, 4-mg vs Placebo	0.025	≤0.001	Significant
3	HAQ-DI, 4-mg vs Placebo	0.045	≤0.001	Significant
4	DAS28-CRP, 4-mg vs Placebo	0.025	≤0.001	Significant
5	ACR20, 4-mg vs Adalimumab (non-inferiority)	0.025	≤0.001	Significant
6	SDAI remission, 4-mg vs Placebo	0.02375	≤0.001	Significant
7	MJS duration, 4-mg vs Placebo	0.0459677	≤0.001	Significant
8	DAS28-CRP, 4-mg vs Adalimumab	0.0451199	≤0.001	Significant
9	MJS severity, 4-mg vs Placebo	0.05	≤0.001	Significant
10	Worst Tiredness, 4-mg vs Placebo	0.03	≤0.001	Significant
11	Worst Joint Pain, 4-mg vs Placebo	0.05	≤0.001	Significant
12	ACR20, 4-mg vs Adalimumab (superiority)	0.05	0.014	Significant

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-CRP = Disease Activity Score 28 using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; MJS = Morning Joint Stiffness; SDAI = Simplified Disease Activity Index; vs = versus.

[a] Order of procedure steps not uniquely defined. Representative example shown.

Figure 80: Illustration of the graphical multiple hypothesis testing procedure for Study JADZ



HM0: ACR20 at 24 weeks, BARI monotherapy vs MTX monotherapy (non-inferiority)

HM1: ACR20 at 24 weeks, BARI monotherapy vs MTX monotherapy (superiority)

HC1: ACR20 at 24 weeks, BARI+MTX vs MTX monotherapy

HM2: Change from baseline in DAS28-CRP at 24 weeks, BARI monotherapy vs MTX monotherapy

HC2: Change from baseline in DAS28-CRP at 24 weeks, BARI+MTX vs MTX monotherapy

HM3: Change from baseline in HAQ-DI at 24 weeks, BARI monotherapy vs MTX monotherapy

HC3: Change from baseline in HAQ-DI at 24 weeks, BARI+MTX vs MTX monotherapy

HM4: Change from baseline in mTSS at 24 weeks, BARI monotherapy vs MTX monotherapy

HC4: Change from baseline in mTSS at 24 weeks, BARI+MTX vs MTX monotherapy

HM5: SDAI remission at 24 weeks, BARI monotherapy vs MTX monotherapy

HC5: SDAI remission at 24 weeks, BARI+MTX vs MTX monotherapy

Table 39: Results of Multiplicity-controlled Hypothesis Testing in Study JADZ

Realized Step in Procedure[a]	Primary or Key Secondary Endpoint	Type I Error Rate Allocated to Test	Nominal P-value	Result in Significance Testing
1	ACR20, 4-mg monotherapy vs MTX (non-inferiority)	0.05	≤0.001	Significant
2	ACR20, 4-mg + MTX vs MTX	0.045	≤0.001	Significant
3	DAS28-CRP, 4-mg + MTX vs MTX	0.045	≤0.001	Significant
4	HAQ-DI, 4-mg + MTX vs MTX	0.045	≤0.001	Significant
5	ACR20, 4-mg monotherapy vs MTX (superiority)	0.0275	0.003	Significant
6	DAS28-CRP, 4-mg monotherapy vs MTX	0.0275	≤0.001	Significant

Realized Step in Procedure[a]	Primary or Key Secondary Endpoint	Type I Error Rate Allocated to Test	Nominal P-value	Result in Significance Testing
7	HAQ-DI, 4-mg monotherapy vs MTX	0.0275	≤0.001	Significant
8	SDAI remission, 4-mg + MTX vs MTX	0.0063333	≤0.001	Significant
9	SDAI remission, 4-mg monotherapy vs MTX	0.0036667	0.003	Significant
10	mTSS, 4-mg + MTX vs MTX	0.0316667	0.026	Significant
11	mTSS, 4-mg monotherapy vs MTX	0.05	0.158	Not Significant

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-CRP = Disease Activity Score 28 using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; MTX = methotrexate; SDAI = Simplified Disease Activity Index; vs = versus.

[a] Order of procedure steps not uniquely defined. Representative example shown.

11.1. JADW Sensitivity Analyses

At the primary analysis timepoint (Week 12), the vast majority of patients remained in the study on randomized treatment to provide observed data for the primary and key secondary analyses (placebo: 86%; baricitinib 2-mg: 91%; baricitinib 4-mg: 94%). A 'worst comparison' imputation was applied that assigned ACR20 response to patients who had discontinued or had missing data from the placebo group while assigning non-response to patients from the baricitinib groups. Even under such an extreme form of missing data imputation, baricitinib 4-mg provided a significantly higher ACR20 response rate than placebo (55% vs 41%, p=0.007). The trend also favored baricitinib 2-mg but was no longer statistically significant (48% vs 41%, p=0.149).

Tipping point analyses were applied to key secondary endpoints at the primary analysis timepoint. Assuming that the missing data from the placebo group followed the same mean response as was observed in patients without missing data, missing data from the baricitinib groups were made incrementally less favorable until the comparison was no longer statistically significant. Table 40 shows the multiples of the treatment difference in the observed data that were required of the imputed data, but in the opposite direction as observed. For example, for DAS28-CRP, the missing data would have had to trend 4-5 times the magnitude of effect of the observed data, but in the opposite direction, to overturn the statistically significant findings.

Table 40: Tipping Point Multiples for Key Secondary Endpoints in Study JADW

Key Secondary Endpoint (Week 12)	Baricitinib 2-mg vs Placebo			Baricitinib 4-mg vs Placebo		
	Observed Difference	Delta at Tipping Point	Tipping Point Multiple	Observed Difference	Delta at Tipping Point	Tipping Point Multiple
DAS28-CRP	-0.71	> +3.5	3.9	-0.98	> +6.0	5.1
HAQ-DI	-0.17	> +2.0	10.8	-0.22	> +3.0	12.6

Abbreviations: DAS28-CRP = Disease Activity Score 28 using C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index.
Delta equals the amount added to each imputed observation in the baricitinib group. No delta was added to the placebo group.
Indicated treatment is in addition to existing (1-2) background cDMARDs.

11.2. JADX Sensitivity Analyses

At the primary analysis timepoint (Week 12), the vast majority of patients remained in the study on randomized treatment to provide observed data for the primary and key secondary analyses (placebo: 91%; baricitinib 2-mg: 94%; baricitinib 4-mg: 94%). Even under the extreme "worst comparison" analysis, baricitinib 4-mg provided a significantly higher ACR20 response rate than placebo (61% vs 49%, p=0.012), as did baricitinib 2-mg (67% vs 49%, p≤0.001). Results of tipping point analyses as applied to key secondary endpoints at the primary analysis timepoint are shown in Table 41. For example, for DAS28-CRP, the missing data would have had to trend >6-9 times the magnitude of effect of the observed data, but in the opposite direction, to overturn the statistically significant findings.

Table 41: Tipping Point Multiples for Key Secondary Endpoints in Study JADX

Key Secondary Endpoint (Week 12)	Baricitinib 2-mg vs Placebo			Baricitinib 4-mg vs Placebo		
	Observed Difference	Delta at Tipping Point	Tipping Point Multiple	Observed Difference	Delta at Tipping Point	Tipping Point Multiple
DAS28-CRP	-0.76	> +8.0	9.5	-0.85	> +6.5	6.6
HAQ-DI	-0.20	> +3.0	14.0	-0.20	> +1.5	6.5
Morning Joint Stiffness duration (minutes)				-41.2	> +60	0.5
Morning Joint Stiffness Severity, NRS				-0.89	> +3.0	2.4
Worst Tiredness, NRS				-0.63	> +0.5	0
Worst Joint Pain, NRS				-0.99	> +4.5	3.5

Abbreviations: DAS28-CRP = Disease Activity Score 28 using C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; NRS = numeric rating scale.
Delta equals the amount added to each imputed observation in the baricitinib group. No delta was added to the placebo group.

11.3. JADZ Sensitivity Analyses

At the primary analysis timepoint (Week 24), the vast majority of patients remained in the study on randomized treatment to provide observed data for the primary and key secondary analyses (MTX: 87%; baricitinib 4-mg: 92%; baricitinib 4-mg + MTX: 88%). Tipping point analyses were applied to the primary and key secondary endpoints at the primary analysis timepoint. Table 42 shows the multiples of the treatment difference in the observed data that were required of the imputed data, but in the opposite direction as observed. For example, for DAS28-CRP, the missing data would have had to trend > 3-4 times the magnitude of effect of the observed data, but in the opposite direction, to overturn the statistically significant findings.

Table 42: Tipping Point Multiples for Key Secondary Endpoints in Study JADZ

Key Secondary Endpoint (Week 24)	Baricitinib 4-mg vs MTX			Baricitinib 4-mg + MTX vs MTX		
	Observed Difference	Delta at Tipping Point	Tipping Point Multiple	Observed Difference	Delta at Tipping Point	Tipping Point Multiple
ACR20	+14.1%	< -45%	2.2	+17.2%	< -68%	3.0
DAS28-CRP	-0.70	> +3.0	3.3	-0.89	> +4.5	4.1
HAQ-DI	-0.26	> +2.0	6.7	-0.21	> +1.25	5.0

Key Secondary Endpoint (Week 24)	Baricitinib 4-mg vs MTX			Baricitinib 4-mg + MTX vs MTX		
mTSS	-0.27	0	n/a	-0.35	> +0.3	0

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-CRP = Disease Activity Score 28 using C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; mTSS = modified Total Sharp Score; MTX = methotrexate.
Delta equals the amount added to each imputed observation in the baricitinib group. No delta was added to the methotrexate group.

11.4. JADV Sensitivity Analyses

At the primary analysis timepoint (Week 12), the vast majority of patients remained in the study on randomized treatment to provide observed data for the primary and key secondary analyses (placebo: 93%; baricitinib 4-mg: 97%). Even under the extreme 'worst comparison' analysis, baricitinib 4-mg provided a significantly higher ACR20 response rate than placebo (70% vs 47%, $p \leq 0.001$). Results of tipping point analyses as applied to key secondary endpoints at the primary analysis timepoint are shown in Table 43. For example, for DAS28-CRP, the missing data would have had to trend >5 times the magnitude of effect of the observed data, but in the opposite direction, to overturn the statistically significant findings.

Table 43: Tipping Point Multiples for Key Secondary Endpoints in Study JADV

Key Secondary Endpoint (Week 12)	Baricitinib 4-mg vs Placebo		
	Observed Difference	Delta at Tipping Point	Tipping Point Multiple
DAS28-CRP	-1.26	> +8	5.3
HAQ-DI	-0.32	> +3	8.4
mTSS (Week 24)	-0.44	> +3.7	7.4
Morning Joint Stiffness duration (minutes)	-29.4	> +135	3.6
Morning Joint Stiffness Severity, NRS	-1.03	> +10	8.7
Worst Tiredness, NRS	-0.78	> +7.0	8.0
Worst Joint Pain, NRS	-1.13	> +10	7.8

Abbreviations: DAS28-CRP = Disease Activity Score 28 using C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; mTSS = modified Total Sharp Score; MTX = methotrexate; NRS = numeric rating scale.
Delta equals the amount added to each imputed observation in the baricitinib group. No delta was added to the placebo group.