Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Baricitinib

Proprietary Product Name: Olumiant

Sponsor: Eli Lilly Australia Pty Ltd

March 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% (improvement) Score
ACR50	American College of Rheumatology 50% (improvement) Score
ACR70	American College of Rheumatology 70% (improvement) Score
AE	Adverse event
ALT	Alanine transaminase
Anti-CCP	Anti-cyclic citrullinated peptide
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
AUC	Area under the drug-concentration time curve in plasma
$AUC_{0-\infty}$	Area under the drug-concentration time curve in plasma from time zero to infinity
BAR	Baricitinib
BCS	Biopharmaceutics Classification System
BD	Twice daily (*bis in die*)
BRCP	Breast cancer resistance protein
BSA	Body surface area
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CHMP	Committee on Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum serum drug concentration
CPK	Creatine phosphokinase
CrCL	Creatinine clearance
CRP	C-reactive protein

Abbreviation	Meaning
CS	Corticosteroids
CV	Coefficient of variation
DAS	Disease Activity Score
DAS28	Disease Activity Score + 28 joint assessment
DMARD	Disease modifying anti-rheumatic drug
EAIR	Exposure adjusted incidence rate
ECG	Electrocardiograph
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
ES	Erosion Score
ESR	Erythrocyte sedimentation ratio
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDA	Food and Drug Administration
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMR	Geometric mean ratio
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCQ	Hydroxychloroquine
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IUPAC	International Union for Pure and Applied Chemistry
IV	Intravenous

Abbreviation	Meaning
JAK	Janus kinase
JSN	Joint space narrowing
K_m	Michaelis constant; substrate concentration at half the maximum velocity of a reaction
LEF	Leflunomide
LEP	Linear extrapolation
LS	Least squares
LTE	Long term extension
MATE2-K	Multidrug and toxin extrusion protein 2-K
MCP-1	Monocyte chemoattractant protein-1
MHRD	Maximum human recommended dose
mITT	Modified Intention-To-Treat
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NK	Natural killer
NOAEL	No observable adverse effect level
NRI	Non Responder Imputation
NSAID	Non-steroidal anti-inflammatory drug
OAT	Organic anion transporter
PBMC	Peripheral blood mononuclear cell
PBO	Placebo
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PO	Orally (*per os*)

Abbreviation	Meaning
PopPK	Population pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
PY	Patient years
QD	Once daily (*quaque die*)
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SD	Standard deviation
SDAI	Simplified Disease Activity Index
$t_{1/2}$	Half life
Th	T helper (cell)
t_{max}	Time to maximum drug concentration
US	United States
VTE	Venous thromboembolism
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	19 January 2018
Date of entry onto ARTG:	23 January 2018
ARTG number:	277905
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Baricitinib
Product name:	Olumiant
Sponsor's name and address:	Eli Lilly Australia Pty Ltd 112 Wharf Road, West Ryde, NSW, 2114
Dose form:	Film coated tablets
Strength:	2 mg and 4 mg
Container:	Blister pack
Pack sizes:	7 and 28 tablets
Approved therapeutic use:	*Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately, or who are intolerant, to one or more DMARDs.* *Olumiant can be taken as monotherapy or in combination with cDMARDs, including methotrexate (MTX).*
Route of administration:	Oral
Dosage:	Therapy with Olumiant should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis. The recommended dose of Olumiant is 4 mg once daily. Olumiant may be used as monotherapy or in combination with cDMARDS.

Product background

This AusPAR describes the application by the sponsor to register the new chemical entity baricitinib as Olumiant for the following indication:

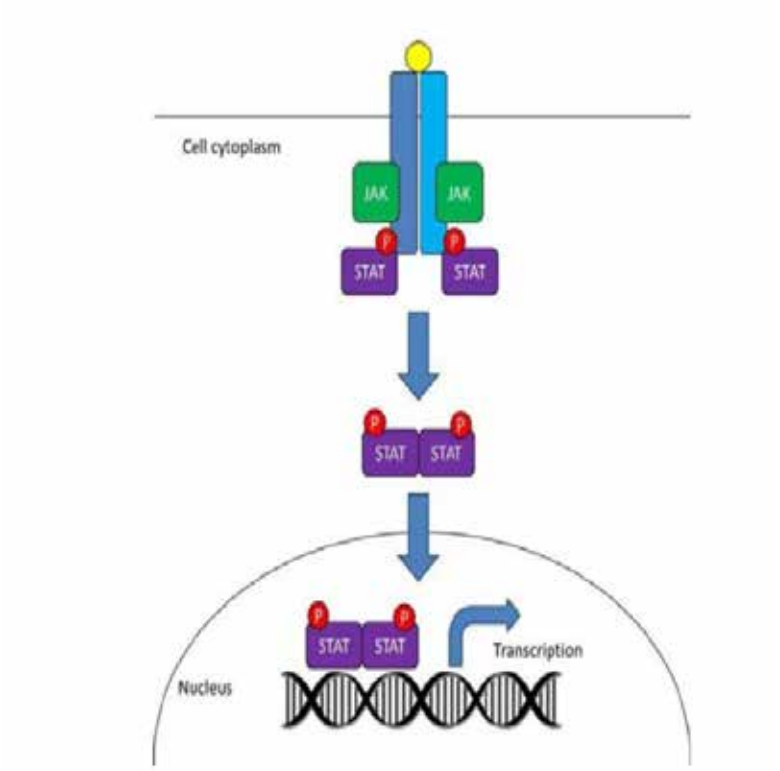
> *Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients.*
>
> *Olumiant has been shown to improve physical function, reduce the signs and symptoms of RA and inhibit the rate of progression of joint damage.*

Baricitinib is a new chemical entity for the treatment of moderate to severe rheumatoid arthritis (RA). The sponsor is requesting 2 mg and 4 mg strength film coated tablets for once daily oral administration. The mechanism of action of baricitinib (BAR) in rheumatoid arthritis is understood to be via Janus kinase inhibition.

In humans there are 4 types of Janus kinase enzymes: JAK 1, JAK2, JAK3 and tyrosine kinase 2. Part of the tyrosine kinase family, these are intracellular enzymes that transit signals from cytokines binding to receptors on the cell surface to signal transducers and activators of transcription (STATs) that are important in inflammatory processes.

Figure 1 (shown below) provides a depiction of the JAK-STAT signalling pathway influenced by BAR and tofacitinib. The JAK/STAT cascade is a mechanism by which an extracellular signal can stimulate an intranuclear transcription response. Cytokines (yellow dot) binding to the cell surface receptors (blue columns) results in activation JAK and the cross phosphorylation of receptors. STATs (purple rectangles) dimerise and move to the nucleus were they bind to regulatory sequences to activate the expression of pro-inflammatory proteins, including those involved in RA.

Figure 1: Diagrammatic schema of the JAK-STAT signalling cascade



JAK1 is preferentially expressed in T lymphocytes and mediates the common gamma (γ) chain cytokines, including interleukins (IL) IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, which are integral to lymphocyte activation, proliferation and function. The predicted side effects of JAK1 inhibition include infection, hyperlipidaemia and possible natural killer (NK) cell

effects. JAK2 affects erythropoietin, thrombopoietin, interferon and Granulocyte-macrophage colony-stimulating factor (GM-CSF). The predicted side effects of JAK2 inhibition include infection, anaemia, neutropaenia and thrombocytopaenia. BAR also significantly inhibits IL-6 signalling (JAK1 and JAK2 inhibition) and abrogates the expression of the IL-23 receptor (mostly JAK2 inhibition), which subsequently blocks the differentiation of T helper (Th) 17 cells, important mediators in the pathogenesis of RA.

RA is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. Patients with moderate to severely active disease have persistent systemic inflammation with elevated acute phase proteins and pro-inflammatory cytokines contributing to symptoms of fatigue, pain, joint stiffness and associated comorbidities of cardiovascular disease, infection, mental health disorders and malignancies. RA patients have an increased risk of venous thromboembolism.

Current pharmaceutical therapy options include non-steroidal anti-inflammatory drugs (NSAID), selective cyclooxygenase 2 (COX-2) inhibitors, and conventional disease modifying antirheumatic drugs (cDMARDs) such as methotrexate (MTX). Biological DMARDs (bDMARDs) approach the control of RA from different mechanisms, including tumour necrosis factor inhibition (adalimumab, etanercept, golumimab, infliximab and certolizumab pegol), IL-1 (anakinra) or IL-6 (tocilizumab) inhibition, T cell co-stimulation modulation (abatacept) and B cell depletion (rituximab) and JAK inhibition (tofacitinib). The high molecular weight biological medicines bind to cell surface molecules or secreted proteins and inhibit or modulate the intercellular pathways without impact on intracellular message signalling whereas the JAK inhibitors act intracellularly. Typical bDMARDs for ACR20 response rates are 50 to 65% and for ACR50, 35 to 50% in clinical trials.[1]

Regulatory status

No previous submissions for baricitinib (Olumiant) have been submitted for evaluation in Australia.

BAR 2 mg was approved in the United States of America (USA) on 31 May 2018.

BAR was authorised in May 2017in the European Union (EU) for the following indication:

> *'Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Olumiant may be used as monotherapy or in combination with methotrexate'. (see sections 4.4, 4.5 and 5.1 for available data on different combinations)'.*

Health Canada approved BAR 2 mg on 20 August 2018

There are two related drugs currently registered in Australia. Tofacitinib for RA and ruxolitinib which is registered for the treatment of myelofibrosis in certain circumstances and polycythaemia rubra vera.

The submission was presented in electronic format and comprised data covering quality, nonclinical and clinical domains along with their associated summary documents.

[1] ACR responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a ≥20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥20% improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	1 August 2016
First round evaluation completed	17 January 2017
Sponsor provides responses on questions raised in first round evaluation	16 March 2017
Second round evaluation completed	4 December 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	26 October 2017
Sponsor's pre-Advisory Committee response	9 November 2017
Advisory Committee meeting	30 November 2017 – 1 December 2017
Registration decision (Outcome)	19 January 2018
Completion of administrative activities and registration on ARTG	23 January 2018
Number of working days from submission dossier acceptance to registration decision*	163

*Target timeframe for standard applications is 220 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Drug substance (active ingredient)

The active pharmaceutical ingredient (API) baricitinib is a non-hygroscopic white to practically white to light pink powder. The drug substance is baricitinib its chemical name

is {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile according to the IUPAC nomenclature.[2]

Baricitinib is practically insoluble in water, slightly soluble in 0.1 N HCl and 0.01 N HCl and very slightly soluble in ethanol. In other physiological pH media (pH 4.5 acetate buffer, pH 6.0 phosphate buffer and pH 7.6 phosphate buffer), the API is practically insoluble.

Baricitinib (molecular weight: 371.4) is an azetidine with 3 aromatic rings. Baricitinib can exist in a number of polymorphic forms. The polymorphic form is the anhydrous crystalline form I.

Baricitinib is achiral.

The pH of baricitinib is 7.31 (for 10 mg/mL suspended in water). The dissociation constants (pKas) are 4.0 (weakly basic) and 12.6 (weakly acidic).

The proposed tablets of baricitinib contain the free base form of baricitinib drug substance which exhibits high solubility, according to Biopharmaceutics Classification System (BCS) (that is, the highest dose strength is soluble in less than 250 mL water over a pH range of 1 to 7.5), and low-to-moderate in vitro permeability in the Caco-2 cell model.

Baricitinib administered orally is rapidly absorbed and absorption is dose proportional (Phase II studies showed). The median time to maximum drug concentration (t_{max}) is approximately 1 h. The absolute bioavailability is approximately 80% (78.9%). Administration with meals was not associated with a clinically relevant effect on exposure. The definitive food effect study (Study JADH) using Phase II tablets, a high fat meal decreased the mean area under the drug-concentration time curve in plasma (AUC) and maximum serum drug concentration (C_{max}) of baricitinib by approximately 11% and 18%, respectively, and delayed the median t_{max} by 0.5 h following administration of 8 mg baricitinib. The magnitude of these changes was within the inter-subject variability of the pharmacokinetics (PK) of baricitinib and was, therefore, not considered clinically meaningful. Thus, baricitinib was administered in Phase III studies without regard to the timing of meals.

Steady state was reached between the second and third doses. The following pharmacokinetic parameters were obtained: $C_{max,ss}$ 53.4 ng/mL (28% coefficient of variation (CV)), t_{max} 1 h (range 0.5 to 3.0), $AUC_{\tau, ss}$ 477.6 ng.h/mL (40.7% CV).

Baricitinib metabolism is mediated by CYP3A4 with approximately 6% of the dose identified as undergoing biotransformation.[3] No metabolites were quantifiable in plasma. In a clinical pharmacology study, baricitinib was excreted predominately as unchanged drug in urine (69%) and faeces (15%) and only 4 minor oxidative metabolites (3 in urine, 1 in faeces) were identified.

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. Baricitinib is a substrate of the P-glycoprotein (Pgp), breast cancer resistant protein (BCRP), organic antion transporter 3 (OAT3) and Multidrug and toxin extrusion protein 2-K (MATE2-K) transporters, which play roles in drug distribution.

[2] IUPAC: International Union of Pure and Applied Chemistry

[3] Cytochrome P450 (CYP) enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

Renal elimination is the principal mechanism for the clearance of baricitinib through glomerular filtration and active secretion via OAT3, Pgp, BCRP and MATE2-K.In a clinical pharmacology study, approximately 75% of the administered dose was eliminated in the urine, while about 20% of the dose was eliminated in the faeces. The half-life is approximately 13 h in patients with RA.

Structural characterisation was provided using appropriate methods.

The drug substance specification includes tests and limits for any unspecified impurity. The limits for the each unspecified impurity are in line with the International Conference on Harmonisation (ICH) identification threshold (ICH Q3A (R2) guidance).[4] The active substance specifications include tests for description, identification, particle size distribution, impurities, assay, loss-on-drying, residual solvents and microbial quality.

There are no specified impurities. Impurities were described, classified as process-related impurities, or degradants. Potential genotoxic impurities were discussed were below the qualification threshold. Residual solvents are controlled in the API according to ICH requirements.

Baricitinib drug substance is a compound with low-to-moderate permeability and high solubility under the conditions designated by the BCS. The API is considered to be BCS Class 3 (high solubility (that is, the highest dose strength is soluble in less than 250 mL water over a pH range of 1 to 7.5), low permeability).

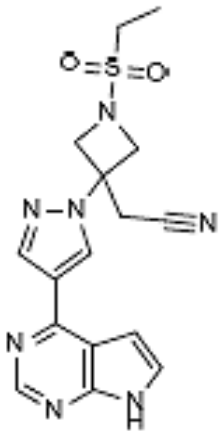
Nomenclature

Olumiant (baricitinib) has the IUPAC name of 2-(3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl) acetonitrile.

Structure

The following figure (Figure 2) describes the chemical structure of baricitinib.

Figure 2: Structural formula of baricitinib



$C_{16}H_{17}N_7O_2S$; molecular mass = 371.42

[4] ICH Q3A (R2): Guideline on impurities in new drug substances; current Step 4 version, dated 25 October 2006. The guideline addresses the chemistry and safety aspects of impurities, including the listing of impurities in specifications and defines the thresholds for reporting, identification and qualification.

Drug product

The proposed film coated tablets are distinguished by size, colour (shades of pink) and shape:

- 2 mg: 'Light pink, oblong, debossed with 'Lilly' script on one side and '2' on the other'.
- 4 mg: 'Medium pink, round, debossed with 'Lilly' script on one side and '4' on the other'

The tablet manufacturing process uses standard processes such as mixing, dry granulation, sieving, roller compaction, blending, compression, film coating and packaging. The process has been validated and in-process controls are adequate for the dose form.

The excipients are conventional.

The tablets are packed in polyamide (PA)/aluminium (Al)/polyvinyl chloride (PVC)/Al blisters and PVC/PE/Polychlorotrifluoroethylene (PCTFE) (Aclar)/Al blisters, in cartons containing 7 and 28 tablets.

The finished product specifications include tests for description (visual), identification (IR, for the API and colour reactions for relevant pigments titanium dioxide and iron oxide red), assay (HPLC), impurities (HPLC), uniformity of dosage units (EP), and dissolution (HPLC/UV detection). Assay limits comply with Therapeutic Goods Order 78 (TGO 78).[5] Impurity limits have been qualified. Tablet dissolution is tested using a paddle apparatus.

The stability data provided supports a shelf life of 24 months when stored below 30°C in the proposed packaging.

Biopharmaceutics

Initial studies in healthy subjects and early Phase II studies used capsule formulations containing the phosphate salt of baricitinib. Subsequently, an immediate-release tablet formulation (referred to as Phase II tablet) containing baricitinib free base, a thermodynamically stable anhydrous form, was developed. The final commercial tablet formulation containing baricitinib free base was developed and used for all the Phase III studies in RA patients.

All Phase III studies used the proposed finished product formulations and appearance.

Throughout development, 5 clinical biopharmaceutic studies in healthy subjects were conducted investigating relative bioavailability and factors affecting the bioavailability of baricitinib.

The commercial tablet drug product formulation and manufacturing process were used throughout the Phase III clinical program and for the primary stability program; hence no formal bioequivalence study was conducted. Nevertheless, Study 14V-MC-JAGO (Study JAGO) showed that the bioavailability of a single 4 mg Phase II tablet and a single 4 mg commercial tablet was comparable.

In addition, studies were performed to characterise the effect of drug substance particle size, food, and increased gastric pH on the bioavailability of baricitinib. Increase in gastric pH, following administration of a proton pump inhibitor (omeprazole), with baricitinib commercial tablets had no significant effect on the bioavailability of baricitinib (Study JAGF).

Pharmacokinetic studies included are discussed in the clinical evaluation report [see Attachment 2].

[5] Therapeutic Goods Order No. 78: General Requirements for Tablets and Capsules

The free base form of the drug substance was selected for commercialisation due to improved physicochemical properties relative to the salt forms evaluated. The phosphate salt form of the API was used to support Phase I and early Phase II clinical studies.

- In Phase I and IIa clinical studies, a capsule was developed 4 mg to 10 mg strengths.
- In Phase IIb studies, a different capsule size was used and capsules were made from a common blend for 1 mg to 4 mg capsules.
- In other Phase II studies, a tablet formulation using the free base form of the drug substance was identified. Additional tablet strengths were developed for other Phase II studies (Phase II tablet formulation).
- The initial commercial formulation development led to the Phase II tablet formulation with a dose of 8 mg. The Phase II tablet formulation used API with different particle sizes to understand the impact of drug substance particle size distribution (PSD) on pharmacokinetics. Particle size had no significant impact on exposure.

The PK of baricitinib is dose proportional up to 30 mg.

The key biopharmaceutic studies provided findings are summarised below.

Study I4V-MC-JAGM (absolute bioavailability study)

The absolute bioavailability of baricitinib was investigated in a Phase I open label study conducted in healthy subjects (7 male; 1 female) to estimate the absolute bioavailability, and to characterise the PK, of baricitinib following administration of a single oral dose of 4 mg baricitinib and a single 1 h intravenous (IV) baricitinib infusion of 4 µg [13C4D315N]-baricitinib. Subjects received a single oral dose of baricitinib (4 mg), and at approximately the same time an IV administration of 4 µg [13C4D315N]-baricitinib was started. The study title is '*an absolute bioavailability study of baricitinib in healthy subjects using the intravenous tracer method*'.

The study compared a single dose of 1 x 4 mg tablet , administered orally in the fasted state with [13C4D315N]-baricitinib administered as an infusion solution of 0.25 µg/mL at 10.7 mL.h, 16 mL volume.

The absolute bioavailability (area under the drug-concentration time curve in plasma from time zero to infinity ($AUC_{0-\infty}$) of baricitinib was 78.9% (90% confidence interval (CI): 76.9 to 81.0%), median t_{max} IV was 1 h (range 0.5 to 2 h). For oral baricitinib, plasma concentrations declined in a biphasic manner after t_{max}, and the $t_{1/2}$ was 8.6 h. For IV baricitinib, the $t_{1/2}$ was shorter (4.1 h), as the terminal elimination phase was not fully defined because concentrations were only quantifiable up to 24 h post-dose.

The study design, conduct and analysis were considered to be satisfactory. See Attachment 2 for further details.

Study I4V-MC-JADH (relative bioavailability study)

The study title in the report is '*Relative bioavailability of the LY3009104 free base test formulation compared to the reference phosphate salt formulation and the effect of food on the bioavailability of the test formulation in healthy subjects*'.

The relative bioavailability of 8 mg (2 x 4 mg tablets) baricitinib (proposed formulation, as the free base) compared to the Phase II baricitinib phosphate salt capsule formulations (2 formulations with particle sizes of 20 and 50 µm) and the effect of a high fat meal on the bioavailability baricitinib administered as the free base tablet, when administered to healthy subjects.

This was an open label, 4 period 4 sequence 4 treatment, randomised, crossover study. Subjects received a single oral dose of 8 mg baricitinib as each of the following 4 treatments:

1. Two 4 mg phosphate salt capsules, administered in the fasted state (reference).
2. 8 mg base tablet (target API particle size of [information redacted]), administered in the fasted state (test).
3. 8 mg free base tablet (target API particle size of [information redacted]), administered in the fasted state (test).
4. 8 mg free base tablet (target API particle size of [information redacted]), administered after a high fat, high calorie meal (test).

In the fasted state, there was no statistically significant difference in the AUC or C_{max} of baricitinib between the free base tablets (2 formulations with particle sizes of [information redacted]) and the phosphate salt capsule with the 90% CIs spanning unity. The 90% CIs for AUC and C_{max} were within the bioequivalence limits of 0.80 to 1.25. There was no significant difference in t_{max} between the formulations. The mean $t_{1/2}$ of baricitinib was similar among the formulations in the fasted state.

For the tablet (free base [information redaced]) formulation, significant reductions were observed in $AUC_{0-\infty}$ and AUC_{0-t} of 11% and C_{max} of 18% in the fed state compared to the fasted state, with the 90% CIs not spanning unity. The 90% CIs were within the bioequivalence limits of 0.80 to 1.25 for AUC, but the lower limit of the 90% CI for C_{max} fell slightly below the bioequivalence boundary at 0.727.

The median t_{max} occurred later in the fed state compared to the fasted state, with the difference (0.5 h) being statistically significant. The mean $t_{1/2}$ of baricitinib was similar under fed and fasted conditions.

Exposure to baricitinib was found to be relatively insensitive to the effects of drug substance form (phosphate salt versus free base), particle size distribution in the range studied, and drug product formulation.

The definitive food effect study was conducted using the Phase II tablets, which have similar in vitro dissolution to, and were shown in the relative bioavailability study (Study JAGO) to be comparable to the commercial tablets. A high fat meal decreased the mean AUC and C_{max} of baricitinib by approximately 11% and 18%, respectively (Study JADH), and delayed the t_{max} by 0.5 h following administration of 8 mg baricitinib as free base in Phase II tablets.

The CI of the mean ratio of the fed and fasted AUC were 80 to 125% and the change in C_{max} is contained within the variability in the PK of baricitinib, therefore, was not considered clinically meaningful. On this basis, the sponsor concluded that, baricitinib can be administered with or without food.

The mean C_{max}, $AUC_{0-\infty}$ t_{max} values for baricitinib following administration the free base tablet formulations were similar to the phosphate salt capsule (for the [information redacted] tablet AUC 90% CI was 1.02 (0.95 to 1.10); C_{max} 90% CI was 0.98 (0.87 to 1.10); and t_{max} was 1.0 (0.5 to 3.0) and for the [information redacted] tablet AUC was 1.02 (0.95 to 1.09), and C_{max} 90% CI was 0.96 (0.85 to 1.08) and t_{max} was 1.0 (0.5 to 3.0)).

The study design, conduct and analysis were considered to be satisfactory. See Attachment 2 for further details.

Study I4V-MC (JE)-JAGO (bioequivalence of market and clinical trial formulations)

This was a Phase I, single centre, open label, randomised, 5 period, 4 sequence, and crossover study in healthy male Japanese subjects. The study title is 'Relative

bioavailability of the baricitinib (Study LY3009104) commercial tablet compared to the Phase II tablets and the effect of food on the bioavailability of the commercial tablet in healthy Japanese subjects.'

This investigated the relative bioavailability of two 4 mg baricitinib commercial tablets compared with one 8 mg baricitinib Phase II tablet in healthy subjects and the effect of a low fat meal on bioavailability of the 4 mg baricitinib commercial tablet in healthy subjects. The formulations compared were:

- 4 mg Phase II tablet
- 4 mg commercial tablet
- 8 mg Phase II tablet

Comparative dissolution data were provided for the tablets, (tested at 5, 15, 30, 45 mins). Dissolution of all batches was > 85% at the 15 min time point and > 93% at the 30 min time point and was demonstrated to be similar.

This study concluded that the bioavailability of a single 4 mg Phase II tablet and a single 4 mg commercial tablet was comparable ($AUC_{0-\infty}$) geometric mean ratio (GMR) = 0.99; 90% CI 0.95 to 1.02, C_{max} GMR = 0.96; 90% CI 0.88 to 1.04.

The 2 mg and 4 mg commercial tablets were shown to be similar by dissolution testing. Dose proportionality between 2 mg and 4 mg was also demonstrated for the commercial tablets in Phase III studies (primary Phase II/III population pharmacokinetic (popPK) analysis.

The capsules that were used for the dose finding portion in Study JADN (Part A) were bridged to the baricitinib commercial tablets used in Phase III based on data from this study (Study JAGO), along with Study JADH.

The study design, conduct and analysis were considered to be satisfactory. See Attachment 2 for further details.

Quality summary and conclusions

In the sponsor's post-first round response dated 13 April 2017, the sponsor amended the provisional ARTG record (PAR) description of the tablets. The finished product specifications were amended to be consistent with this in the sponsor's email dated 24 April 2017.

There are no other outstanding issues with the chemistry and quality control aspects of the products.

IV. Nonclinical findings

Introduction

The sponsor has submitted a high quality ICH;[6] compliant dossier to support the registration of baricitinib (Olumiant). Olumiant is not intended for use in juveniles or children; maximum human recommended dose (MHRD) 4 mg once daily (QD) orally (PO); 0.08 mg/kg/day, 132 mg/m^2 (based on 50 kg body weight and Michaelis constant (K_m) = 33); maximum duration of use is unstated but is assumed to be chronic (that is, potentially

[6] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Us

≥ 7 years)). Baricitinib is a selective reversible inhibitor of JAK types 1 and 2 (JAK1 and JAK2; targets JAK-signal transducer of activators of transcription (STAT) pathways). Related members of the JAK inhibitor class of drugs include momelotinib, ruxolitinib and pacritinib for myeloproliferative disorders and tofacitinib for rheumatoid arthritis.

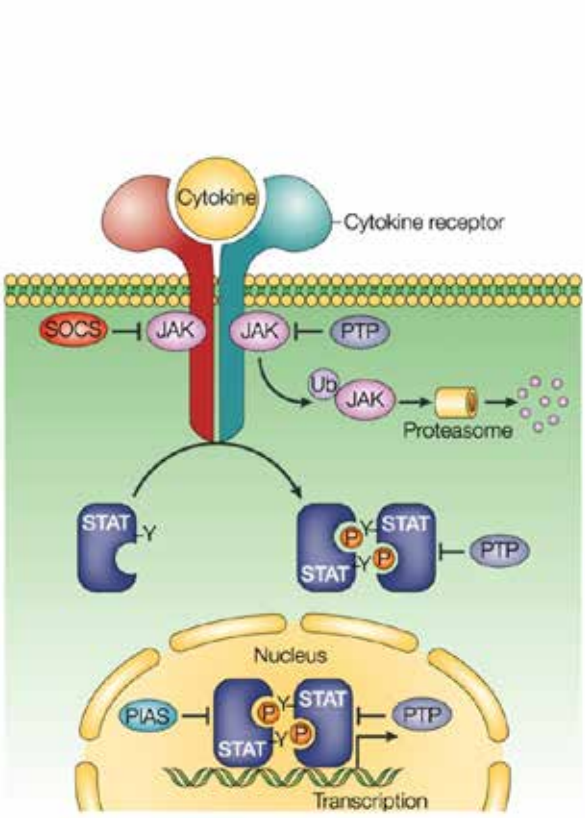
Pharmacology

No studies with concurrent cDMARD treatment were supplied.

Primary pharmacology

The general mode of action of the JAK-STAT pathways and associated cytokines are as follows:[7]

Figure 3: General mode of action of the JAK-STAT pathway



Janus kinases	Associated cytokines
Janus kinase 1	interleukin-2, 4, 6, 7, 9, 10, 11, 13, 15, 19, 20, 21, 22, 24, 26, 29 oncostatin M leukaemia inhibitory factor granulocyte colony stimulating factor tumour necrosis factor
Janus kinase 2	erythropoietin growth hormone prolactin thrombopoietin oncostatin M leukaemia inhibitory factor granulocyte colony stimulating factor leptin tumour necrosis factor interleukin-3, 5, 6, 13 interferon gamma
Janus kinase 3	interleukin-2, 4, 7, 9, 15, 21
Tyrosine kinase 2	interleukin-10, 12, 22, 26, 29 interferon alfa/beta/omega interleukin-28 alfa/beta

Kubler P (2014) Janus kinase inhibitors: Mechanisms of action. Aust Prescr; 37:154-171

Baricitinib has a high selectivity for JAK1 and JAK2 with lower potency for JAK3 and tyrosine kinase 2 (TYK2); that is, it simultaneously targets multiple pro-inflammatory cytokine pathways implicated in the pathogenesis of RA (IL-6, GM-CSF and interferons (IFN)).

In vitro

The relative potencies of the effects of baricitinib based on 50% inhibitory concentration (IC_{50}) values derived from in vitro studies that used recombinant truncated JAK catalytic domains were: JAK2 (IC_{50} = 5.7 nM, around 0.08 x MHRD unbound C_{max}), and approximately equal to JAK1 (IC_{50} = 5.9 nM, around 0.08 x MHRD unbound C_{max}) > TYK2 (IC_{50} = 53 nM, around 0.7 x MHRD unbound C_{max}) > JAK3 (IC_{50} > 400 nM, more than or

[7] Kubler P (2014) Janus kinase inhibitors: Mechanisms of action. Aust Prescr; 37:154-171

around 6 x MHRD unbound C_{max}). Baricitinib administered at the MHRD is likely to display potent, selective JAK1 and JAK2 inhibition and some degree of TYK2 inhibition and minimal JAK3 inhibition.

Baricitinib inhibited phytohaemagglutinin (PHA) + cytokine (stimulatory cytokines IL-2, IL-23, IL-12, IL-6) mitogenesis, JAK2/STAT3/STAT5 phosphorylation and downstream IL-17, IL-22, IFN-γ and monocyte chemoattractant protein-1 (MCP-1) production at concentrations < 0.8 x MHRD unbound C_{max} in human T cell/peripheral blood mononuclear cell (PBMC)/whole blood cultures. Overall, these data indicate that baricitinib administered at ≤ MHRD may inhibit IL-6/IL-2/IL-12/IL-23 mediated activation of JAK1/JAK2-JAK2/STAT pathways in human T cells and may inhibit subsequent downstream IFN-γ, IL-17, IL-22 and MCP-1 responses. This likely reduces IL-23-mediated differentiation of naïve $CD4^+$ T cells;[8] into T helper type 17 (Th 17) cells;[9] and IFN-γ producing T helper type 17 (Th 1) cells. All of these pathways are implicated in RA.

Dogs were about twice as sensitive to the effects of baricitinib compared with humans and rats (human IC_{50} =104 nM, rat IC_{50} 128 nM, dog IC_{50} = 49 nM) based on in vitro whole blood mitogenesis assays (consistent with higher incidence of opportunistic secondary infections in the canine chronic toxicology studies). Blood protein binding of baricitinib inactivates its pharmacological activity.

The comparative effects of baricitinib and tofacitinib in activated human peripheral blood mononuclear cell (PBMC) cultures were:

- Baricitinib inhibition of cytokine signalling was most potent for interferons and least potent against IL-10 and JAK1/3 signalling dependent cytokines including IL-4, IL-15 and IL-21.
- Baricitinib IC_{50} values were generally comparable to those of tofacitinib for IL-6, IL-10, IFN-α and IFN-γ stimulation (baricitinib IC_{50} range 6 to 246 nM (approximately equal to 0.08 to 3.4 x MHRD unbound C_{max}) depending on cell and cytokine type).
- Baricitinib IC_{50} levels for inhibition of production of the following cytokines were less than the MHRD unbound C_{max} (that is, < 72 nM) for most (but not necessarily all) PBMC cell types: IL-4, IL-5, IL-15, IL-21, IL-6, IFN-γ, IFN-α and G-CSF.
- Compared with baricitinib, tofacitinib is a more potent inhibitor of IL-10 stimulation of monocytes and IFN-α stimulated phosphorylated Signal transducer and activator of transcription 1 (pSTAT1)/pSTAT3/pSTAT5 phosphorylation (most apparent in Natural killer (NK) cells, CD4+ T cells and monocytes). Baricitinib is a more potent inhibitor of G-CSF signalling compared with tofacitinib, that is, baricitinib may be a more potent JAK2 and TYK2 inhibitor. The greatest differences between baricitinib and tofacitinib IC_{50} values were for those cytokines that signal through a JAK1/3 complex (IL-4, IL-15 and IL-21; baricitinib has lower JAK3 potency compared with tofacitinib).
- For both baricitinib and tofacitinib, the most potent inhibition of STAT3 and/or STAT5 phosphorylation (that is, the lowest IC_{50} values) occurred with IFN-α and IFN-γ signalling.

Overall, the likely most important difference between baricitinib and tofacitinib in vivo is that tofacitinib should have a greater inhibitory effect on NK cell function compared with baricitinib.

[8] CD4+ T helper cells are white blood cells that are an essential part of the human immune system. They are called helper cells because one of their main roles is to send signals to other types of immune cells, including CD8 killer cells, which then destroy the infectious particle.

[9] Th17 cells, by virtue of their production of IL-17 and IL-17F, are generally thought to be pro-inflammatory and play an important role in host defense against infection, by recruiting neutrophils and macrophages to infected tissues.

Ex vivo

Baricitinib inhibits the IL-6-STAT3 pathway in vivo, consistent with the in vitro data. Baricitinib inhibited ex vivo IL-6 stimulated STAT3 phosphorylation in whole blood assays in a dose and exposure time dependent manner following PO dosing of dogs at approximately 1 to 23 x MRHD (body surface area (BSA) comparisons). Maximal inhibition was at 1 h post dosing (earliest time point evaluated). Notably, following dosing at approximately 1 x MHRD (BSA comparison) STAT3 inhibition at time = 24 h was approximately 0.1 x that present at time = 1 h in this sensitive species, that is, the baricitinib therapeutic window at the MHRD is likely ≤ 24 h (consistent with the goal of primary pharmacological coverage for approximately equal to 50% of the day after daily dosing).

In vivo

In mice, high PO doses of baricitinib (10 mg/kg twice daily (BD), approximately equal to 23 x MHRD; BSA) caused approximately to 50% inhibition of 1-fluoro-2,4-dinitrobenzene (DNFB) induced contact hypersensitivity in the mouse ear swelling test.

In the mouse bovine collagen type II induced arthritis model, treatment with baricitinib at doses more than or approximately 7 x MHRD (BSA) for 16 day following disease induction was associated with dose-related decreases in clinical severity (≥ 39% decrease compared with that of controls) with no effects on serum anti-collagen antibody levels. Following BID dosing at approximately 23 x MHRD (BSA), baricitinib treatment significantly improved a composite score (inflammation, pannus, bone damage) of joint damage by 47%, compared with that of controls.

In the mouse anti-collagen type II antibody arthritis model, BID dosing with baricitinib at approximately 2 and 23 x MHRD respectively (BSA) resulted in 13% and 56% improvement in clinical signs of disease, respectively compared with that of controls. Treatment at approximately equal to 23 x MHRD (BSA) reduced pannus, bone damage, cartilage damage, signs of inflammation, and resulted in a 53% improvement in aggregate disease score compared with that of controls.

In the rat adjuvant arthritis model, treatment with baricitinib at around 2, 7 and 23 x MHRD (BSA comparisons) resulted in a significant dose related decrease in disease scores (≥ 24%) within 2 days of commencement of treatment. Dosing at 2 times the MHRD (BSA) resulted in a 50% decrease in paw volume compared with control after 2 weeks of treatment. Baricitinib treatment at approximately ≥ 2 x MHRD (BSA) also resulted in significant dose related suppression of joint inflammation (≥ 27% reduction), reduced tarsal width (≥ 19%), reduced bone resorption (≥ 15% reduction) and restoration of normal radiographic architecture of the tarsus. Baricitinib dosing at 23 x MHRD (BSA) for 2 weeks inhibited disease induced IFN-γ, IL-12a, IL-17, IL-21, and IL-22 mRNA (all ≥ 55% inhibition) in draining lymph nodes.

Overall, the in vivo studies submitted provided qualitative proof of concept of efficacy but direct quantitative dose extrapolation to humans is confounded by uncertainties regarding the relative sensitivities of the animal models compared with human clinical disease.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamics

Baricitinib (concentrations ≤ approximately 14 x MHRD unbound C_{max}) displayed no pharmacologically relevant interactions in a standard validated, controlled cell-based assay battery that included a wide range of receptors, ion channels and transporters.

Baricitinib at approximately 3 x MHRD unbound C_{max} selectively inhibited JAK2 and JAK3 without inhibiting 28 other kinases in human peripheral blood mononuclear cell and in

monocytic cell line lysates. It was most potent against JAK1, JAK2, and TYK2 with IC_{50} values between around 0.4 to 0.9 x MHRD unbound C_{max}, had moderate affinity for CaMK2d and CaMK2g at approximately 2 x MHRD unbound C_{max} and had negligible activity at ≥ approximately 7 x MHRD unbound C_{max} for more than 250 other kinases.

Secondary pharmacologically-induced adverse effects are unlikely at the proposed baricitinib MHRD.

Safety pharmacology

Effects on motor activity (decreased voluntary motor activity) only occurred in rats at > approximately 23 x MHRD PO (BSA).

While the effects on cardiac sodium channel ($Na_V1.5$ (SCN5a)) and potassium (I_{KS}) channels were not evaluated, the risk of QT interval prolongation via potassium channel (hERG) inhibition by baricitinib was shown to be minimal (IC_{50} > 1800 x the unbound clinical C_{max}).[10] Repeat dose toxicology studies in dogs at doses up to ≥ approximately 24 times the MHRD (AUC) showed no adverse effects on electrocardiogram (ECG) parameters. Slight elevations of heart rate and slight, transient lower arterial pressures were observed in dogs, but only at supratherapeutic doses (≥ approximately 19 x MHRD; BSA).

No effects on respiration were observed in rats following oral baricitinib dosing at C_{max} exposures approximately 23 x MHRD (BSA). The risk of adverse respiratory system events at the MHRD is low.

Pharmacokinetics

The oral pharmacokinetics of baricitinib in animals modelled the human situation (high relative exposures achieved; no human-specific metabolites). Baricitinib systemic exposure is similar following single or repeated PO dosing. For the purposes of nonclinical risk assessment, baricitinib and its phosphate salt are pharmacokinetically equivalent in rodents (equivalency assumed in dogs).

Absorption

Based on in vitro studies in caco-2 cells, baricitinib had a low to moderate apparent apical-to-basolateral enterothelial cell permeability coefficient. Drug associated radioactivity was rapidly absorbed (t_{max} = 0.75 to 1 h) following single doses in mice, rats and dogs. The plasma drug-associated radioactivity pharmacokinetic $t_{½}$ in mice was approximately 5 to 7 times lower than in rats and dogs. A small sex difference in plasma drug-associated radioactivity was apparent in rats with $t_{½}$ in males being approximately 1.6 x higher compared with females. Single dose pharmacokinetic parameters for whole blood and plasma ($AUC_{0\text{-}24h}$, C_{max}, t_{max}, $t_{½}$) were essentially equivalent across all species.

Repeat-dose toxicokinetics

Repeat daily PO dose toxicokinetic data were derived from toxicology studies in mice (28 to 176 days), rats (28 to 176 days) and dogs (1 month to 39 weeks). Baricitinib PO absorption was rapid (t_{max} 0.5 to 2 h) across species. $AUC_{0\text{-}24h}$ and C_{max} were inconsistently dose proportional over the 3 to 500 mg/kg dose range. Pharmacokinetic adaptation was minimal (generally < approximately 2 x but notably > approximately 2 x lower in hRAS males dosed at < 300 mg/kg/day in the carcinogenesis study). In most instances

[10] The QT interval is the time between the start of the QRS complex and the end of the T wave in an electrocardiogram. It represents the duration between the onset of depolarisation and the completion of repolarisation of the myocardium.

pharmacokinetic gender differences were small (< approximately 2 x for AUC_{0-24h} and C_{max}) and plasma accumulation did not occur.

Distribution

Baricitinib is unlikely to be involved drug-drug interactions involving plasma protein displacement reactions.[11] Across species, the in vitro and ex vivo protein binding of baricitinib was approximately 50% (range 33 to 60) and serum protein binding was similar to plasma protein binding.

Selective partitioning of radiolabelled (^{14}C)-baricitinib into blood cells did not occur in mice, rats, or dogs, following single PO dosing, with blood: plasma radioactivity concentration ratios of approximately 0.7 to 1.2 across species (no meaningful gender differences).

Baricitinib was rapidly absorbed (plasma t_{max} = 2 h) and widely distributed (tissue t_{max} =2 h; except large intestine t_{max} =8 h). The relative tissue levels of drug associated radioactivity in non-pigmented rats were small intestine > renal cortex > large intestine > liver > non-pigmented skin > caecum > aorta. Distribution to the gut contents, bile and urine reflected the route of exposure and major routes of elimination. Only low concentrations were detected in central nervous system (CNS) (vascular rather than extravascular neuronal distribution), bone and eye. Clinically-relevant retention of drug-derived radioactivity was not apparent at time > 168 h. Distribution in pigmented rats resembled that in non-pigmented animals except for concentration in the uveal tract (no toxicology correlates).

Metabolism

Based on in vitro human biomaterial studies baricitinib undergoes limited (10 to 16%) cytochrome P450 isozyme CYP3A4-mediated oxidation to 3 major metabolites: M3, M4 and M10. Similar results were observed in non-human biomaterial models; however low levels (0.1 to 0.6% of parent) of an animal-specific oxidised metabolite (M1) occurred in rat, dog and monkey preparations (no toxicology correlates).

Overall, the in vivo metabolite profile in animals resembled human metabolism. In humans there were no circulating metabolites, no human specific metabolites, three minor metabolites in urine and one minor metabolite in faeces (together accounting for 6% of the total dose). All identified human metabolites occurred in animals at excretion fractions ≥ human levels in at least one laboratory species with the exception of M22. In humans 3.2% of the PO dose was excreted in urine in the form of metabolite M22 whereas in laboratory species, it was present in urine and/or faeces at ≤ 0.7% of the dose. Unlike in the in vitro biomaterials studies, M4 was not detected in vivo in any of the evaluated species. None of these differences were of any apparent toxicological significance.

Excretion

In all species, baricitinib was largely excreted unchanged. Interspecies variation in excretory pathways was present (major routes: humans = urine, rodents = faeces, dogs = urine and faeces). In animals about 50% of the total dose is excreted unchanged whereas in humans 83.3% of the dose is excreted unchanged. $AUC_{0-\tau}$ in RA patients was increased by 1.3 and 1.6 fold in mild and moderate renal impairment, respectively.

[11] Palleria C, et al. J Res Med Sci. 2013 Jul;18(7):601-10; EMA CPMP/EWP/560/95/Rev.1 Corr. 2 Guideline on the investigation of drug interactions 2012.

Pharmacokinetic drug interactions

The nonclinical data imply that clinically relevant competitive substrate type drug-drug interactions are unlikely to occur at the following transporter systems: OAT1, organic cation transporter (OCT) 1, OCT2, OATP1B1, OATP1B3 and multidrug and toxin extrusion transporter 1 (MATE1). A low risk of competitive substrate type interactions is possible at OAT3, P-glycoprotein and MATE2-K. Notably, a 2 fold increase in AUC occurred with concurrent OAT3 inhibition (by probenecid; correlated with a 70% decrease in renal clearance). Moreover, clinically relevant inhibitory type drug-drug interactions are unlikely at OATP1B1 and p-glycoprotein. Weak (likely not clinically relevant) transporter inhibition type interactions are possible at OAT1, OCT1, OAT3, OCT2, BCRP, OATP1B3, MATE1, MATE2-K.

Dosing with baricitinib at the MHRD is unlikely to be associated with drug-drug interactions associated with inhibition of CYP isozymes CYP3A4, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6 or CYP1A2.[3] Due to the small fraction of baricitinib that is metabolised, clinically-relevant competitive substrate interactions at CYP3A4 are considered unlikely. Baricitinib at the MHRD is likely not a clinically relevant inducer of CYP1A2, CYP2B6, or CYP3A and is unlikely to be an activator of the human pregnane X xenosensor.

Toxicology

Acute toxicity

Acute baricitinib toxicity at the MHRD is unlikely in normal healthy individuals. Acute toxicity due to baricitinib + cDMARD treatment was not evaluated. Across species (mice, rats, dogs) the maximum lethal dose exceeded the maximum tested doses (≥ approximately 300 x MHRD; AUC and BSA).

Oral (PO) baricitinib phosphate was mildly toxic in normal healthy CD-1 mice (clinical signs: hypothermia and partially closed eyes were noted following dosing at approximately 350 x MHRD; AUC). Signs of peripheral vasodilation (ears, paw and scrotal erythema) occurred in rats at very high doses. Dogs were more sensitive compared with rodents with clinical signs occurring at ≥ approximately 15 x MHRD (BSA; clinical signs: nictitating membrane prolapse, lacrimation, emesis, decreased activity, ears erythema and tremor/ataxia).

Baricitinib was nontoxic in a rabbit acute dermal toxicity study (50% lethal dose (LD_{50}) ≥ approximately 5700 x MHRD; BSA).

Repeat-dose toxicity

Consistent with the proposed route of human clinical exposure, PO repeat dose toxicity was evaluated in ICH/Good Laboratory practice (GLP) compliant studies mice (2 strains), rats and dogs.

Relative exposure

The following table describes the relative exposures in animals versus humans (Table 1).

Table 1: Relative exposure across species

Species	Study duration (Study ID)	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL or µM.h)	Exposure ratio[#]
Mouse	4 weeks CD-1 ED27 (Study T08-07-08)	♂10	8.53 µM.h	≈7
		♂75	48.5 µM.h	≈37
		♂250	164 µM.h	≈126
		♂500	191 µM.h	≈147
		♀10	8.22 µM.h	≈6
		♀75	48.1 µM.h	≈37
		♀250	199 µM.h	≈153
		♀500	215 µM.h	≈165
	4 weeks Wild type, CByB6F1-Tg (HRAS) 2Jic mice ED28 (Study 8268827)	♂75	14765 ng·h/mL	≈31
		♂150	21793 ng·h/mL	≈46
		♂300	24030 ng·h/mL	≈50
		♀75	21755 ng·h/mL	≈46
		♀150	22664 ng·h/mL	≈47
		♀300	31271 ng·h/mL	≈65
	3 months CD-1 ED90 (Study T08-09-01)	♂10	2838 ng·h/mL	≈6
		♂75	20057 ng·h/mL	≈42
		♂150	49399 ng·h/mL	≈103
		♀10	2411 ng·h/mL	≈5
		♀75	18497 ng·h/mL	≈39
		♀150	35768 ng·h/mL	≈75
	26 weeks Hemizygous RasH2-Tg ED176 (carcinogenicity; Study 8291245)	♂15	1340 ng·h/mL	≈3
		♂40	2030 ng·h/mL	≈4
		♂300	26400 ng·h/mL	≈55
		♀10	2470 ng·h/mL	≈5
		♀30	9160 ng·h/mL	≈19

Species	Study duration (Study ID)	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL or µM.h)	Exposure ratio#
		♀150	37200 ng·h/mL	≈78
Rat	1 month SD ED28 (Study T07-11-01)	♂2	1.24 µM.h	≈1
		♂10	7.37 µM.h	≈6
		♂40	34.5 µM.h	≈27
		♀2	1.34 µM.h	≈1
		♀10	7.72 µM.h	≈6
		♀40	47.8 µM.h	≈37
	6 months SD ED181 (Study T08-04-05)	♂0.5	0.478 µM.h	≈0.4
		♂5	3.68 µM.h	≈3
		♂25	27.9 µM.h	≈21
		♂100/60	114 µM.h	≈88
		♀0.5	0.712 µM.h	≈0.5
		♀5	5.02 µM.h	≈4
		♀25	38.1 µM.h	≈29
		♀100/60	95.3 µM.h	≈73
	Minimum 90 weeks F344 ED176 (carcinogenicity; Study 8253534)	♂ 1	410 ng·h/mL	≈1
		♂ 3	1161 ng·h/mL	≈2
		♂ 8	2874 ng·h/mL	≈6
		♀ 3	1188 ng·h/mL	≈2
		♀ 8	3801 ng·h/mL	≈8
		♀ 25	12964 ng·h/mL	≈27
Dog (Beagle)	1 month ED27 (Study T07-12-03)	♂ 0.15	0.411 µM.h	≈0.3
		♂ 0.45	1.46 µM.h	≈1
		♂ 3	10.7 µM.h	≈8
		♀ 0.15	0.395 µM.h	≈0.3
		♀ 0.45	1.49 µM.h	≈1

Species	Study duration (Study ID)	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL or µM.h)	Exposure ratio[#]
		♀ 3	12.8 µM.h	≈10
	6 month ED154/182* (Study T08-04-04]	♂ 0.25	363 ng·h/mL	≈0.8
		♂ 1/0.75†	1374 ng·h/mL	≈3
		♂ 5/2.5‡Δ	5608 ng·h/mL	≈12
		♂ 20/15/5Δ	12851 ng·h/mL	≈27
		♀ 0.25	401 ng·h/mL	≈0.8
		♀ 1/0.75†	1259 ng·h/mL	≈3
		♀ 5/2.5‡Δ	7168 ng·h/mL	≈15
		♀ 20/15/5Δ	11477 ng·h/mL	≈24
	39 week ED231/269◅ (Study 8221785 (T10-02-01))	♂ 0.25	285.3 ng·h/mL	≈0.6
		♂ 0.5	446 ng·h/mL	≈1
		♂ 3	3246 ng·h/mL	≈7
		♂ 9/6	9211 ng·h/mL	≈19
		♀ 0.25	261 ng·h/mL	≈0.5
		♀ 0.5	449 ng·h/mL	≈1
		♀ 3	4085 ng·h/mL	≈9
		♀ 9/6	8238 ng·h/mL	≈17
Human (Population PK modelling)	Steady state (See: justification for selection of human pharmacokinetic values)	(4 mg)	477.6 ng·h/mL 1.3 µM.h	–

[#] =animal: human plasma $AUC_{0-24\ h}$; * =ED182 for 0.25 mg/kg/day and 1.0/0.75 mg/kg/day groups; ED154 for 5/2.5 mg/kg/day and 10/15.5 mg/kg/day groups; treatment of many animals for demodicosis and associated opportunistic secondary infections was a potential confounding factor in the toxicokinetic data; † =On ED17 the dose was decreased to 0.75 mg/kg/day for the remainder of the study. Dosing was discontinued for 1 female in this dose group, the animal was allowed to recover and was subsequently necropsied on ED179; ‡ =On ED17 the dose was decreased to 2.5 mg/kg/day for the remainder of the study; Δ =For the 5/2.4 mg/kg/day and 20/15/5 mg/kg/day dose groups, progressive clinical findings necessitated early euthanasia (euthanised *in extremis* or terminated early). Last day of dosing was ED154; ◅ =Day 231 for 3 mg/kg and 9/6 mg/kg groups; Day 269 for 0.25 mg/kg and 0.5 mg/kg groups; treatment of many animals for demodecosis and associated opportunistic secondary infections was a potential confounding factor in the toxicokinetic data.

In humans, the mean $C_{max,ss}$ was 53.4 ng/mL (0.14 μM) and the mean 24 h dosing interval $AUC_{0-\tau,ss}$ was 477.6 ng.h/mL (1.3 μM.h);[12] after multiple 4 mg dosing in patients with RA. Human plasma protein binding is 50% that is unbound C_{max} = 26.7 ng/mL =72 nM.

These data are based on the population pharmacokinetic analyses of the primary Phase II and Phase III studies.[13] The pharmacokinetic values used were selected based on the following parameters: (a) the proposed clinical MHRD was used; (b) the proposed clinical route of exposure was used; (c) the values were derived from patients being treated for RA (the intended target population) rather than normal healthy subjects; and (d) the population pharmacokinetic analyses provided by the sponsor took into account all of the available human data (that is represented the largest *n* available). The data may not take into account the effects of concurrent treatment with cDMARDs.

All the animal repeat dose studies used baricitinib phosphate as the test article except the carcinogenicity studies. Based on comparative toxicokinetic studies of the phosphate salt and the free base in mice (dose range male 75 to 300; female 25 to 150 mg/kg/day) and rats (dose range: male 1 to 8; female 3 to 25 mg/kg/day) the C_{max} and $AUC_{0-\infty}$ ratios for the different drug forms were approximately 1 that is no toxicologically meaningful differences were detected.[14] No data is available for dogs; however it is assumed that the findings in rodents also apply to this species.

Major toxicities

Across species the major toxicological effects were primary pharmacologically mediated that is negative effects on the leukon and lymphoid system and increased susceptibility to infection.

Dogs were more susceptible to baricitinib-associated severe opportunistic infection (predominantly pyodemodicosis; correlated with in vitro primary pharmacology data implying increased sensitivity of dogs to effects on the JAK1/STAT3/IL6 pathway as well as their lower % plasma protein binding).

Adverse effects on the immune system (various combinations of adverse lymphopaenic leukopaenia and/or lymphoid tissue depletion and/or bone marrow hypocellularity) across species were occurred following subacute to chronic repeated dosing at approximately 3 to 5 x MHRD in mice; 21 to 25 x MHRD in rats; and 8 to 10 x MHRD in dogs (AUC comparisons). These effects occurred at lower doses with longer duration treatments. The high relative exposure margins for these effects in animals are consistent with the rarity of adverse lymphopaenia in the human clinical data.

Panleukopaenia (including neutropaenia) was only definitively detected in females in the 1 month rat study following dosing at approximately 37 x MHRD (AUC). These findings are consistent with the rarity of adverse neutropaenia in the human clinical data. However, lymphopaenia and adversely decreased basophils, eosinophils and large unstained cells were observed following lower levels of exposure (no observed adverse effect level (NOAEL) similar to MHRD; AUC).

Evidence of baricitinib associated opportunistic infections was only apparent at high relative exposure margins following dosing of rats and mice for ≥ 3 months (mice: approximately 39 to 42 x MHRD; rats approximately 4 to 21 x MHRD; AUC). In the 6 month dog study, baricitinib treatment at ≥ approximately 0.8 x MHRD (AUC) was

[4]Units of ng/mL or ngxhr/mL can be converted to nM or nMxhr, respectively, by multiplying the ng units by 2.6924, which takes into account the MW of 371.42

[13] Population Pharmacokinetic and Pharmacodynamic Analyses of Study: I4V-MC-JADV; I4V-MC-JADZ; I4V-MC-JADW; I4V-MC-JADX; I4V-MC-JADC; I4V-MC-JADA; and I4V-JE-JADN and Population PK/PD Report Amendment. Dossier §5.3.3.5

[14] Study Nos. MAKR12_8278998 & RAUV11_8259423

associated with the occurrence of severe, intractable, progressive, untreatable disseminated pyodemodicosis and associated opportunistic fungal and bacterial infections as well as an increased incidence (relative to control) of interdigital pyogranulomas (with an increased incidence of more than one affected foot; likely associated with demodicosis). Demodicosis was accompanied by widespread inflammation (brain, lung, kidney, and gallbladder; likely secondary to antigen deposition in small vascular beds). Notably *Pneumocystis carinii* associated pulmonary inflammation was detected in 1 of 4 females dosed at approximately 9 x MHRD (AUC).

Severe, disseminated, intractable pyodemodicosis was also the key finding following dosing of dogs at ≥ approximately 0.6 x MHRD (AUC) for 9 months and was also associated with an increased incidence of interdigital pyogranulomas and pedal pressure sores. Baricitinib dosing at approximately 7 to 9 x MHRD (AUC) was poorly tolerated in this study, despite the use of drug holidays, due to clinical signs most likely associated with opportunistic secondary infections.

Overall, these findings indicate an increased risk of opportunistic infections in individuals with prolonged treatment. An increased risk of de novo and recrudescent infection was apparent in the human clinical data and has been noted in the PI.

Other toxicities

Increased background sensitivity to cardiomyopathy (cardiac fibrosis) was observed in CD-1 rats treated for 6 months at a relative exposure (AUC) of approximately 80 times (not clinically relevant). Cardiomyopathy was not detected in the human clinical data and inhibition of JAK/STAT pathways in rats is cardioprotective in the presence of diabetic cardiomyopathy.

The adverse elevations in serum liver enzymes observed in the 9 month dog study (2 to 3 x increase of aspartate transaminase (AST), alanine transaminase (ALT) and gamma glutamyl transaminase (GGT) compared with controls at 7 to 17 x MHRD, AUC) correlated with portal hepatitis and bile duct hyperplasia. The relationship between test article exposure and these effects is uncertain given that confounding polypharmacy for treatment of demodicosis including the use of NSAIDs known to be hepatotoxic in dogs was present. Given that similar findings were not observed in rats it is unlikely that liver toxicity is clinically relevant.

Renal tubular crystalline nephropathy was observed in mice dosed for ≥ 1 month at very high doses approximately 65 x MHRD, AUC). Adverse renal events were not detected in the human clinical data. The effect is likely mouse specific and secondary to their higher baseline level of urine concentration.

Genotoxicity

Overall, baricitinib displays no classical genotoxic potential based on a high quality, validated ICH S2 (R1) standard battery (an in vitro bacterial reverse mutation suite, an in vitro mammalian cell chromosomal aberration test and an in vivo micronucleus test).[15]

Carcinogenicity

In compliance with ICH requirements for chronically administered drugs, carcinogenesis studies were conducted in rats and mice (PO dosing at up to the MTD with baricitinib for 2 years in rats and 6 months in HRAS transgenic mice). The HRAS transgenic mouse study was validated by the inclusion of an N-methyl-N-nitrosourea control. The safety properties of the metabolites of baricitinib were adequately assessed in these studies.

[15] ICH S2 (R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use; Current Step 4 version dated 9 November 2011

Baricitinib was not associated with relevant human neoplastic disease. Notably high PO baricitinib doses were associated with dose-dependent increased survival due to decreased incidence of lethal haematopoietic neoplasia in males and lethal mammary neoplasia in females. The human relevance of these findings is uncertain.

Non-neoplastic effects in these studies were consistent with those described in the repeat dose toxicity section.

Reproductive toxicity

The sponsor supplied a high quality ICH compliant reproductive toxicity screening package. High relative exposures were achieved. The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity which may affect early embryonic development. This mode of action likely applies across the whole JAK inhibitor drug class.

Relative exposure

The following table describes the relative exposures in animals versus humans (Table 2).

Table 2: Relative exposure in reproductive toxicity studies

Species	Study [Study ID]	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio#
Rat (SD)	Fertility [WIL-353240]	5 (NOAEL male fertility and early embryofetal development; NOAEL female toxicity)	♂1875	4
			♀1972	4
		15 (NOAEL male fertility)	♂5859	12
		25 (NOAEL maternotoxicity)	♀11332	24
		50	♂26870	56
		100	♀40444	85
	Embryofetal development [T08-07-01; main study]	2 (NOAEL maternotoxicity and embryofetal development)	1092	2
		10	4866	10
		40	26259	55
	Pre-postnatal development F_0 LD4 [WIL-353280]	2 (NOAEL F_1 development)	840	2
		5	2110	4
		25 (NOAEL F_0 ♀)	10300	22
Rabbit (NZW)	Embryofetal development GD20	3	1096	2

Species	Study [Study ID]	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL)	Exposure ratio[#]
	[T08-07-02]	10 (NOAEL maternotoxicity and embryofetal development)	3027	6
		30	20094	42
Human (healthy volunteers)	steady state	4 mg, equal to approximately 0.08 mg/kg/day	477.6	–

[#] =animal: human plasma $AUC_{0-24\ h}$

A single dose study in pregnant rats demonstrated extensive transplacental exposure to drug associated radioactivity (fetal: maternal ratio approximately 2; *n* = 1). Although fetal levels were not detected at 24 h post dose, ongoing high level exposure would be expected with maternal repeated daily dosing.

Transmammary exposure to baricitinib occurred following PO dosing of the parental generation (F_0) dams in the rat pre-postnatal study. Plasma concentrations in nursing offspring were initially 65 to 100 x less than parental levels at time = 1 h but were generally similar by time = 8 h (last sampling time point) that is a transmammary pharmacokinetic delay relative to maternal plasma levels was apparent.

Fertility, reproduction and postnatal development

Findings in the rat combined male/female fertility and early embryonic development study included decreased overall mating performance, decreased male copulation index (approximately a 30% decrease), a dose related trend towards reduced male fertility index (approximately a 30% decrease) following dosing at approximately 56 x the MHRD (AUC). Baricitinib treatment also significantly decreased female conception index (approximately 30% decreased) and induced a dose related trend towards decreased conception index (approximately 30% decreased) following dosing at about approximately 85 x MHRD (AUC). In female rats there were decreased numbers of corpora lutea (approximately 30% decreased) and implantation sites (approximately 50% decreased), increased pre-implantation loss (approximately 4 x increased), increased numbers of early in utero deaths (approximately 15 x increased) and increased combined early and late in utero deaths following dosing at approximately 85 x MHRD (AUC). The no observable effect level (NOEL) for fertility and impaired early embryonic development was approximately 4 x MHRD (AUC).

Since there were no effects on spermatogenesis (as assessed by histopathology) or semen/sperm endpoints in male rats or mating indices in either sex, decreased mating performance was likely due to effects on female fertility and/or early pre-implantation embryonic development.

In the rat embryofetal development study, maternotoxic (≥ approximately 10 x MHRD; AUC) PO dosing with baricitinib over Gestation days (GD) 6 to 17 induced an increased incidence of adverse limb bone malformations (2 from1/24 litters at 10 mg/kg/day; 15 from 5/24 litters at 40 mg/kg/day) and an increased incidence of adverse rib malformations (6 from 4/24 litters at 10 mg/kg/day; 3 from 1/24 litters at 40 mg/kg/day). Baricitinib at high PO doses (40 mg/kg/day over GD 6 to 17, approximately 55 x MHRD; AUC) also induced fetal rib variations (bent seventh cervical rib and other bent ribs).

Oral dosing (≤ approximately 30 x MHRD; AUC) of rabbits was not associated with fetal malformations or variations despite the presence of maternal mortality. However a significant decrease in mean number of live fetuses/litter (7% decrease compared with controls) was noted in the high dose group (approximately 42 x MHRD; AUC; maternotoxic). This was correlated with a significant increase in the mean number of late in utero deaths (approximately 12 fold increase compared with controls) and significantly decreased fetal weight (10.9% decrease compared with control).

In the pre-/postnatal study in rats, adverse effects in the first filial (F_1) generation (including confirmation of the skeletal malformation findings noted in the rat embryofetal development study) only occurred at high dosing multiples (approximately 22 x MHRD; AUC) of the F_0 females. Adverse intergenerational effects are unlikely at the MHRD.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[16] This category is appropriate because of the observed malformations and the known importance of the JAK/STAT pathways in embryonic development.

Local tolerance

Baricitinib is not a strong ocular irritant based on the results of a valid bovine corneal opacity and permeability test (BCOP) and there was no evidence of local effects on the skin in a rabbit dermal toxicity test. There was no evidence of adverse local effects in the gastrointestinal tract in single or repeat dose toxicology studies.

Immunotoxicity

Baricitinib likely induces strong, primary pharmacologically mediated, immunosuppression. Consistent with the human clinical findings, an increased risk of infection/decreased immunological suppression of commensal organisms was apparent in the repeat dose toxicology studies (particularly in dogs; consistent with the possible increased susceptibility of this species to the primary pharmacological effects of baricitinib).

Phototoxicity

Based on the results of a neutral red uptake phototoxicity screening assay, baricitinib lacks any phototoxic potential.

Nonclinical summary and conclusions

Summary

Baricitinib is a selective JAK 1, JAK 2 and TYK2 inhibitor that inhibited cytokine (IL-2, IL-6, IL-12, or IL-23) or mitogen stimulated JAK2/STAT3/STAT5 signalling and downstream cytokine (IFN-γ, IL-17, IL-22 and MCP-1) responses. Dogs had increased sensitivity to the effects on the IL-6 to STAT3 pathway.

PO baricitinib treatment (≤ approximately 50% JAK1/2 inhibition for 0.5 days post dose) resulted in decreased disease severity (no effects on serum anti-collagen antibody levels) in three different rodent models of RA.

[16] Australian Pregnancy Category D: Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

At the MHRD there is a low risk of adverse secondary pharmacodynamics and safety pharmacology effects. Baricitinib has moderate affinity for CaMK2d and CaMK2g.

Pharmacokinetics in animals modelled the human situation (no human-specific metabolites; high relative exposures achieved). PO absorption and tissue distribution was rapid and plasma $t_{½}$ was short. After repeated PO dosing, exposure was occasionally supra dose-proportional, minimal pharmacokinetic adaptation occurred, and there were no notable sex differences. Baricitinib is approximately 50% protein bound across species. Tissue concentrations reflected routes of administration and excretion (some non-adverse concentration in the pigmented uvea). In humans, baricitinib was largely excreted unchanged (limited CYP3A4 oxidation resulting in 4 major metabolites constituting approximately 6% of the PO dose). Higher levels of metabolism occurred in other species (approximately 60% excreted unchanged). Renal excretion dominated in humans; faecal excretion dominated in rodents and dogs were intermediate.

The risk of drug-drug interactions at liver and kidney transporters or via the pregnane X xenosensor is low or negligible.

The major toxicological effects at > MHRD were pharmacologically-mediated lymphoid depletion (lymphopaenic leukopaenia, bone marrow hypocellularity, lymphoid tissues ± gut-associated lymphoid tissue (GALT)/Peyer's patch depletion). Panleukopaenia and/or neutropaenia and increased risk of infection occurred only at high exposures after PO dosing in rats. Repeated PO dosing of dogs at ≥ MHRD for ≥ 6 months was associated with severe pyodemodicosis, increased incidence of interdigital bacterial pyogranulomas (likely demodicosis) and increased incidence of pedal pressure sores (all likely immunosuppression related).

Baricitinib does not pose a genotoxicity or carcinogenicity risk.

Substantial transplacental and galactogenic baricitinib exposure is likely. In rats, high, maternotoxic exposures to baricitinib adversely impaired male and female fertility and induced early embryonic death. Adverse effects on skeletal development (limb bone and rib malformations; rib variations) were noted in the rat, but not the rabbit, embryofetal study at high doses. Extreme maternal dosing of rabbits was associated with fetolethality. Based on the rat pre-postnatal study dosing at the MHRD does not result in adverse intergenerational effects. Australian Pregnancy Category D is appropriate.[15]

There were no local tolerance issues for baricitinib and it has no phototoxic potential.

Conclusions and Recommendation

The sponsor has submitted sufficient data to establish the mode of action of baricitinib, to provide proof of concept in rodent models of arthritis and to establish its safety properties. Registration is supported from the nonclinical perspective.

The key nonclinical risk associated with baricitinib treatment is opportunistic infection.

Baricitinib is appropriately categorised as Pregnancy Category D.[15] Baricitinib, the drug is not recommended for use during pregnancy and lactation.

The nonclinical evaluator recommended amendments to the draft PI.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

As described under *Product background* and *Nonclinical findings* above, BAR is a selective inhibitor of the JAK family of kinases, with greater affinity for the JAK1 and JAK2 systems, and less potency for JAK3 and tyrosine kinase 2. The JAK system is an intracellular pathway regulatory system that affects the release of cytokines and amplification of the inflammatory response. The JAKs phosphorylate their associated signal transducers and activators of transcription (STATs) resulting in STAT activation, which in turn leads to the expression of several genes important for cell activation, survival and proliferation. BAR modulates the JAK-STAT pathway by transiently occupying the adenosine triphosphate (ATP) binding pocket of the JAK, thereby preventing the kinase from phosphorylating other JAKs or STATs. Inhibition of either monomer of the JAK dimer blocks the production and signalling of several pro-inflammatory cytokines such as IL-6, as well as interferon. In combination, these effects decrease lymphocyte activation, proliferation and function, which are key immune response targets in successfully treating active RA.

Guidance

The EU guidelines adopted by the TGA relevant to this submission, in addition to the general guidelines are:

- CPMP/EWP/556/95 rev 1/Final: Points to consider on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. Replaces: CPMP/EWP/556/95 (Adopted by TGA February 2001) Effective: 29 January 2007.
- Pages 127 to 132 of Rules 1998 (3C); 3CC6a: Clinical investigation of medicinal products for long-term use. Replaces: pp. 163 - 165 of Rules 1989 Effective: 12 February 2002.

Contents of the clinical dossier

This submission includes 26 completed clinical studies comprising 19 clinical pharmacology studies, 3 Phase II studies and 4 Phase III studies in RA patients as well as data from an ongoing long-term extension study was also included as follows:

- 19 specific clinical pharmacology studies have conducted (18 in healthy volunteers and 1 in adult subjects with RA) plus pharmacokinetic (PK) data was collected all 7 of the Phase II and III clinical studies (listed below).
- 2 combined population PK and PK/pharmacodynamic (PD) analyses of pooled data obtained from the Phase I studies in healthy subjects (known as the Phase I/IIa dataset) and data from the 7 Phase II/III trials (known as the primary Phase II/III PopPK analysis).
- 4 pivotal, Phase III efficacy/safety studies (Studies JADZ, JADV, JADX and JADW).
- 3 supporting Phase II, dose-finding studies (Studies JADC, JADA and JADN) and a long term extension study (Study JADY).
- Safety data from 26 Phase I to III trials as listed above plus information regarding the safety of BAR in the treatment of 2 other conditions (skin psoriasis: Study JADP; and diabetic nephropathy: Study JADB).
- A Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Biopharmaceutical Studies and associated Analytical Methods, Summary of Clinical Pharmacology Studies and literature references.

An additional Phase III randomised, placebo-controlled study (Study JAGS) to support registration in China is currently ongoing and is not presented in this application.

As of 10 August 2015, a total of 513 subjects were exposed to BAR in the completed clinical pharmacology trials and a total of 3822 patients were exposed to BAR in the completed Phase I to III RA studies as well as an additional 358 subjects involved two Phase II studies in other potential treatment indications (skin psoriasis and diabetic nephropathy). Thus, the extent of exposure of the safety database meets the expectations of ICH guidance: '*The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions*'.

The submission contained 3 completed, placebo-controlled Phase II studies, which enrolled a total of 571 adult patients with moderately to severely active RA who had an inadequate response to conventional DMARD and in a minority of patients to biologic DMARD. Doses of BAR investigated the Phase II program ranged between 1 mg once daily to 10 mg once daily. Twice daily dosing was also assessed in a limited number of patients.

The 4 completed Phase III studies were designed to investigate the efficacy and safety of BAR in different populations (MTX naive, conventional DMARD inadequate responders and biologic DMARD inadequate responders) at 2 dose levels (2 mg and 4 mg once daily) and compared to 2 common and established active comparators (weekly low dose oral MTX and adalimumab). In response to the European Medicine Agency's (EMA) Committee on Medicinal Products for Human Use (CHMP) comments, 2 studies were conducted in the conventional DMARD inadequate responder population, of which one study required patients to receive concomitant MTX as background therapy. This approach assured a homogeneous patient population with inadequate response, thus mitigating concerns about heterogeneity between patients with intolerance and inadequate response to prior treatment.

Persistence of clinical response to BAR (that is, improvement in the signs and symptoms of RA) is provided in this submission by the 2 year clinical trial report for Study JADY (which is ongoing) and this trial followed patients receiving BAR 2 and 4 mg once daily therapy.

Paediatric data

The FDA have granted a waiver for the treatment of chronic juvenile idiopathic arthritis for children from birth to less than 2 years of age as the conditions for which BAR is intended, rarely occur in this age group. However, a paediatric investigation plan for the treatment of juvenile idiopathic arthritis for children aged from 2 to 18 years has been agreed with the EMA and received deferral status with the FDA. The clinical data for BAR use in juvenile idiopathic arthritis is expected to be submitted to the EMA in 2023 and to the FDA in 2024.

Good clinical practice

The studies presented in this submission are stated to have been conducted according to Good Clinical Practice (GCP) standards, and the study reports are consistent with adherence to GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission contained a total of 19 clinical pharmacology studies, which enrolled 513 healthy adult subjects and 53 patients with RA. Special population studies included 36 subjects with renal impairment (Study JADL) and 8 subjects with hepatic impairment

(Study JAGC). Two of the clinical pharmacology studies (Studies JADM and JAGO) were conducted exclusively in 50 healthy Japanese subjects. Intrinsic and extrinsic factors that could affect the PK profile of BAR, as well as the potential effect of BAR on the PK of commonly co-administered medications such as MTX and statin therapy were evaluated in specific individual trials. Across the clinical pharmacology studies, the PK of BAR was assessed for single doses over a range of 1 to 40 mg; and for multiple doses up to 20 mg once daily for 10 days, up to 10 mg daily for 28 days (given as either 10 mg once daily or 5 mg twice daily) and up to 15 mg once daily for 28 days. Table 3 (shown below) shows the studies relating to each PK topic, and the location of each trial summary. None of the PK studies had major deficiencies that excluded their results from consideration.

Table 3: Submitted pharmacokinetic studies for baricitinib

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK (single dose)	JADF	
	General PK (multi-dose)	JADE	*
	Bioequivalence (single dose)	Relative: JADH + JAGO Absolute: JAGM	* *
	Food effect	JADF JADH + JAGO	*
PK in special populations	Target population (single dose)	Nil	
	Target population (multi-dose)	JADB	
	Hepatic impairment	JAGC	*
	Renal impairment	JADL	*
	Japanese Subjects	JADM	*
	Age (particularly, elderly patients)	Phase II/III PopPK	
	Other special population: Subject body weight	Phase II/III PopPK	
Genetic or gender related PK	Males versus females	Phase II/III PopPK	
	Other genetic variable: Race/ethnicity	Phase II/III PopPK	
PK interactions	Omeprazole (effect of gastric pH)	JAGF	*
	Effect of other drugs on BAR	JAGJ, JAGK, JAGH, JAGG, JADB	*
	Effect of BAR on other drugs	JAGI, JAGD, JAGL, JADB	*

PK topic	Subtopic	Study ID	*
Population PK analyses	Healthy subjects	Phase I/IIa Pop PK	*
	Target population	Phase II/III Pop PK	*

* Indicates the primary PK aim of the study.

Evaluator's conclusions on pharmacokinetics

In this submission, the PK properties of BAR has been assessed in 18 Phase I studies involving otherwise healthy volunteers (some with co-variables of interest such as renal or hepatic impairment), 9 drug-drug interaction studies, 1 Phase I trial (Study JADB) involving 53 adult subjects with RA taking concurrent MTX and 7 Phase II/III clinical studies contributing data to population PK and PK-PD analyses.

The key PK conclusions identified in the submission are as follows:

- Orally administered BAR is rapidly (median t_{max} of approximately 1.0 h (range: 0.5 to 3.0 h)) and well absorbed (absolute bioavailability of 79%) from the gastrointestinal tract.
- The proposed commercial formulation and dosage strengths of BAR to be made available in Australia are identical to the 2 mg and 4 mg tablet strengths used in the pivotal Phase III clinical trials, which have demonstrated bioequivalence when produced at a commercial scale to the preceding formulations.
- Ingestion of BAR following a high fat meal compared to drug administration under fasted conditions, results in a decrease in BAR C_{max} of 18%, a decrease in AUC of 11%, and a delay in t_{max} of 0.5 h (Study JADH). The sponsor asserts that the administration of BAR with meals is not associated with a clinically relevant effect on drug exposure and during the Phase II/III studies BAR was taken without regard to meals.
- Steady state is reached after second and third doses of BAR (Study JADE) with minimal drug accumulation after multiple drug ingestion (accumulation ratio of 1.11 for C_{max} and 1.15 for AUC in the PopPK analysis). Hence, multi-dose PK for BAR is largely predictable with single dose data.
- Regarding dose proportionality, exposure to BAR increases in a proportional manner in the dose range of 1 to 30 mg.
- Mean apparent volume of distribution at steady state after oral dosing with BAR 2 mg and 4 mg was 108 L with 19.3% CV (PopPK data). Mean volume of distribution following IV administration was 75.7 L with 21% CV (Study JAGM) suggesting tissue distribution. BAR is a substrate for various drug transporter systems including Pgp, OAT3, MATE2-K and BRCP, which play a role in drug distribution.
- BAR is approximately 50% bound to human plasma proteins.
- From the human (^{14}C) Study JADG, approximately 75% of BAR is excreted in the urine (mainly as parent drug) and 20% is excreted in faeces. There are 4 minor oxidative metabolites (3 in urine and 1 in faeces).
- The mean $t_{1/2}$ of BAR in the plasma ranges is 10 h for healthy adult subjects and 12.5 h for patients with RA.
- Renal elimination is the main route of elimination for BAR through glomerular filtration and active secretion via OAT3, Pgp, BRCP and MATE2-K.

- Subjects with moderate (creatinine clearance (CrCL) 30 to 60 mL/min) and severe (CrCL < 30 mL/min) renal impairment have 2-fold and 4-fold increases in BAR AUC values compared to those with normal renal function (Study JADL). However, subjects with mild renal impairment (CrCL 60 to 90 mL/min) have only small insignificant increases in AUC compared to those with normal renal function.
- The PK of BAR does not appear to be substantially affected by age, gender, ethnicity, hepatic impairment or body weight.
- The PK characteristics of BAR in relation to C_{max} and AUC demonstrate low to moderate degrees of intra-subject and inter-subject variability across the tested dose range.
- A total of 9 in vivo drug-drug interaction studies in humans have been performed. The results indicate that many frequent concomitant medications such as MTX, azole-type drugs, ibuprofen, diclofenac, cyclosporine, digoxin, the oral contraceptive pill and simvastatin do not have clinically significant effects on the PK of BAR and vice versa. However, probenecid (a strong OAT3 inhibitor) increases exposure to BAR (doubling of AUC). In addition, the concomitant ingestion of omeprazole (that is, the effect of increased gastric pH) has shown to delay the absorption of BAR by 0.75 h, and to cause a decrease in C_{max} of 23%, but produces no significant change in AUC (Study JAGF).

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4, shown below, lists the studies relating to each pharmacodynamic (PD) topic. None of the PD studies had deficiencies that excluded its results from consideration.

Table 4: Submitted pharmacodynamic studies for baricitinib

PD Topic	Subtopic	Study ID	*
Primary pharmacology	Effect on phosphorylated STAT formation	JADF and JADE	*
Secondary pharmacology	Effect on QT interval	JADO	*
	Effect on haematological parameters	Phase II/III population	
Factors producing differences in PD response	Effect of gender	Nil performed	
	Effect of renal impairment	JADL	*
	Effect of ethnicity	Nil performed	
	Effect of age	Nil performed	
PD interactions	Drugs and vaccines	Nil performed	
Population PD and PK-PD analyses	Healthy subjects	Nil performed	
	Target population	Phase II/III population	*

* Indicates the primary PD aim of the study.

Evaluator's conclusions on pharmacodynamics

In this submission, the PD properties of BAR has been assessed in 3 Phase I studies, two of which involved healthy volunteers (Studies JADE and JADF) and 1 enrolled otherwise healthy subjects with renal impairment (Study JADL), as well as the 7 Phase II/III clinical trials involving subjects with RA plus 1 PopPK-PD analysis.

Inhibition of the JAK-STAT pathway by BAR is reversible in nature. The decrease in the cytokine stimulated pSTAT3 formation in response to single and multiple doses of BAR therapy was measured in 3 clinical pharmacology studies (Studies JADE, JADF and JADL). The PD data from these 3 studies were consistent and showed a dose dependent inhibition of pSTAT3 formation in response to cytokine stimulation in the single dose range of 1 to 20 mg (Study JADF), and with multiple once daily doses of 2 to 20 mg for 10 days (Study JADE). Similar levels of inhibition were observed using either IL-6 or TPO as the stimulus. Maximal inhibition of pSTAT3 formation occurred 1-2 h post-dose, coincident with the observed time to reach C_{max}. There is a direct relationship between plasma BAR concentration and change in pSTAT levels. The maximal inhibition of pSTAT ranged from 40% at the lowest dose of BAR (1 mg) to 70 to 80% inhibition at the highest dose of BAR (20 mg). The pSTAT3 levels returned to baseline levels by 24 h for all dose groups following single and multiple doses. In the multiple dose study, the extent of inhibition observed on Day 10 was not statistically different from that observed on Day 1, and pSTAT3 returned to baseline levels in a similar manner to that after single dose ingestion. Thus, there is no evidence for a cumulative effect on cytokine stimulated pSTAT3 formation with repeated dosing of BAR. Although changes in pSTAT levels mirror the PK profile of BAR, the PK/PD relationship is not direct for the clinical efficacy endpoints such as ACR and Disease Activity Score + 28 joint assessment (DAS28) response, where there is a delay in any observable change.[17,18] Therefore, the PK half-life does not translate into the efficacy PD half-life, and efficacy is more likely to relate to the daily average exposure (or AUC) to BAR. Finally, Study JADO identified that BAR in doses up to 40 mg does not cause any significant effects on cardiac repolarisation such as prolongation of the QT interval in normal healthy subjects.

Dosage selection for the pivotal studies

Pharmacokinetic and pharmacodynamic studies

The Phase I clinical pharmacology studies assessed BAR in the dose range of 1 mg to 20 mg once daily (including 5 mg and 10 mg twice daily regimens). Doses of BAR up to 10 mg once daily were generally safe and well tolerated in healthy volunteers (Study JADE) and in patients with RA (Study JADB) for up to 28 days of continuous therapy. Maximum inhibition of IL-6 stimulated pSTAT3 formation (70% to 80% of baseline) was observed with the BAR 10 and 20 mg dose. Therefore, BAR doses of 4 mg, 7 mg and 10 mg once daily were selected for further investigation in the initial Phase IIa, proof-of-concept Study JADC.

Phase II dose finding studies

Three Phase II studies provided dose-response data across a range of BAR doses:

- Study JADC was a proof-of concept study involving 145 subjects and tested BAR doses of 4 mg, 7 mg and 10 mg once daily.

[17] The DAS28 is a measure of disease activity in rheumatoid arthritis. DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment.

- Study JADA (n = 301 subjects) evaluated BAR doses of 1 mg, 2 mg, 4 mg and 8 mg once daily plus a BAR dose of 2 mg twice daily was also examined.
- Study JADN was conducted in 145 Japanese patients and tested BAR doses of 1 mg, 2 mg, 4 mg and 8 mg once daily.

All 3 of the Phase II studies assessed the proportion of patients who achieved ACR20 response at 12 weeks as the primary efficacy endpoint. Studies JADA and JADN included open label, extension phases as follows; 1 year of single blind extension in Study JADN and 2 years of open label extension in Study JADA. Patients completing Study JADA were also eligible to enrol in the long term extension Study JADY. The clinical response data for each of these studies is provided in detail in section 7 of this report.

In Study JADC, the proportion of patients achieving the primary efficacy endpoint (ACR20 response at 12 weeks) was similar across the BAR 4 mg, 7 mg and 10 mg once daily regimens, suggesting that all 3 doses reside on the plateau of the dose response curve for BAR in RA. Lower doses of BAR 1 and 2 mg once daily were added to Study JADA to identify the minimum efficacious dose and to characterise the initial linear part of the dose response curve. The dose of 4 mg once daily was retained in Study JADA due to the robust efficacy response observed and a dose of 8 mg once daily was chosen as the highest BAR dose to further confirm its maximum efficacy. The twice daily dose arm in Part B of Study JADA was intended to evaluate any differences in the overall clinical profile when the same total daily dose was given twice daily versus once daily. The Japanese Phase II Study JADN examined the same doses of BAR as Part A of the Phase IIb Study JADA (that is, BAR 1, 2, 4 and 8 mg once daily). The choice to examine similar doses of BAR in this trial as Study JADN and Study JADA was based on observations from the global (Studies JADF and JADE) and Japanese (Study JADM) Phase I studies which suggested that there were no PK differences due to ethnicity between global and Japanese patients.

Phase III pivotal studies investigating more than one dose regimen

The dose selection of BAR for testing in the Phase III trials was based on the results of 2 of the Phase II Studies JADC and JADA, as well as PK/PD models of efficacy and safety. The results of the third Phase II trial (Study JADN) were not available at the time of dose selection for the Phase III study program. BAR 4 mg once daily appeared to reside 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. Both the 1 mg and 2 mg doses of BAR appeared to be biologically active, but the observed and modelled treatment benefits were not considered compelling in the context of available therapies for RA. BAR was well tolerated at each dose level investigated. However, there was a higher incidence of non-serious adverse events and declines in mean haemoglobin concentrations compared to placebo (PBO) and lower doses of BAR with the 10 mg daily regime. The tolerability and safety profile of the 4 mg once daily dose was similar to that observed for the lower doses of BAR and PBO. Twice daily dosing did not improve efficacy and was associated with more laboratory abnormalities. The same observation was observed in studies of BAR in patients with diabetic nephropathy (Study JAGQ). Despite the modest efficacy observed with the 2 mg once daily dose of BAR in Study JADA and the significant overlap in the AUC between the 2 mg and 4 mg doses, the 2 mg once daily dose was investigated in 2 PBO controlled Phase III studies to further characterise the relative efficacy/safety. However, the 2 mg once daily dose of BAR was not predicted to perform well versus active comparators and, therefore, was not included in the active-controlled Phase III studies.

Evaluator's conclusions on dose finding for the pivotal studies

The totality of data from the Phase I and II studies and the PopPK/PD models support the once daily administration of BAR 4 mg as the recommended dose given the clinically

relevant rates of important outcome measures and no apparent concentration relationship for the 2 and 4 mg dose levels on the safety endpoints of anaemia or neutropaenia. Additionally, drug exposure associated with the BAR 2 mg dose in some patients were on the plateau of the exposure response curve indicating that the 2 mg dose will be effective in some patients. The sponsor has thoroughly investigated the effect of food on the PK of BAR and appropriately recommended that it can be given orally with or without food in the pivotal Phase III studies. Study JADL and Pop PK analyses have revealed the need for dose modification in patients with significant renal impairment. In the Phase III studies, the recommended dose of BAR in patients with CrCL 30 tot 60 mL/min was 2 mg once daily and patients with CrCL of < 30 mL/min were excluded from these trials. No drug interaction with MTX was identified in the Phase I/II studies so 3 of the pivotal Phase III studies allowed the use of BAR in combination with weekly low dose MTX.

Comments regarding the appropriateness and adequacy of concurrent and/or comparator therapies in the Phase III studies are also pertinent to the interpretation of the reported outcomes. Study JADZ was a comparison between MTX and BAR and the other Phase III trials had background concurrent conventional DMARD therapy. The mean and median doses of concomitant background treatment with conventional DMARD therapy (predominately MTX) was consistent with contemporary clinical practice in Australia. However, recent expert opinion concludes that such prior therapy reflects sub-optimal practice before the commencement of biologic therapy in patients with active RA (Duran et al, 2016). In particular, the maximal concurrent dose of MTX should be used in the comparator arm of all biologic therapy trials (up to 25 mg/week, by the SC route if dose > 15 mg/week for MTX) as sub-optimal MTX dose in the comparator arm may bias efficacy results in favour of biological agents. Moreover, low dose oral corticosteroid (prednisone ≥ 10 mg/day) and NSAID use was recorded in more than half of all patients (equally dispersed among the treatment arms) in the 4 pivotal BAR studies, which reflects appropriate concomitant drug use in individuals with active RA, and is consistent with prescribing patterns in Australia.

Efficacy

Studies providing efficacy data

The efficacy of BAR in patients with moderately to severely active RA has been evaluated in 4 completed Phase III studies (Studies JADZ, JADV, JADX and JADW); as well as 3 completed Phase II studies (Studies JADA, JADC and JADN) and 1 ongoing, long term extension (LTE) trial (Study JADY).

Study JAGS is another Phase III trial, but has not been included in this submission.

Each of the completed Phase III studies investigated diverse range of RA patient populations, spanning the treatment continuum from DMARD naive patients (Study JADZ), to patients with an inadequate response to conventional DMARD (Studies JADV and JADX) and patients with an inadequate response to biologic DMARD (Study JADW).

In settings where study drug was added to stable background conventional DMARD therapy, the efficacy of BAR was compared to PBO (Studies JADV, JADX, and JADW) and to adalimumab (Study JADV). In the setting where patients had no prior or background conventional DMARD therapy (Study JADZ), BAR was used alone or in combination with MTX, and was compared to MTX monotherapy.

The BAR 4 mg once daily dose was included in all Phase III studies and the 2 mg once daily dose was only included in 2 Phase III studies that incorporated PBO control. The BAR 2 mg once daily dose was not included in studies that had active comparators because the

results of the Phase II studies suggested a low probability that BAR 2 mg/day would demonstrate satisfactory efficacy.

Table 5 provides a summary of the patient populations and design characteristics of the Phase II and III controlled studies in support of the registration of BAR. The 4 pivotal Phase III studies will be considered together in this report as their design, inclusion criteria and statistical analyses were similar, and this report will highlight the differences between the studies.

Table 5: Features of Phase II and III studies in the Olumiant clinical development program

	Phase 2 Studies (Dose Ranging)			Phase 3 Studies – Completed				Phase 3 Studies – Ongoing [a]	
Study	JADC N=125	JADA N=301	JADN N=145	JADZ N=584	JADV N=1305	JADX N=684	JADW N=527	JAGS N=167[a]	JADY N=2519[a]
Population	cDMARD-IR bDMARD-IR	MTX-IR No bDMARDs	MTX-IR No bDMARD-IR	DMARD Naive	MTX-IR No bDMARDs	cDMARD-IR No bDMARDs	bDMARD-IR	MTX-IR No bDMARDs	Extension Study
Background Therapy	0 to 4 cDMARDS	MTX ± 2 cDMARDs	MTX ± 1 cDMARDs	None	MTX ± 1 cDMARDs	0 to 2 cDMARDs	1 or 2 cDMARDs	MTX ± 1 cDMARDs	0 to 2 cDMARDs
Treatment Arms	Placebo BARI 4-mg QD BARI 7-mg QD BARI 10-mg QD	Placebo BARI 1-mg QD BARI 2-mg QD BARI 4-mg QD BARI 8-mg QD BARI 2-mg BID	Placebo BARI 1-mg QD BARI 2-mg QD BARI 4-mg QD BARI 8-mg QD	MTX Mono BARI 4-mg Mono BARI 4-mg + MTX	Placebo Adalimumab 40-mg Q2W BARI 4-mg QD	Placebo BARI 2-mg QD BARI 4-mg QD	Placebo BARI 2-mg QD BARI 4-mg QD	Placebo BARI 4-mg QD	BARI 2-mg QD BARI 4-mg QD
Primary Endpoint (ACR20) at Week	12	12	12	24	12	12	12	12	NA
First Opportunity for Rescue	None	None	None	24	16	16	16	16	Variable
Structure Assessed	No	Yes (MRI)	No	Yes	Yes	Yes	No	Yes	Yes
Duration (Wks)	24	128	64	52	52	24	24	52	Up to 48 months
Additional Features	—	2-year open-label extension, then eligible for JADY	1-year single-blind extension	—	PROs collected by electronic handheld diaries	PROs collected by electronic handheld diaries	—	—	Randomised dose step-down; Switch from controls to baricitinib

Abbreviations: b/cDMARD = biologic/conventional disease-modifying anti-rheumatic drug; MRI = magnetic resonance imaging; NA = not applicable; PRO = patient-reported outcomes.
No bDMARDs = no previous exposure to biologic DMARDs; No bDMARD-IR = could have previous exposure to biologic DMARDs, but could not have failed treatment with the bDMARD.
[a] Enrollment as of 10 August 2015. Study is ongoing.

Evaluator's conclusions on efficacy

In support of the registration of BAR for the treatment of active RA, this submission contains 4 completed Phase III Studies JADZ, JADY, JADX and JADW, all of which were nominated as pivotal by the sponsor. The submission also included efficacy data from 3 completed Phase II Studies JADC, JADA and JADN and 1 ongoing, LTE trial (Study JADY) for supporting data purposes. The overall clinical development program for BAR provides a dataset that appropriately reflects the clinical RA population in Australia. The Phase II/III studies enrolled a spectrum of patients with active RA, including patients who have never received prior DMARD therapy (Study JADZ), patients who have an inadequate response to MTX (the most commonly used treatment for RA; Study JADV) and patients who are refractory to treatment with conventional DMARDs (Study JADX) and/or biologic therapies (Study JADW). Based upon the evaluation of efficacy data from the completed Phase III clinical studies through to the primary time point (24 weeks in JADZ and 12 weeks in Studies JADV, JADX, and JADW), treatment with BAR 4 mg once daily in adult patients with moderately to severely active RA yielded consistent and robust results for statistically and clinically improving the signs and symptoms of the disease as well as improving physical function. Compared to all comparators (PBO, MTX and adalimumab), statistically significant and durable improvements were observed from the initial weeks of treatment across a diverse range of efficacy measures for BAR, including the primary endpoint of ACR20 response. Consistent improvements with BAR 4 mg/day were also seen across composite scores of disease activity such as the Clinical Disease Activity Index

(CDAI) and DAS28-CRP response. Many subjects achieved low disease activity or clinical remission which is highly desired outcome of treatment supported by the literature. BAR 4 mg once daily also produced rapid and sustained improvements in several patient reported outcomes of relevance such as the duration of morning joint stiffness and its severity, severity of worst tiredness and joint pain.

All of the Phase III studies were randomised, double-blinded and parallel group controlled in design and enrolled adult patients with a confirmed diagnosis of RA. Subjects were required to have moderate-severe disease activity at Baseline with ≥ 6 tender and swollen joints and have raised serum inflammatory markers (C-reactive protein (CRP) x 1 to 1.2 upper limit of normal (ULN)) and/or joint erosions or positive autoantibody tests at Baseline. The baseline demographic and disease related characteristics of patients in the Phase III trials are diverse but similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. The majority of patients were female, of Caucasian ethnicity, and within the expected age range of 45 to 65 years. However, there are some caveats to the generalisability of the treatment population. For example, all of the studies excluded patients who were at a significant risk of infection or malignancy, or who had various abnormal laboratory results at Baseline (for example, abnormal haematology or liver function tests).

The clinical efficacy data available up to 24 months in Study JADY indicated that the majority of responding patients appear to maintain their treatment related benefit with continued BAR treatment. In addition, for PBO patients who switched to BAR at 3 to 6 months, the rates of ACR response observed 12 weeks later were similar to those achieved in the originally treated BAR cohort.

Dose recommendations

The efficacy of BAR 2 mg once daily was also assessed in 2 of the Phase III Studies JADX and JADW and demonstrated that when used in combination with MTX, BAR 2 mg once daily produces improvement in the signs and symptoms of RA (as measured by ACR criteria) and physical function (as measured by Health Assessment Questionnaire Disability Index (HAQ-DI)) compared to PBO. However, the BAR 4 mg dose consistently provided more rapid onset and a numerically higher response compared to PBO than the BAR 2 mg dose. Treatment with BAR 2 mg/day resulted in lower clinical response rates than treatment with BAR 4 mg/day.

BAR was administered as 4 mg/day monotherapy in Study JADZ and the results indicated that it was superior to MTX monotherapy for clinical outcomes in DMARD naïve patients with early disease. In this trial, when BAR was combined with MTX, only a modest additional clinical benefit was observed for less structural joint damage, but not with respect to symptoms and function.

Radiographic claim

Three of the Phase III studies (Studies JADZ, JADV and JADX) were designed to evaluate the claim of inhibition of structural damage. In all 3 studies, the primary X-ray endpoint was the LS mean change from Baseline to 24 weeks in Modified Total Sharp Score (mTSS). In 2 of the Phase III trials (JADZ and JADV), plain X-rays were also evaluated at 52 weeks of treatment as a supporting analysis. In Study JADZ (DMARD naïve, early disease population), a statistically lower increase in the LS mean mTSS was observed at Week 24 for BAR + MTX (+ 0.29 sharp unit increase from Baseline) versus MTX monotherapy (+0.61 sharp unit increase), but this was not demonstrated for BAR monotherapy (+0.39 sharp unit increase) versus MTX alone. At 52 weeks in Study JADZ, the combination treatment group showed a statistically lower LS mean increase from Baseline in mTSS (+0.40 sharp units) compared with MTX alone therapy (+1.02 sharp units; p = 0.004). The BAR monotherapy group recorded a +0.80 sharp unit increase from Baseline to Week 52, which was not statistically significant versus MTX monotherapy (p = 0.324). A supporting

analysis of the main X-ray endpoint was the proportion of subjects in each treatment group who did not show an increase from Baseline in sharp units over time. At 52 weeks in Study JADZ, the combination treatment group of BAR + MTX showed a statistically lower proportion of subjects with no X-ray progression (79.9%; 159/215) compared with MTX alone therapy (66.1% (127/192); p = 0.002). The BAR monotherapy group recorded 68.8% of subjects (106/154) with no X-ray progression at Week 52, which was not statistically greater than MTX monotherapy (p = 0.165).

The pre-specified main X-ray outcome of interest in Study JADV was the comparison between the BAR and PBO treatment groups at Week 24, and supportive analyses included the comparison between BAR and adalimumab therapies at Weeks 24 and 52. Compared to PBO (+0.84 sharp unit increase from Baseline mean of 44.64), a statistically significant lower increase in mTSS progression (meaning less structural X-ray progression) was observed at Week 24 for BAR (+0.29 sharp unit increase from Baseline mean of 42.46; p = 0.001). Compared to BAR, the adalimumab treatment group showed a numerically similar increase from Baseline to Week 24 (+0.33 sharp unit increase from Baseline mean of 44.35). At 52 weeks, there was a continued small increase in the LS mean mTSS for both BAR (+ 0.71 sharp unit) and adalimumab (+0.60 sharp unit), which was not statistically different in the pair-wise active treatment comparison (p = 0.69). In Study JADX, a statistically lower rate of structural progression in the LS mean change from Baseline in mTSS was observed at Week 24 for the BAR 4 mg group (+0.16 sharp unit increase from Baseline) versus PBO (+0.58 sharp unit increase), but the pair-wise comparison between PBO and BAR 2 mg/day (+0.30 sharp unit increase from Baseline) for this outcome did not reach statistical significance. Compared to PBO (73.2%; 142/192), a larger proportion of patients had no progression in mTSS (change from Baseline ≤ 0) at Week 24 for the BAR 4 mg group (80.5%; 161/200), but the difference was not statistically significant. The rate of no X-ray progression at 24 weeks in the BAR 2 mg arm was 71.3% (149/209), which was numerically lower than PBO.

In conclusion, the limited X-ray data thus far with BAR 4 mg/day (alone or in combination with MTX or other conventional DMARDs) does not demonstrate a consistent and robust benefit in terms of inhibition of joint structural progression to support this sub-claim in the proposed treatment indication for BAR. In addition, the TGA adopted EU regulatory guideline;[19] states that to make a claim of radiographic benefit in RA, X-rays should be taken at fixed and pre-defined time points at least 1 year apart for a minimum of 2 years, so it is premature to consider a sub-claim of X-ray benefit with BAR using the current submission dataset. An explanation for why BAR did not convincingly show X-ray benefit across all treatment populations is that the predicted mean rates of X-ray progression for subjects receiving background MTX would be expected to be 2.6 to 2.8 sharp units per year (based on published data in MTX-inadequate response populations) and in all of the Phase III studies, the control group progression rates were < 1 sharp unit per year and the percentage of subjects with X-ray progression (change in mTSS at 1 year of > 0 unit) at 52 weeks was low at ≤ 30%. Because the magnitude of progression in the control groups were substantially less than expected, the ability to demonstrate treatment related differences (BAR versus control) was limited. One of the strengths of the radiographic dataset is the inclusion of an active comparator arm (MTX and/or adalimumab) over an extended period of follow-up, which has assisted in determining the potential magnitude of X-ray benefit.

[19] CPMP/EWP/556/95 rev 1/Final: Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

Not applicable as there were no studies in the BAR clinical development program that assessed safety as the sole primary outcome.

Pivotal and/or main efficacy studies

The safety and tolerability of BAR in patients with moderately to severely active RA has been principally evaluated in 4 completed Phase III studies (Studies JADZ, JADV, JADX and JADW) and 1 ongoing, LTE trial (Study JADY). Each of the completed Phase III studies investigated a diverse range of RA patient populations, spanning the treatment continuum from DMARD naive patients (Study JADZ), to patients with an inadequate response to conventional DMARD (Studies JADV and JADX) and patients with an inadequate response to biologic DMARD (Study JADW). In settings where study drug was added to stable background conventional DMARD therapy, the safety of BAR was compared to PBO (Studies JADV, JADX, and JADW) and to adalimumab (Study JADV). In the setting where patients had no prior or background conventional DMARD therapy (Study JADZ), BAR was used alone or in combination with MTX, and was compared to MTX monotherapy. The BAR 4 mg once daily dose was included in all Phase III studies and the 2 mg once daily dose was only included in 2 Phase III studies that incorporated PBO control.

The following safety data was collected in the 4 pivotal Phase III studies (as well as the LTE Study JADY):

- Adverse events (AEs) in general were assessed by completion of the AE Case Report Form (CRF) and physical examination performed every 1 to 4 weeks until Week 24, and then every 8 to 12 weeks thereafter (or upon early withdrawal).
- AEs of particular interest, including infections (overall, serious and opportunistic, including tuberculosis and herpes zoster infection), gastrointestinal perforation, malignancy and Major Adverse Cardiovascular Events (MACE) were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology, clinical chemistry, urinalysis and urine pregnancy testing (in female subjects) were performed at Baseline, every 1 to 4 weeks until Week 24 and then every 8 to 12 weeks thereafter. A fasting lipid profile was collected at Baseline and Weeks 12, 24 and 52. Haematological abnormalities (including anaemia, neutropaenia, lymphopaenia and thrombocytosis), changes in lipid parameters, impairment of renal function, increased blood creatine phosphokinase (CPK) levels and abnormalities of liver enzymes (particularly, elevated serum transaminases) were laboratory AEs of special interest with BAR.
- Screening tests for tuberculosis (Chest X-ray and QuantiFERON Gold testing; or PPD skin testing in countries without QuantiFeron Gold testing) were taken at Baseline, but not routinely collected thereafter.
- Vital signs such as blood pressure, heart rate and subject weight were performed at each scheduled study visit.
- ECG was taken at Baseline and at Week 24 to 52 (depending on the study).
- AEs were summarised by the Medical Dictionary for Regulatory Activities (MedDRA) classification using the System Organ Class (SOC) and Preferred Term (PT) nomenclature.

Other studies

Other efficacy studies

The safety and tolerability of BAR in patients with moderately to severely active RA has been supported by data collected in 3 completed Phase II studies (Studies JADA, JADC and JADN). The Phase II trials collected similar types of safety data but with increased intensity/surveillance compared to the Phase III studies.

The submission also contained a synopsis only of Study JAGS. This trial is ongoing and remains blinded. No efficacy or safety data by treatment group was available in this submission. As of 10 August 2015, study drug had been given to 167 patients with moderately to severely active RA who recorded a previous inadequate response to MTX therapy in China (108 patients), Argentina (43 patients) and Brazil (16 patients). No deaths have been reported up to 10 August 2015. There have been 4 SAEs reported in patients who have received study medication: intervertebral disc protrusion, gastric perforation, anaemia and pneumonia. Pneumonia was the only SAE considered by the investigator to be related to study drug. This event occurred 157 days after the beginning of blinded study drug and the patient recovered without sequelae.

Studies with evaluable safety data: clinical pharmacology studies

A total of 19 clinical pharmacology studies were included in this submission, 18 of which were conducted in 557 healthy volunteers and there was one Phase I trial in 53 adult subjects with RA (Study JADB). The majority of the clinical pharmacology studies were single dose BAR studies but some of trials involved multiple dosing with the collection of safety and tolerability for up to 28 days.

Studies evaluable for safety only

Study JADP in skin psoriasis and Study JAGQ in diabetic kidney disease have also been included in this submission to provide additional safety data. Study JADP was a randomised, double-blind, PBO controlled, dose ranging Phase II trial evaluating the use of BAR 2 mg, 4 mg, 8 mg and 10 mg once daily in 271 patients with moderate to severe plaque psoriasis. Study JAGQ was a 24 week, randomised, double-blind, PBO controlled, dose ranging Phase II trial evaluating the safety and renal efficacy of BAR 0.75 mg daily, 0.75 mg twice daily, 1.5 mg daily and 4 mg daily in 130 patients with impaired renal function (CrCL 25 to 70 mL/min) and albuminuria due to type 2 diabetes mellitus despite treatment with angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker.

Patient exposure

In this submission, a total of 3822 subjects have received BAR at any dose and for any treatment indication, including 3464 patients with RA representing a total exposure of 4214.1 patient years (PY) (Table 6). For subjects with RA, 2166 patients (62.5% overall) have received BAR treatment for at least 1 year and 467 subjects (13.5% overall) have received BAR for at least 2 years. Table 6 provides a summary of the total exposure to BAR and PBO therapies in the Phase I to III clinical studies (for all treatment indications).

Table 6: Summary of exposure to baricitinib in clinical studies

	BARI 4-mg RA PC		BARI 2-mg vs 4-mg RA		Ext BARI 2-mg vs 4-mg RA		All BARI RA			All BARI[c]		
	PBO	BARI 4-mg	BARI 2-mg	BARI 4-mg	BARI 2-mg	BARI 4-mg	Phases 1-3	Phases 2-3	Phase 3	Phases 1-3	Phases 2-3	Phase 3
Number of patients, n	1070	997	479	479	479	479	3464	3411	2862	3822	3769	2862
Patient days of exposure (days)												
Mean	102.6[a] 134.4[b]	107.0[a] 150.0[b]	104.7[a] 141.7[b]	104.9[a] 143.0[b]	331.5	364.2	444.3	450.8	441.7	425.5	431.1	441.7
Minimum	1[a] 1[b]	1[a] 1[b]	1[a] 1[b]	1[a] 1[b]	2	2	1	1	1	1	1	1
Median	113[a] 166[b]	113[a] 169[b]	113[a] 168[b]	113[a] 169[b]	257.0	342.0	441.0	444.0	450.5	418.5	421.0	450.5
Maximum	235[a] 235[b]	155[a] 211[b]	134[a] 197[b]	155[a] 211[b]	888	1603	1631	1631	987	1631	1631	987
Total patient-years	300.4[a] 393.8[b]	292.2[a] 409.4[b]	137.3[a] 185.8[b]	137.6[a] 187.5[b]	434.8	477.7	4214.1	4210.0	3461.4	4452.2	4448.2	3461.4
Number of patients with ≥X weeks of exposure, n (%)												
16 weeks	722 (67.5)[a]	754 (75.6)[a]	333 (69.5)[a]	334 (69.7)[a]	-	-	-	-	-	-	-	-
24 weeks	505 (47.2)[b]	653 (65.5)[b]	254 (53.0)[b]	281 (58.7)[b]	-	-	-	-	-	-	-	-
52 weeks	-	-	-	-	172 (35.9)	231 (48.2)	2166 (62.5)	2166 (63.5)	1877 (65.6)	2230 (58.3)	2230 (59.2)	1877 (65.6)

Abbreviations: PC = placebo-controlled

- Indicates that this time point was not analyzed.

[a] Data from treatment period up to Week 16.

[b] Data from treatment period up to Week 24, with data up to rescue.

[c] In addition to patients with RA, also includes patients with psoriasis and diabetic kidney disease from Studies JADP and JAGQ.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Increases in serum transaminases (alanine transaminase (ALT) and aspartate transaminase (AST)) have been noted with other JAK inhibitors (tofacitinib and ruxolitinib) as well as with commonly used DMARDs such as MTX and LEF, plus in RA patients in general. However, up to 16 weeks of treatment with BAR 4 mg versus PBO in the primary integrated safety set, a similar proportion of patients experienced up to 3-fold, 5-fold and 10-fold increases above the ULN for serum ALT and AST values. In the secondary integrated safety set, similar proportions of patients treated with BAR 2 mg and 4 mg therapy recorded significant increases in serum transaminases, which remained consistent and stable over extended treatment follow-up.

No patient in the all exposure BAR population met Hy's law criteria for abnormalities of liver function tests. Among patients in the all exposure BAR RA population, 2.9% (98/3406) of subjects had an increase in serum ALT of 3 x ULN, 0.9% (29/3406) had an increase of up to 5 x ULN and 0.2% (7/3406; 2 cases were not treatment-emergent) had an increase to ≥ 10 x ULN. None of the cases with ≥ 10 fold ALT increases were considered to be probably related to BAR following blinded sponsor review. Approximately 80% of individuals with significantly increased (≥ 3 x ULN) serum transaminases had resolution or improvement in their results with short term follow-up.

Renal function and renal toxicity

Treatment with JAK inhibitors including BAR is associated with small, reversible and dose-dependent increases in serum creatinine and blood urea nitrogen levels through an unknown mechanism. In the Phase III studies, BAR was associated with rapid, small dose-dependent increases in mean serum creatinine values, which plateaued after 8 to 12 weeks of treatment. The change reflected clinically insignificant increases from Baseline in serum creatinine values (< 5 µmol/L) in the majority of BAR treated patients, but in some subjects large, clinically relevant increases in serum creatinine were recorded. Up to Week 16 in the primary integrated safety set, treatment emergent increases in serum creatinine values were recorded in 2.4% (23/951) of BAR 4 mg patients and 1.9%

(19/989) of PBO treated subjects, with no statistically significant difference between treatment groups. Up to Week 16 in the secondary integrated safety set, increases in serum creatinine values were recorded in 2.5% (11/444) of BAR 2 mg patients and 3.6% (16/441) of BAR 4 mg treated subjects, with no statistically significant difference between treatment groups. In the extended secondary integrated safety set, increases in serum creatinine values were recorded in 4.0% (18/445) of BAR 2 mg patients and 6.8% (30/441) of BAR 4 mg treated subjects.

In the all exposure BAR RA population, Common Terminology Criteria for Adverse Events (CTCAE) grade increases in renal function from < 1 to ≥ 1 were common (4.9%; 156/3166), however, the large majority of patients increased to a maximum of Grade 1 (146 of 156 patients). Treatment-emergent CTCAE Grade increases in serum creatinine from < 2 to ≥ 2 and from < 3 to ≥ 3 were uncommon (0.3% (12/3211) and 0.1% (4/3211), respectively). In almost all instances of CTCAE Grade ≥ 2 increases, a direct causal relationship to BAR could not be concluded due to either confounding patient factors (for example, pre-existing renal disease and concomitant illnesses) or because the increase in serum creatinine was transient and resolved with either no interruption of BAR or a temporary interruption with a subsequent negative re-challenge and continuation of treatment.

Other clinical chemistry: Increased serum CPK values

Increases in serum creatinine phosphokinase (CPK) values have been described with JAK inhibitors. Up to Week 16 in the primary integrated safety set, a statistically greater number of patients treated with BAR 4 mg/day (31.0%; 279/893) recorded increases in serum CPK values compared to PBO (7.5%; 72/594). In addition, Grade 3 or higher increases in serum CPK values were recorded in a numerically greater number of BAR treated subjects (0.7%; 7/950) versus PBO (0.2%; 2/1021).

Up to Week 16 in the secondary integrated safety set, increases in serum CPK values were recorded in 18.4% (83/451) of BAR 2 mg patients and 31.1% (136/438) of BAR 4 mg treated subjects, with a statistically significant difference between the treatment groups being observed. In the extended secondary integrated safety set, increases in serum creatinine values were recorded in 26.2% (118/451) of BAR 2 mg patients and 37.7% (165/438) of BAR 4 mg treated subjects ($p < 0.05$). Grade 3 or higher increases in serum CPK values were uncommon but recorded in a numerically greater number of BAR 4 mg versus 2 mg treated subjects (1.5 to 2.5% versus 0.8 to 1.0% of subjects).

In the all exposure BAR population, treatment with BAR was rarely associated with a rapid (within 1 week) increase in CPK values that plateaued after 8 to 12 weeks of treatment (median increase from Baseline of 50 U/L). CPK values rapidly returned to normal following cessation of BAR (Studies JAGQ, JADP, and JADN). In patients with RA, increases in CPK were largely asymptomatic and were not associated with AEs. Treatment with BAR versus PBO was associated with a higher proportion of patients with treatment-emergent CTCAE grade shifts in CPK values. The large majority of these shifts was observed at a single visit and did not lead to interruption or discontinuation of BAR. No subjects developed renal or other organ injury in association with Grade 3/4 CPK increases. Discontinuation of BAR due to an increased CPK level or muscle symptom AE was uncommon (0.2% overall; 8/3464). The sponsor has included in the proposed PI a warning for prescribers to be aware of the occurrence of elevated CPK levels with BAR treatment.

Haematology and haematological toxicity

The haematologic growth promoters erythropoietin, G-CSF, GM-CSF and thrombopoietin signal via the JAK-STAT pathway. Excessive inhibition of these signalling pathways could impair the body's ability to produce erythrocytes, leucocytes or platelets. Myelosuppression has been reported to varying degrees with other JAK inhibitors such as

ruxolitinib and tofacitinib. Given that erythropoietin signals through JAK2 and that haemoglobin decreases have been seen with doses of BAR exceeding 4 mg/day in the Phase II studies, the sponsor has proposed in the PI that BAR should be avoided in patients with haemoglobin < 80 g/L.

Up to Week 16 in the primary integrated safety set, a small but numerically higher number of subjects treated with BAR 4 mg (27.4%) recorded a decrease in haemoglobin level below the lower limit of normal compared to PBO (24.5%). The rates of lymphopaenia were similar between the 2 groups (0.7 to 0.9%). In the secondary integrated safety set, there was a numerically proportion of subjects treated with BAR 4 mg (26.4%) who recorded a decrease in haemoglobin level below the lower limit of normal compared to BAR 2 mg (25.1%), but this observation was not statistically significant. In the extended cohort, the rates of anaemia were slightly higher with BAR 4 mg versus 2 mg therapy (35.0% versus 30.9%, respectively).

In the Phase III clinical studies, neutrophil counts decreased during the first month of treatment with BAR (2 and 4 mg) compared to PBO with a statistically significant decrease in neutrophil counts with BAR 4 mg/day compared to PBO. Neutrophil counts then remained stable over time after 1 month. Up to Week 16 in the primary integrated safety set, more patients treated with BAR 4 mg/day developed CTCAE Grade 3 or 4 neutropaenia compared to PBO (0.3% versus 0, respectively). Up to Week 16 in the secondary integrated safety set, more subjects treated with BAR 2 mg versus 4 mg developed CTCAE Grade 3 or 4 neutropaenia (0.6% versus 0.2%), which persisted in the extended follow-up period. After stopping BAR treatment, neutrophil counts returned toward pre-treatment values for the majority of subjects.

Administration of BAR was also associated with an increase in platelet count which peaked about 2 weeks after starting treatment, and then generally returned towards baseline and remained stable thereafter. The proportion of patients experiencing a shift in platelet count from ≤ 600 to > 600 x 10^9/L was higher for BAR 4 mg compared to PBO in the primary integrated set (2.0% versus 1.1%, respectively) as well as for BAR 4 mg versus 2 mg in the secondary integrated safety set (2.3% versus 1.1%, respectively). A review of cases with treatment emergent platelet counts > 700 x 10^9/L indicated that these values were not associated with clinical thrombotic AEs and permanent discontinuation of BAR for thrombocytosis was rare (0.1%).

Treatment-emergent haemoglobin values of < 80.0 g/L were recorded in 0.5% of patients (16/3407) in the all exposure BAR RA population and permanent discontinuations due to anaemia were rare (< 0.3 per 100 PY of exposure), most of which occurred in patients who were anaemic at baseline and/or who developed a possible or known source of bleeding. However, up to one third of all patients (33.8%; 829/2451) developed at least 1 low haemoglobin level in this dataset suggesting the occurrence of at least mild anaemia is common, but potentially confounded by RA and other treatments. In the all exposure BAR RA population, the incidences of other haematologic abnormalities remained consistent with the controlled data observations. In particular, the incidence of Grade 3 to 4 lymphopaenia was 1.9% (66/3403), Grade 3/4 neutropaenia was 0.7% (23/2386) and thrombocytosis was 2.4% (80/3380). Haematological abnormalities resulted in < 1% of all subjects permanently discontinuing BAR but was a common cause for temporary dose interruptions.

Lipid profiles

Treatment with BAR was associated with statistically significant increases in serum total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol with no change in the overall LDL/HDL ratio as well as triglycerides and apolipoprotein B. Lipid levels reached a plateau at Week 12 and in patients for whom statin therapy was initiated, LDL cholesterol usually returned to normal or baseline levels.

Compared to PBO in the primary integrated safety set, BAR 4 mg/day treatment at 16 weeks resulted in statistically more patients exhibiting abnormally high lipid readings such as 33.6% versus 10.3% having LDL cholesterol ≥ 3.36 mmol/L. The secondary integrated safety set supported the observation that BAR therapy was associated with inducing lipid profile abnormalities compared to PBO, but also indicated a BAR dose effect relationship for this safety concern. For example, the Week 16 incidence of LDL cholesterol being ≥ 3.36 mmol/L was 28.5% for BAR 4 mg/day therapy versus 20.2% for BAR 2 mg/day (and 11.6% for PBO).

In the all exposure BAR RA population, the pattern and incidence of increases in serum LDL cholesterol and triglycerides with prolonged exposure remained consistent with observations in the controlled study periods. The proportion of patients with categorical increases in lipid parameters based on the National Cholesterol Education Program ATP III criteria were 19.8% (365/1842) for serum total cholesterol (from < 5.17 mmol/L to ≥ 6.21 mmol/L), 13.7% (242/1768) for LDL cholesterol (from < 3.36 mmol/L to ≥ 4.14 mmol/L) and 12.9% (298/2309) for triglycerides (from < 1.69 mmol/L to ≥ 2.26 mmol/L). Increases in HDL cholesterol from low values (< 1.03 mmol/L) to normal or high values (≥ 1.03 mmol/L) were recorded in 43.2% (96/222) of subjects.

Electrocardiograph findings and cardiovascular safety

Up to Week 16 in the integrated safety analyses (primary and secondary), very few patients developed treatment emergent prolongation in the QT interval on routine ECG monitoring, up 0.5% of subjects in the PBO arms and 1 subject each (0.1 to 0.2%) treated with BAR 2 mg and 4 mg/day. Syncope was rare in all treatment groups (PBO as well as BAR 2 and 4/ mg) and did not appear to be treatment related.

In the all exposure BAR population, 3 subjects (0.1%) developed treatment emergent QT interval prolongation and 1 patient was identified as having ventricular tachycardia. Syncope was rare and affected 0.4% (17/3822) of patients at an Exposure adjusted incidence rate (EAIR) of 0.38 in the all exposure BAR population.

The Phase I Study JADO (a specific QT interval trial) investigated the effects of BAR upon ECG parameters in healthy subjects and found no evidence that BAR prolongs the QT interval to a clinically significant degree.

Vital signs and clinical examination findings

Weight gain

In the integrated safety analysis sets, a statistically greater proportion of patients treated with BAR 2 mg or 4 mg (approximately 7%) compared to PBO (approximately 2%) experienced weight gain of ≥ 7% from baseline to Week 16. The proportion of patients reporting weight gain of ≥ 7% was numerically greater with BAR versus PBO for patients in all size strata, but weight gain was largest for patients with baseline body weight < 60 kg. An analysis of the percentage change from Baseline to Week 24 in waist circumference followed the same trend. The differences from Baseline in weight, BMI and waist circumference between BAR 4 mg/day and PBO indicate that treatment with BAR is leading to an increase in weight. Weight gain has been described in association with effective control of RA using a variety of approved DMARDs including MTX, TNF inhibitors and tofacitinib. Consistent with these prior findings, statistically significant weight increases were also observed for MTX treated subjects in Study JADZ, and for adalimumab treated patients compared to PBO in Study JADV. It has been postulated that these changes largely reflect improvements in disease activity, improved nutrition and reversal of RA related cachexia.

Hypertension

Hypertension AEs were reported by a numerically larger proportion of patients treated with BAR 2 mg (3.3%) and 4 mg (2.6 to 3.1%) compared to PBO (1.1 to 1.8%) in both of

the integrated safety datasets. However, this observation was not consistently observed across all of the Phase II and III studies in subjects with active RA.

Immunogenicity and immunological events

Because BAR is an oral targeted synthetic DMARD (in contrast to biologic DMARD therapy administered by IV infusion or SC injection) it is not expected nor observed to produce immunogenicity reactions. In the all exposure BAR population, 5 possible anaphylactic reactions have been reported (including 1 occurring prior to BAR treatment and 2 cases long after treatment cessation), but none were confirmed upon review of case details. Three patients reported angioedema and in all of the cases the cause was specified as a concomitant medication (antibiotic or ACE inhibitor). There is no data to suggest a causal relationship between BAR and hypersensitivity AEs.

Serious skin reactions

Because BAR is an oral targeted synthetic DMARD (in contrast to biologic DMARD therapy administered by IV infusion or SC injection) it is not expected to produce an increased incidence of allergic or photosensitive skin reactions. In the all BAR exposure population, serious skin reactions were not observed at an increased incidence or severity in those exposed to BAR. Treatment emergent skin exfoliation was reported as an AE by 5 patients in the all exposure BAR population. The AEs were all rated as mild or moderate in severity, and no action was taken for any event. In 4 of the patients, the AEs followed hospitalisation for other confounding reasons. The temporal relationship to hospitalisation in most cases suggests that intercurrent illness, its treatment or in-hospital environmental contact may have contributed to the AEs.

Major adverse cardiovascular events (MACE)

Patients with RA are at an increased risk of Major Adverse Cardiovascular Events (MACE) and the level of risk is also related to disease activity over time. During the Phase III trial program, an independent committee adjudicated on potential MACE. Overall, no significant differences in the rates of MACE between BAR and PBO, between BAR and active comparators (adalimumab and MTX) and between the doses of BAR (2 to 4 mg/day) were seen during short and medium term drug exposure; [see Attachment 2]. A total of 16 BAR treated patients in the Phase III studies had at least 1 positively adjudicated MACE at 0.46 MACE per 100 PY. Another 25 BAR treated patients in the Phase III studies had at least 1 positively adjudicated cardiovascular AEs (for example, heart failure and coronary revascularisation) excluding MACE (0.72 AEs per 100 PY). The current dataset is limited by the relatively small number of subjects who have received prolonged treatment with BAR and the small number of MACE episodes in each analysis set. Given the uncertainty surrounding the long term clinical implications of atherogenic lipid changes seen with BAR with respect to MACE outcomes in RA, the sponsor has included MACE in the RMP as an important potential risk with BAR. However, the currently available data does not support the recognition of MACE as an important identified risk with BAR therapy.

In addition, the rates of MACE did not appear to increase over time with continued BAR treatment (that is, up to 96 weeks of continuous therapy); refer to Attachment 2.

Safety in special populations

Pregnancy and lactation

The effects of BAR on human fetal development are unknown. The JAK/STAT pathway has been shown to be involved in early embryonic development, particularly in relation to skeletal development. As of 10 August 2015, 15 women had become pregnant during their study participation including 12 exposed to BAR during their first trimester of pregnancy, 2 women received adalimumab only and 1 patient received PBO only. Pregnancy outcome information is available for 10 of the 12 pregnancies, and the other 2 pregnancies had pending outcomes. Of the 12 women exposed to BAR, 5 delivered healthy infants (either

full-term or premature) and 5 had either spontaneous (n = 4) or elective abortions (n = 1). There was also 1 pregnancy in the partner of a male patient exposed to BAR. This pregnancy was carried to term and the infant had no evidence of fetal malformation. After the data cut-off date of 10 August 2015, 4 additional pregnancies in study participants and 1 additional pregnancy in the partner of a male patient have been reported (all occurred in Study JADY in patients taking BAR 4 mg/day). Two pregnancies resulted in elective termination, 1 resulted in a premature birth with no evidence of adverse fetal outcome and 1 pregnancy was ongoing. The pregnancy exposure via the treated male partner is also ongoing. It is unknown whether BAR is excreted into human milk by lactating women.

Patient subgroups

The sponsor has also conducted an analysis of the safety data according to various subgroups based on demographic and co-morbid factors. The subgroup analyses included age (for example, < 65 years, ≥ 65 years and ≥ 75 years), gender, race, subject weight (< 60 kg, 60 to 100 kg and > 100 kg) and impaired renal function at Baseline. Some of the subgroups were too small in number to make reliable data interpretations; however, none of the factors appeared to significantly influence the exposure adjusted incidence rate or type of AEs, apart from older subjects being associated with a higher incidence of SAEs and discontinuations due to AEs, which was primarily explained by myelosuppressive AEs and vascular disorders. There was no analysis of concomitant use of oral CS on the incidence or type of AEs.

Safety related to drug-drug interactions and other interactions

Clinical pharmacology studies have been conducted to examine the potential for other drugs to affect the PK of BAR. Among inhibitors and inducers of CYP3A (ketoconazole/fluconazole and rifampicin, respectively) and inhibitors of the OAT3 transporter (probenecid) examined in clinical pharmacology studies, only probenecid had a clinically meaningful effect on the PK of BAR. Concomitant administration of probenecid doubled the exposure (AUC) to BAR and as such a BAR dose of 2 mg once daily is recommended if OAT3 inhibitors with a strong inhibition potential, such as probenecid, are administered concomitantly. Other OAT3 inhibitors that are common co-medications in RA patients, such as ibuprofen and diclofenac, have less inhibition potential than probenecid and were predicted using PK modelling to not interact significantly with BAR. Clinical pharmacology studies have also been conducted to examine the potential of BAR to inhibit or induce CYPs and drug transporters and, therefore potentially affect the PK of co-administered drugs. BAR does not appear to have a clinically significant effect on the PK of any of the probe substrates studied (simvastatin, ethinyl estradiol/levonorgestrel, digoxin and MTX). Studies of BAR therapy co-administered with vaccines, biologic DMARDs and with other JAK inhibitors have not been conducted.

Post-marketing data

Not applicable as BAR has not received marketing authorisation anywhere in the world at the time of this submission.

Evaluator's conclusions on safety

In this submission, the clinical safety dataset for the use of BAR in adult patients with active RA consists of 4214 PY of drug exposure involving 3464 patients enrolled in one Phase I drug interaction trial (Study JADB), 7 completed Phase II/III studies and one ongoing LTE trial (Study JADY). The overall safety database for BAR therapy consists of 3822 patients (4452 PY of drug exposure) treated with any dose of BAR as this cohort includes data from 2 completed Phase II trials in psoriasis (Study JADP) and diabetic nephropathy (Study JAGQ). For adult subjects with active RA at Baseline, 2166 patients have received treatment for at least 1 year and 467 subjects have received BAR therapy

for at least 2 years. In terms of the BAR doses being requested for approval in this submission, > 1000 patients have received 4 mg once daily therapy and 479 patients have received 2 mg once daily treatment in the PBO controlled population. The majority of BAR treated patients in the all exposure RA dataset received concurrent MTX, with more than half taking concomitant NSAIDs and/or concurrent low dose oral CS. Overall, there is a sufficient volume of data to make a meaningful assessment of BAR safety for up to 2 years of treatment in the newly proposed treatment indication of active RA.

Compared to PBO, a numerically higher incidence of serious AEs and AEs resulting in permanent treatment discontinuation were observed with BAR treatment, with some of the AE types (mainly, various laboratory abnormalities including increased serum CPK and lipid levels) occurring at a higher incidence in the higher dose BAR treatment cohort (4 mg once daily versus 2 mg once daily). Infection was the most common AE recognised with BAR and these occurred at a higher frequency with BAR 2 and 4 mg once daily treatment versus control therapy during the true PBO-controlled treatment periods (first 16 to 24 weeks for the pivotal Phase III trials). The majority of infections were mild in severity, self-limiting, and were predominately upper respiratory tract infection (URTI), urinary tract infection or nasopharyngitis. The use of concurrent MTX did not appear to increase the overall risk of AEs, including infection related AEs (Study JADZ). Nausea (often in the absence of other gastrointestinal symptoms) was more commonly reported with BAR 4 mg/day therapy versus PBO, and approximately half of all cases occurred within 2 weeks of commencing treatment. Acne and alopecia have also been reported in < 2% of patients treated with BAR.

In the integrated safety dataset populations, there was an increased incidence of overall but not serious infection with BAR versus PBO and active comparators, which is surprising for the PBO controlled comparison. Although there was no clear signal of increase risk of opportunistic infection with BAR, in the long-term safety population 3 cases of *Pneumocystis* pneumonia (all in Japanese subjects) and 5 non-serious cases of oesophageal candidiasis have been recorded. During the controlled trial periods, 2 patients developed overt tuberculosis infection in the BAR clinical study program (1 treated with BAR 4 mg/day and the other received adalimumab). In the uncontrolled LTE period, 6 additional cases of tuberculosis (TB) (3 unconfirmed by microbiology) have been reported with BAR. All observed TB cases occurred in countries where TB is prevalent and the sponsor has included a warning about the risk of TB and screening pre-treatment in the proposed PI. In the long-term exposure population, 16 subjects (all in Asia) have recorded detectable HBV DNA after receiving BAR, including 8 cases in the controlled periods of the trials. However, there was a clear increased risk of herpes zoster and oral herpes viral infections with BAR versus PBO. This finding may be expected given the effects of JAK inhibition. A BAR dose effect was observed for the risk of herpes zoster infection. The majority of herpetic infections were rated as mild or moderate in severity, and responded to standard treatment.

Permanent discontinuations from treatment due to AEs up to 24 weeks occurred at a higher frequency with BAR 4 mg/day (EAIR of 11.5-13.9 per 100 PY) versus PBO (EAIR of 8.6 to 11.1 per 100 PY), MTX (EAIR of 6.4) and adalimumab (EAIR of 4.9). Compared to MTX and PBO, the main reason for more patients ceasing BAR 4 mg/day was an increased incidence of herpes zoster infection. Compared to adalimumab, the main explanation for the increased incidence of treatment discontinuation with BAR 4 mg/day was the 2-fold increased EAIR of infection. Cessation of BAR 2 mg/day up to 24 weeks occurred at a similar incidence to PBO (10.8% versus 11.1%, respectively, in the secondary integrated safety set).

A total of 36 deaths (27 in BAR treated subjects) have been reported in the all exposure BAR population up to 30 November 2015, including 5 MACE and 4 cancer related deaths in BAR treated subjects. Mortality rates and the causes of death were similar between BAR

and PBO or comparator therapies (MTX and adalimumab) in relatively short term treatment follow-up (up to 2 years). The rate of MACE in the RA dataset is within expectations for the treatment population and the types of MACE observed did not identify any specific safety signals with BAR. However, longer periods of treatment follow-up are required to inform about these 2 potential safety concerns.

Increases in serum CPK values and lipid levels are recognised safety concerns with JAK inhibition and were observed with BAR in the RA treatment studies. Up to 24 weeks, the overall incidence of LDL cholesterol values ≥ 3.36 mmol/L were 2 to 3 fold higher with BAR 4 mg/day treatment (≥ 40%) compared with PBO (13.5 to 17.0%) and were also numerically greater compared to active comparator therapies (29% with MTX monotherapy and adalimumab). The long-term clinical consequences of increased rate of atherogenic lipid profiles associated with BAR remains unknown. BAR 2 mg/day treatment had a slightly lower frequency of inducing elevated lipid profiles (approximately one third) compared to BAR 4 mg/day. Small increases in serum CPK values were frequent with BAR therapy but the percentage of patients who recorded Grade 3 or higher elevations in CPK were 0.8 to 1.5% (slightly higher incidence with BAR 4 mg versus 2 mg). There was also a slightly higher incidence of anaemia and Grade 3 or 4 neutropaenia and lymphopaenia observed with both doses compared to PBO as well active comparator treatment with MTX and adalimumab. There was also a slightly higher incidence of thrombocytosis (platelet count > 600 x 10^9/L) observed in patients treated with BAR.

In summary, the safety data indicates that BAR has an acceptable overall safety profile up to 2 years of therapy in the treatment of adult patients with moderately to severely active RA. There is limited long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and MACE, which will require additional longitudinal safety follow-up. From my assessment of the safety dataset, there are some significant safety concerns with BAR therapy including the risk of infection, opportunistic infection (mainly, oral herpes and zoster infection), increased serum CPK values, anaemia, neutropaenia, thrombocytosis, abnormal liver function tests (raised serum transaminases) and dyslipidaemia. These safety concerns are consistent with the known profile of JAK inhibitor therapy in adult patients with RA. Significant pharmacovigilance will be required if approval is granted for registration of BAR for the treatment of RA. This would include vigilance for serious and opportunistic infections, MACE and malignancy (particularly, non-melanoma skin cancers).

First round benefit-risk assessment

First round assessment of benefits

Table 7 (shown below) gives the benefits along with the strengths and uncertainties as was assessed at the first round evaluation.

Table 7: First round assessment of benefits

Indication: Treatment of active rheumatoid arthritis in adult patients	
Benefits	Strengths and Uncertainties

Indication: Treatment of active rheumatoid arthritis in adult patients	
BAR produces improvements in the symptoms and signs of active RA (as per the ACR clinical response criteria) that are superior to PBO and MTX and non-inferior to adalimumab.	Consistently observed in Phase III trials.
BAR results in improved physical function in patients with active RA (as per HAQ-DI responses) that are superior to PBO and MTX and non-inferior to adalimumab.	Consistently observed in Phase III trials.
BAR results in improvements in several patient reported outcomes such as duration and severity of morning stiffness in patients with active RA that are superior to PBO and MTX and non-inferior to adalimumab.	Consistently observed in Phase III trials.
BAR may result in statistically lower rates of structural disease progression at 24 and 52 weeks compared to PBOI and MTX alone, but the magnitude of that effect is of unclear clinical significance.	Preliminary data only; not consistent across the 3 pivotal trials. Regulatory guideline of relevance recommends at least 2 years of data in assessing X-ray claim.
Persistence of clinical response for up to 2 years in the subgroup of patients who are tolerating and responding to BAR 4 mg/day.	Supported by the efficacy outcomes reported in the interim report for the LTE Study JADY.
Significant clinical response to BAR 4 mg/day monotherapy versus MTX alone, which is not different to that seen with BAR + MTX. This supports the request for registration of the BAR monotherapy treatment option.	Supporting BAR monotherapy data largely restricted to the observations of 1 pivotal study (Study JADZ) which enrolled DMARD naïve subjects with early disease (limited population generalisability).
Convenient mode of administration (oral ingestion) with an acceptable dosing schedule (once daily without regard to food).	Supported by PK data for BAR. Alternative DMARD therapy with biologic requires IV or SC drug administration.
Clinical efficacy response with BAR therapy observed across a diverse patient spectrum and in all patient subgroups.	Supported by the Phase II/III clinical study program and the integrated efficacy analysis sets.

First round assessment of risks

Table 8, shown below, gives the risks along with their strengths and uncertainties as assessed at the first round evaluation.

Table 8: First round assessment of risks

Risks	Strengths and Uncertainties
Increased incidence of infection with BAR versus PBO	Phase III studies.
Increased incidence of nausea with BAR versus PBO	Phase III studies.
Increased incidence of permanent treatment discontinuations due to AEs with BAR versus PBO and adalimumab.	This was consistently observed in the Phase II and III clinical studies.
Increased incidence of herpes zoster infection with BAR versus PBO and adalimumab.	Observed in Phase III trials.
Increased incidence of haematologic abnormalities such as anaemia and Grade 3 or 4 neutropaenia and lymphopaenia with BAR versus PBO and adalimumab.	Observed in Phase III trials.
Increased rates of raised atherogenic lipid profiles with BAR versus PBO and active comparator, however, no increased rate of MACE has been recorded in medium term follow-up.	This was consistently observed in the Phase II and III clinical studies. In the integrated safety dataset, the incidence and type of MACE was not increased with BAR but follow-up is limited to 2 years at present.
Increased rates of raised serum CPK values with BAR versus PBO and active comparator as well.	This was consistently observed in the Phase II and III clinical studies.
Live vaccines and biological DMARD therapies cannot be given concurrently with BAR.	The sponsor has not provided any studies examining for these outcomes.
Potential for drug-drug interactions, of which, probenecid is currently identified to be the main one of concern requiring BAR dose reduction.	The sponsor has conducted a thorough clinical pharmacology development program that has assessed this risk.
BAR has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction, those at risk of reactivated TB, and in pregnant/lactating women.	The population with inadequate data regarding BAR therapy are identified in the current RMP.

First round assessment of benefit-risk balance

The overall benefit-risk balance of BAR, with or without combination non-biologic DMARD (mainly, weekly low dose oral MTX) in adult patients with moderately to severely active RA, who have had an inadequate response to or intolerant of at least 1 DMARD, with respect to reducing the symptoms and signs of RA as well as improving physical function is favourable. Data from the recent disease onset, DMARD naïve population of Study JADZ reveals an unclear benefit-risk balance with BAR (that is, better clinical efficacy but at the cost of increased side-effects compared to the current standard of care: weekly low dose MTX). The claim of radiographic benefit with BAR in RA is an add-on claim to an overall treatment indication, which has not been demonstrated with 4 mg/day monotherapy in a DMARD naïve population (Study JADZ, Week 24 and 52 X-ray results) and the overall radiographic dataset has not reached sufficient maturity to meet the TGA adopted regulatory guideline of relevance, whereby robust X-ray evidence of benefit over 2 years in RA is required.

BAR is a small molecule drug that selectively inhibits JAK1 and JAK2 and it thereby blocks the effects of various pro-inflammatory cytokines. In this submission, BAR has been evaluated in a large clinical program, which complied with CHMP guidelines for evaluation of treatment in RA. The clinical studies have evaluated an adequate number of subjects over a sufficient time frame in the target patient population and demonstrated that BAR 2 and 4 mg once daily is an effective option in reducing the clinical manifestations of active RA. The complete radiographic dataset (up to 52 weeks thus far) suggests superior inhibition of X-ray progression in a second line of treatment RA population (that is, after an adequate trial of conventional DMARDs), and possible superiority in a first line treatment population when used in combination with MTX.

The short and medium term safety profile of BAR observed in the clinical safety dataset included in this submission is largely consistent with expectations. The majority of commonly reported AEs were anticipated side effects in the RA population receiving immunosuppressant drugs (such as various types of mild severity infection) or abnormal laboratory results consistent with JAK inhibition (such as increases in CPK and lipid levels). The risk profile of BAR is based on a total of 2862 BAR treated patients with RA involved in the Phase III studies, as well as additional safety information collected from 3822 patients treated with any dose of BAR in the all exposure population (including 3464 subjects with RA).

In the RA trials, there was an increased incidence of overall infection with BAR compared to PBO. The majority of reported infections were of mild or moderate severity, and involved either the upper respiratory or urinary tracts. Herpes related infections (zoster and oral) were also more frequent with BAR compared to PBO. However, very serious opportunistic infections like TB were reported with BAR.

Raised CPK levels were more frequently observed with BAR than PBO, but most cases were of mild or moderate severity and reversible. There was also an increased incidence of mild-moderate hepatic transaminase elevations and dyslipidaemia with BAR versus PBO. The clinical consequences of an increased incidence of atherogenic lipid abnormalities with BAR was not seen in the dataset thus far but required multi-year follow-up (5 to 10 years of reporting). Cases of anaemia and thrombocytosis were also observed with BAR. Significant changes in laboratory parameters associated with BAR were generally managed by dose interruptions or cessation.

Malignancy represents a theoretical risk with any immunosuppressive therapy, but there is no clear evidence that BAR confers an increased risk for certain types of malignancy such as non-melanoma skin cancers and lymphoma in the current dataset.

First round recommendation regarding authorisation

The clinical evaluator recommends acceptance of the sponsor's request for the registration of BAR (monotherapy or in combination with conventional DMARD) for the treatment of moderately to severely active RA in adult patients who have failed to respond to or are intolerant of at least one conventional DMARD with respect to reducing the symptoms and signs of RA, as well as improving physical function. The evaluator does not recommend acceptance of the sponsor request to include the add-on claim of radiographic benefit with BAR at this stage (based on the dataset in the current submission).

Apart from abatacept, all other approved DMARD therapies for RA do not specifically include a sub-claim of improving physical functioning in the treatment indication wording, yet all of those therapies have demonstrated such an effect with the supporting trial data included in the Clinical Trials section of their PI. For consistency across the DMARD options (excluding abatacept), the evaluator recommends the sub-claim of improving physical functioning be removed from the treatment indication wording for BAR, and the supporting information for this sub-claim (mainly, improvements from Baseline in HAQ-DI scores) remain included in the Clinical Trials section of the PI. Another JAK inhibitor (tofacitinib) approved for use in patients with RA has a specific wording in the treatment indication that it should only be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA. The evaluator recommends that same wording be also included in the BAR treatment indication wording, as BAR has a potential benefit and side effect profile that requires familiarity with its therapeutic impact in a special patient population, which is beyond the scope of non-specialised medical practice.

In addition, the evaluator recommends the treatment indication specifically state that BAR should only be used in a second line treatment population as the benefit: risk assessment in a DMARD naïve population, with predominantly recent onset disease, is unclear. There is only 1 pivotal Phase III trial in the current dataset (Study JADZ), which has examined for efficacy and safety in the DMARD naïve, early disease treatment population. Data from this study reveals an unclear benefit-risk balance with BAR (that is, better clinical efficacy but at the cost of increased side-effects compared to the current standard of care: weekly low dose MTX).

Based on the benefit: risk evaluation, the proposed standard dose of BAR 4 mg once daily is justified, with labelling recommending a lower dose of 2 mg/day for a selected subgroup of patients. The data also indicates that BAR can be used as monotherapy or in combination with conventional DMARD therapy.

Taking all of the above statements into consideration, the recommended treatment indication wording is:

> *Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to 1 or more disease modifying anti-rheumatic drugs (DMARDs) has been inadequate. Olumiant can be given as monotherapy or in combination with methotrexate. Therapy with Olumiant should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA.*

No significant inaccuracies of information have been included in the proposed PI, however, the PI contains insufficient information regarding two important safety aspects: 1) insufficient advice with respect to the use of BAR when significant laboratory abnormalities occur; and 2) minimum time frame between receipt of live vaccination and commencement of BAR.

Should approval of the sponsor's proposed registration of BAR in the treatment indication of active RA is granted, the evaluator recommends that approval be subject to:

- satisfactory response to the clinical questions (see Attachment 2 for details);

- satisfactory response to inadequate safety recommendations in the proposed PI;
- regular periodic safety update reports; and
- the sponsor provides the TGA with the final clinical study reports for the LTE Study JADY and Study JAGS when available.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions (mainly, Questions 1 to 3), the benefits of BAR 4 mg daily therapy for the treatment of adult patients with active RA in the proposed usage are unchanged to those identified in the first round assessment of benefits (see above). The supporting dataset for BAR use in a DMARD naïve population with poor prognostic factors is limited to the single pivotal, Phase III Study JADZ which was a well conducted trial in general, but had significant limitations with respect to the generalisability of that data to clinical practice. In particular, the comparator treatment arm for up to 52 weeks was MTX monotherapy with approximately one quarter of subjects receiving sub-optimal doses of MTX (< 17.5 mg/week) over that extended period of time. In clinical practice and according to treatment guidelines (for example, EULAR);[20] those high risk patients should be treated with higher doses of MTX (20 to 25 mg/week), often in combination with other conventional DMARD therapies if insufficient clinical response cannot be achieved with MTX monotherapy. These features of Study JADZ limit the external validity of its findings. In addition, the screen failure rate for Study JADZ was 50.2% and with approximately one quarter of MTX monotherapy treated subjects receiving an insufficient dose of MTX for unclear reasons (other than they were recruited from Asian countries), there is considerable uncertainty about the trial external validity. The sponsor needs to explain the rationale for that justification and reflect on how those features (for example, lack of a combination conventional DMARD treatment strategy in the comparator arm) affect the external validity of the trial findings to the Australian treatment setting.

Second round assessment of risks

After consideration of the responses to the clinical questions (principally, Question 4), the risks of BAR are unchanged from those identified in the first round assessment. The increased rate of infection and nausea with BAR therapy versus PBO; and the higher incidence of permanent treatment discontinuation due to AEs, raised atherogenic lipid profiles, cytopaenias and herpes zoster infection with BAR versus PBO and adalimumab remains a consistent safety signal. Other clinically significant AEs such as the risk of MACE, death and malignancy remain within expectations for the RA population cohort, but the current dataset for examining these major safety concerns is of limited duration at

[20] EULAR response criteria = The EULAR (European League against Rheumatism) response criteria are based on the assessment of disease activity using the Disease Activity Score (DAS), a statistically-derived index consisting of number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.

present, and such AEs typically require many years of treatment follow-up for adequate assessment.

Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, there is no change to the opinion expressed in the first round assessment. The overall benefit-risk balance of BAR treatment (with or without combination non-biologic DMARD, mainly MTX) in the proposed treatment indication claim of second line therapy is favourable. However, the risk-benefit assessment in the proposed treatment indication of BAR use in DMARD naive subjects with active RA and poor prognostic factors as well as the sub-claim of benefit for slowing the progression of structural damage remains unclear. Clinically relevant efficacy has been observed with BAR therapy in the second and first line treatment RA population, but the external validity of the comparator treatment group in Study JADZ has limited external validity to contemporary Australian practice and internationally accepted guidelines (EULAR). Furthermore, the comparison between BAR and adalimumab in Study JADV with respect to their overall benefit-risk balance needs additional scrutiny as this information impacts upon the presentation of data in the proposed PI. The major risks with BAR therapy (versus PBO) include an increased risk of infection, raised serum transaminases, atherogenic lipid profiles, neutropaenia and lymphopaenia.

Second round recommendation regarding authorisation

The clinical evaluator recommends acceptance of the sponsor's request for the registration of BAR (monotherapy or in combination with conventional DMARDs) for the treatment of moderately to severely active RA in adult patients who have failed to respond to, or are intolerant of, at least 1 DMARD with respect to reducing the symptoms and signs of RA, as well as improving physical function. The evaluator does not recommend registration of the sponsor proposal of a treatment indication for BAR in a DMARD naïve population with poor prognostic features as the benefit: risk assessment in this patient population remains unclear. There is only 1 pivotal Phase III trial in the current dataset (Study JADZ), which has examined for efficacy and safety in the DMARD naïve, early disease treatment population. Data from this study reveals an unclear benefit-risk balance with BAR (that is, better clinical efficacy but at the cost of increased side-effects compared to the current standard of care, weekly low dose MTX). The sponsor has already accepted the removal of the add-on claim of radiographic benefit with BAR at this stage (based on the dataset in the current submission), which is appropriate.

Based on the benefit: risk evaluation, the proposed standard dose of BAR 4 mg once daily is justified, with a lower dose of 2 mg/day recommended for a selected subgroup of patients (for example, those with significant renal impairment). The data also indicates that BAR can be used as monotherapy or in combination with conventional DMARD therapy. The sponsor has agreed to add specific wording to the *Dosage and Administration* section of the PI (but not the treatment indication wording) that BAR should only be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA. This is a non-critical issue to the registration of BAR.

Apart from abatacept, all other approved DMARD therapies for RA do not specifically include a sub-claim of improving physical functioning in the treatment indication wording, yet all of those therapies have demonstrated such an effect with the supporting trial data included in the *Clinical Trials* section of their PI. For consistency across the DMARD options (excluding abatacept), the clinical evaluator continues to recommend the sub-claim of improving physical functioning be removed from the treatment indication wording for BAR, and the supporting information for this sub-claim (mainly,

improvements from Baseline in HAQ-DI scores) should remain included in the *Clinical Trials* section of the PI. The sponsor has disagreed with this recommendation and maintained the specific wording of *'Olumiant has been shown to improve physical function and reduce the signs and symptoms of RA'.* This is an ongoing, non-critical issue to BAR registration.

Taking all of the above statements into consideration, the recommended treatment indication wording for BAR is:

> *Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to 1 or more disease modifying anti-rheumatic drugs (DMARDs) has been inadequate. Olumiant can be given as monotherapy or in combination with methotrexate. Therapy with Olumiant should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA.*

No significant inaccuracies of information have been included in the newly proposed PI, however, the PI contains insufficient information regarding the comparative safety of BAR and adalimumab as observed in Study JADV.

The clinical evaluator recommends the continued registration of BAR for the treatment of active RA is subject to regular periodic safety update reports and when available, the sponsor provides the TGA with the final clinical study report for the long-term Study JADY.

Third round clinical benefit-risk assessment

Benefits

After consideration of the sponsor responses in the latest (additional) evaluation material (see *Additional evaluation material supplied following the second round evaluation* in Attachment 2), the benefits of BAR 4 mg daily therapy for the treatment of adult patients with active RA in the proposed usage are unchanged to those identified the first and second round evaluations. The sponsor has appropriately withdrawn seeking an indication in DMARD naïve subjects with poor prognostic factors. The only other efficacy related issue raised in the latest evaluation material is concern by the FDA that the sponsor has not adequately justified a clear dose related benefit with BAR 4 mg once daily versus BAR 2 mg once daily. The clinical evaluator believes the totality of the submission data supports that BAR 4 mg once daily should be the typical dose of treatment. In particular, the more stringent clinical endpoints of clinical remission are consistently, numerically higher with the BAR 4 mg daily regimen (versus 2 mg daily) in the 2 Phase III studies that examined for dose response. In addition, among the subset of patients who had achieved satisfactory and sustained RA control after at least 15 months of treatment with BAR 4 mg/day and who dose reduced to 2 mg/day in a randomised, double blind manner in the long-term extension Study JADY, a statistically significant increase in RA activity at a subsequent 12 week evaluation was observed compared to subjects who continued BAR 4 mg/day. Overall, the clinical evaluator interprets the data to demonstrate a scientifically robust, additional clinical benefit with BAR 4 mg versus 2 mg daily therapy, which should be registered as the typical posology.

Risks

After consideration of the sponsor responses in the latest (additional) evaluation material, the risks of BAR therapy for the treatment of adult patients with active RA in the proposed usage are unchanged to those identified in first and second round evaluations. The main safety related issue raised in the latest evaluation material is the potential for an increased risk of VTE with BAR. However, the sponsor has provided additional (new) analyses to

explain that this observation may be explained by alternative reasons such as a higher frequency of traditional VTE risk factors in BAR 4 mg treated subjects. The risk of VTE did not accumulate over time (up to 120 weeks of follow-up) and there was no dose response effect with BAR in the extended safety dataset. In addition, there was no association between increases in platelet count (often observed with initiation with BAR therapy) and VTE episodes to make that a plausible biologic link.

Assessment of benefit-risk balance

After consideration of the additional evaluation material, there is no change to the opinion expressed in the first and second round evaluations.. The overall benefit-risk balance of BAR 4 mg once daily treatment (with or without combination non-biologic DMARD, mainly MTX) in the proposed treatment indication of second line therapy is favourable. The sponsor has withdrawn from seeking a treatment indication listing in DMARD naive subjects with active RA and poor prognostic factors. The sponsor has made several significant changes to proposed PI which are considered appropriate and supported by evidence in the submission.

Third round recommendation regarding authorisation

The clinical evaluator recommends acceptance of the sponsor's request for the registration of BAR (monotherapy or in combination with conventional DMARD) for the treatment of moderately to severely active RA in adult patients who have failed to respond to, or are intolerant of, at least 1 DMARD with respect to reducing the symptoms and signs of RA, as well as improving physical function. The sponsor has accepted the removal of the indication claim in the DMARD naïve population with poor prognostic features. The sponsor has provided a sufficient response with new analyses to address the potential concerns raised by the TGA and major overseas regulators (FDA and EMA). Based on a benefit: risk assessment of the latest (updated) evaluation material, the proposed standard dose of BAR 4 mg once daily is justified, with a lower dose of 2 mg/day recommended for a selected subgroup of patients (for example, those with significant renal impairment).

The sponsor has agreed to add specific wording to the PI regarding the potential risk of venous thromboembolism and this aptly addresses the main ongoing potential safety concern with BAR. A specific black box warning (or an equivalent strict label warning in Australia) is not recommended with BAR as this is appropriate when there is reasonable evidence of an association of a serious hazard with the drug. The current level of evidence between BAR and the risk of VTE does not meet that threshold of probability regarding causation for such a stringent label warning. In addition, the sponsor has also responded to the majority of other relevant issues in the latest version of the PI. If BAR is granted registration, this should be subject to provision of an updated RMP and Australian Specific Annex (ASA).

Taking into consideration all of the above statements, the recommended treatment indication wording for BAR is:

> *Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to 1 or more disease modifying anti-rheumatic drugs (DMARDs) has been inadequate. Olumiant has been shown to reduce the symptoms and signs of RA and to improve physical function. Olumiant can be given as monotherapy or in combination with methotrexate. Therapy with Olumiant should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA.*

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[21]

The sponsor submitted EU-RMP version 1.0 (dated 18 January 2016; data lock point (DLP) 2 October 2015) and an ASA version 1.0 (date not specified; presumed January 2016) in support of this application. An updated EU-RMP and ASA were provided in the post first round response on 1 March 2017 (EU-RMP version 1.6, dated 11 January 2017, DLP 1 January 2017; ASA version 0.2, dated 24 February 2017).

The proposed Summary of Safety Concerns included in EU-RMP version 1.6 and their associated risk monitoring and mitigation strategies are summarised below in Table 9. Changes since the EU-RMP version 1 (evaluated in the first round) are shown with a yellow highlight. In addition, the sponsor notified the TGA of their intention to add an important potential risk to the Summary of Safety Concerns at the next RMP update (shown with a blue highlight).

Table 9: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Herpes zoster	ü	ü	ü	ü
	Hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia)	ü	ü	ü	ü
Important potential risks	Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers)	ü	ü	ü	–
	Serious and opportunistic infections (including tuberculosis, Candida infections, PML)	ü	ü	ü	ü
	Myelosupression (agranulocytosis)	ü	ü	ü	–

[21] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Myopathy including rhabdomyolysis	ü	ü	ü	–
	Potential for drug-induced liver injury	ü	ü	ü	–
	Gastrointestinal perforation	ü	ü	ü	–
	Major adverse cardiovascular events (MACE)	ü	ü	ü	ü
	Foetal malformation following exposure in utero	ü	–	ü	ü
	Venous thromboembolic events	ü	ü	ü	–
Missing information	Long-term safety	ü	ü	ü	–
	Use in very elderly (≥ 75 years)	ü	–	ü	–
	Use in patients with evidence of hepatitis B or hepatitis C infection	ü	–	ü	–
	Use in patients with severe hepatic impairment	ü	–	ü	–
	Use in patients with a history of or current lymphoproliferative disease	ü	–	ü	–
	Use in patients with active or recent primary or recurrent malignant disease	ü	–	ü	–
	Use in paediatric patients	ü	ü	ü	–
	Effect on fertility, on pregnancy and the foetus, and use in breastfeeding	ü	–	ü	–
	The effect on vaccination efficacy, the use of live/attenuated vaccines	ü	ü	ü	–
	Use in combination with bDMARDs or with other JAK inhibitors (Note: ASA includes 'potent immunosuppressants')	ü	–	ü	–
	Inhibitory effect of baricitinib on OAT2	ü	ü	ü	–

It was concluded in the first round RMP evaluation that the Summary of Safety Concerns was incomplete. There were several precautions and adverse effects communicated in the PI that were not reflected in the Summary. The sponsor has updated the Summary at the second round and has revised safety concerns to include the TGA recommendations as shown in the table above.

The pharmacovigilance plan was updated in the revised RMP documents to include the additional safety concerns. Routine pharmacovigilance activities were proposed in Australia for the amended Summary of Safety Concerns. Additional pharmacovigilance activities are being conducted overseas and will inform the safety profile. These data will be generalisable to Australian patients.

The sponsor proposes routine risk minimisation for all safety concerns and missing information, and additional risk minimisation in the form of healthcare professional education for the safety concerns of herpes zoster, hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia), serious and opportunistic infections (including tuberculosis, *Candida* infections, and progressive multifocal leukoencephalopathy), MACE, and fetal malformation following exposure in utero. The safety concerns and missing information are reflected adequately in the PI from a RMP perspective.

New and outstanding recommendations from second round evaluation

There are no outstanding recommendations. However, the sponsor commitment to provide the following information in an updated RMP/ASA is noted:

- Inclusion of a survey to measure the effectiveness of the healthcare professional educational materials (ASA only).
- Addition of the important potential risk 'venous thromboembolic events', to be monitored by routine and additional pharmacovigilance activities, and addressed through routine risk minimisation. It is noted that the proposed PI contains a Precaution relating to the risk of venous thromboembolism (including deep vein thrombosis (DVT) and pulmonary embolism (PE)).

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> EU-RMP (version 1.6, dated 11 January 2017, data lock point 1 January 2017) with Australian Specific Annex (version 0.2, dated 24 February 2017), to be revised to include a survey to measure effectiveness of risk minimisation and include the important potential risk of 'venous thromboembolic events', must be implemented as a condition of registration.

Other advice to the delegate

Post-second round, it is advised that the Delegate be aware of the sponsor's commitment to provide an updated EU-RMP/ASA and healthcare professional educational materials prior to launch. This includes updates to reflect the additional important potential risk of venous thromboembolic events, which is not currently listed in the EU-RMP/ASA of this application. The proposed PI contains a Precaution relating to the risk of venous thromboembolism (including deep vein thrombosis and pulmonary embolism). It is

considered at this time that routine risk minimisation is acceptable for this important potential risk.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

The quality evaluator had no outstanding issues with the chemistry and quality control aspects of the BAR tablets, and noted the following:

- BAR (molecular weight: 371.4) is an azetidine with 3 aromatic rings that can exist in a number of polymorphic forms. Form I has been selected for use and the stability of this form demonstrated. BAR is achiral, with a pH of 7.31 (10 mg/mL suspended in water) and dissociation constants (pKas) of 4.0 and 12.6.
- There are currently no compendial monographs for either the drug substance or the drug product in the European, British or US Pharmacopoeias.
- BAR is manufactured by chemical synthesis in a series of steps. Impurities were qualified with acceptable analytic methods and levels of detection. The evaluator expressed no concerns regarding the active substance specifications.
- The proposed commercial drug product (tablets) contains the free base form of the drug which exhibits high solubility and low to moderate permeability (BCS Class 3[22]).
- The drug product manufacturing process consists of pre-lubrication, blending, roller compaction, milling of ribbons, final blending, tablet compression and core coating steps. All excipients used are commonly used in this type of dosage form and were considered to have been adequately described.
- The finished product is a pink tablet. The evaluator found the finished product specifications include tests for description (visual), identification (IR, for the API and colour reactions for relevant pigments titanium dioxide and iron oxide red), assay (HPLC), impurities (HPLC), uniformity of dosage units (EP), and dissolution (HPLC/UV detection). Assay limits comply with TGO78. Impurity limits have been qualified.
- The two tablet strengths will be differentiated by shade of pink and shape (see Figure 4, below, from the RMP). The 2 mg tablet is described as oblong and the 4 mg tablet is round.

[22] The **Biopharmaceutics Classification System (BCS)** is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Figure 4: Physical appearance of 2 mg and 4 mg Olumiant baricitinib tablets

- The tablets are packed in PA/Al/PVC/Al blisters and PVC/PE/PCTFE (Aclar)/Al blisters, in cartons containing 7 and 28 tablets.
- Stability data supported a shelf-life of 2 years when stored below 30ºC in the proposed packaging.

Nonclinical

The nonclinical evaluator considered the nonclinical data sufficient to support the registration, and noted the following:

- BAR is a potent selective JAK1 and JAK2 inhibitor and with some tyrosine kinase 2 inhibition. BAR in isolated enzyme assays showed IC_{50} values for JAK1, JAK2, TYK2 and JAK3 had of 5.9, 5.7, 53, and > 400 nM, respectively. It has minimal JAK3 inhibition. It inhibited IL-2, IL-6, IL12, IL-23 or mitogen JAK2/STAT3/STAT5 signalling and downstream cytokine responses (IFN-γ, IL-17, IL-22 and MCP-1), all of which are implicated in RA.
- BAR given at ≤ 50% JAK1/2 inhibition for 0.5 days post dose resulted in decreases in clinical severity including reductions in paw volume, tarsal width, pannus, bone/cartilage/overall joint damage and inflammation, and restoration of normal radiographic architecture in three different rodent models.
- Animal pharmacology showed rapid oral absorption and tissue distribution (plasma t_{max} 0.75 to 1 h, tissue t_{max} 2 h for most tissues; widely distributed). The plasma $t_{1/2}$ is short (around 1 to 8.6 h, about 5 to 7 fold lower in mice than in rats and dogs). No sex differences were noted and repeat dose studies showed minimal tachyphylaxis.
- BAR was about 50% plasma protein bound in animals and tissue distribution generally reflected the route of administration. A higher concentration in the pigment uveal tract but not in albino animals. The risk of drug-drug interactions at liver and kidney transporters or via the pregnane X xenosensor was low or negligible. Repeated dose exposures at greater than MHRD resulted in a depletion of lymphoid tissue. Panleukopaenia ± neutropaenia and increased infection risk occurred at high exposures and clinical observations likely to be consequence of immunosuppressive events were found in dogs with repeated dosing at ≤ MHRD for ≥ 6 months.
- At the MHRD there is a low risk of adverse secondary pharmacodynamics and safety pharmacology effects. Combined use of BAR and cDMARDs was not assessed in the nonclinical component of the dossier.
- There was no evidence of genotoxicity or carcinogenicity risk, no local toxicities and no phototoxic potential.

- Transplacental and transmammary BAR exposure is considered likely. In rats fetal toxicity at 50 to 80 x MHRD exposure impaired male and female fertility and induced early embryonic death. Adverse effects on skeletal development were seen at ≥ 8 x MHRD in rats. Increased fetolethality was seen at high doses in rabbits (> 100 MHRD; AUC). Rat studies indicated that with dosing at MHRD adverse intergenerational effects are unlikely. Because of the skeletal findings and because JAK/STAT pathways are important for embryofetal development a Pregnancy Category D;[16] was recommended. C_{max} in rat pups occurred 8 h post maternal doses of 2 to 22 x MHRD.[16] Use when breast feeding is not recommended.
- In activated human PBMC cultures BAR and tofacitinib were compared. BAR inhibition was most potent for interferons and least potent against IL-10 and JAK1/3 signalling dependent cytokines including IL-4, IL-5 and IL-21. BAR and tofacitinib IC_{50} values were comparable for IL-6, IL-10, IFN-α and IFN-γ stimulation. Tofacitinib was a more potent inhibitor of IL-10 stimulation of monocytes and IFN-γ stimulated pSTAT1/pSTAT3/pSTAT5 phosphorylation (most apparent in NK cells, CD4+ T cells and monocytes). BAR is a more potent inhibitor of G-CSF signalling than tofacitinib. The greatest differences between BAR and tofacitinib IC_{50} values were for those cytokines that signal through a JAK1/3 complex (IL-4, IL-15 and IL-21), likely due to the lower potency of BAR against JAK3 than tofacitinib. For both BAR and tofacitinib, the most potent inhibition of STAT3 and/or STAT 5 phosphorylation (that is, lowest IC_{50} values) occurred with IFN-α and IFN-γ signalling.

Clinical

The clinical aspects of the submission included:

- 19 pharmacology studies, 2 combined PopPK and PK/PD studies
- 3 Phase II studies (Studies JADC, JADA and JADN)
- 4 Phase III studies (Studies JADZ, JADV, JADX and JADW)
- 1 long term extension study (Study JADY)
- 1 other ongoing RA study
- 2 other studies in psoriasis (Study JADP)and diabetic kidney disease (Study JADB)
- 450 literature references.

Pharmacokinetics

A phosphate salt formulation of BAR in capsules was used in the Phase I/IIa studies but was not pursued because of formulation and manufacturing concerns. The free base form used in the later Phase II and Phase III studies is proposed for commercial supply.

The clinical evaluator found the following regarding the pharmacokinetics of baricitinib:

- The geometric least squares (gLS) mean absolute bioavailability after oral administration ($AUC_{0\text{-}inf}$) using the IV tracer method and radiolabelled (^{13}C and ^{15}N) BAR was 0.789 (90% CI: 0.769, 0.810). The median t_{max} for oral administration was 1 h (range 0.5 to 2 h) and the plasma concentration declined in a biphasic manner and the mean $t_{1/2}$ based on terminal elimination phase was 8.6 h.
- The mean volume of distribution (V_d) was 75.7 L following IV infusion of BAR in healthy volunteers and 108 L in the RA population. As noted from the pre-clinical studies the overall mean plasma protein binding was approximately 50%.
- Metabolism represented < 10% of BAR clearance.

- About 95% is cleared by renal excretion after IV dosing and 75% after oral administration (20% in faeces). In RA patients the estimated apparent drug clearance was 9.42 L/hr with moderate intra-subject variability (34.3%). The mean clearance was 46% lower in RA patients than healthy volunteers and the mean $t_{1/2}$ in RA was 12.5 h (25% higher in healthy subjects (10 h). Renal clearance (glomerular filtration and active secretion) is via OAT3, P-gp, BRCP and MATE2-K.
- PK is dose proportional over the single dose range up to 30 mg and slightly less than dose proportional in multiple once daily dosing in the range from 2 to 20 mg. The 2 mg and 4 mg tablets were found to be dose proportional.
- The accumulation ratio after multiple doses was 1.11 for C_{max} and 1.15 for AUC.
- Evening dosing resulted in slight decreases in C_{max} and a minor delay in t_{max} compared with morning dosing in a study using twice daily dosing.
- In moderate hepatic impairment geometric mean C_{max} increased 8%, $AUC_{0\text{-}inf}$ increased 20%, and median t_{max} and $t_{1/2}$ were similar.
- In non-RA subjects with renal disease, severe renal impairment without haemodialysis (CrCL 15 to 29 mL/min) had a 4 fold increase in AUC and with moderate impairment (CrCL 30 to 59 mL/min) a 2 fold increase. Moderate and severe renal impairment caused a 40 to 46% increase in C_{max}. End stage renal disease with haemodialysis had pre- and post-haemodialysis of 3 and 2 fold increase in $AUC_{0\text{-}inf}$, respectively but no increase in C_{max}. In the PopPK analyses, dose reduction to 2 mg QD was sufficient to reduce exposure in moderate renal impairment.
- OAT3 inhibition from probenacid 1000 mg BD resulted in a 2 fold increase in the $AUC_{0\text{-}\infty}$, decreases in CL_r (69%) and CL/F (51%) but no increase in C_{max} of baricitinib. Simulations involving lower potential OAT3 inhibition (ibuprofen and diclofenac) predicted an increase in exposure of no more than 1.25 fold. No clinically meaningful PK interactions were found with10 mg QD doses of BAR and simvastatin, Microgynon;[23] digoxin, ketoconazole or fluconazole, rifampicin, cyclosporine, or between MTX (7.5 to 25 mg weekly) and BAR 10 mg QD, 15 mg QD and 5 mg BD doses.
- A high fat meal increased t_{max} by 2.6 h, decreased C_{max} by 28% (90% CI: -43 to -11%), but exposure was similar. A low fat meal did not produce a clinically significant difference. In the clinical studies baricitinib was administered without regard to food.
- Increased gastric pH (achieved with 40 mg omeprazole for 8 days) reduced C_{max} 23% and increased t_{max} 0.75 h.
- The evaluator encountered difficulties replicating the sponsor's population PK model. Population PK and PK/PD analyses used data from healthy subjects (the Phase I/IIa dataset) and RA data from 7 Phase II/III trials (primary Phase II/III Pop PK analysis). In the Phase I/IIa studies moderate to low inter-and intra-subject variability was demonstrated. At steady state after multiple 4 mg QD dosing in patients with RA C_{max} was 53.4 ng.mL (CV 21.8%) and the mean $AUC_{t,ss}$ was 477.6 ng*hr/mL (CV 40.7%). Age and Japanese ethnicity were not significant covariates, and although statistically significant for gender on V_d did not affect clearance, C_{max} or exposure.
- With every 10 kg increase in body weight V_d increased 10 L and clearance increased 0.58 L.hr. There was an overall decrease in C_{max} with increasing body weight and the PopPK evaluator noted a 43% increase in exposure in a 50 kg patient compared to a 100 kg patient. The PopPK analysis and the PK/PD analysis suggested the ACR 20/50/70 and DAS28-hsCRP ≤ 3.2 and < 2.6 response to BAR in subjects > 100 kg may be 10 to 30% lower compared to subjects < 60 kg. No dose adjustment is

[23] Microgynon: ethinyloestradiol/levonorgestrel combined oral contraceptive.

proposed based on body weight. The sponsor concluded the differences were not clinically significant.

- The bioequivalence of the capsules used in the Phase I/IIa studies, and the equivalence of 2 x 4 mg commercial formulation tablets with 8 mg Phase II tablet have been demonstrated.

Pharmacodynamics

The following is a summary of the pharmacodynamic (PD) data:

- BAR transiently occupies the ATP binding pocket of the JAK, preventing it from phosphorylating with other JAKs or STATs. This prevents the signalling from pro-inflammatory cytokines such as IL-6 and interferon, thereby decreasing lymphocyte activation, proliferation and function (key immune target in successfully treating active RA).
- BAR is a selective and reversible inhibitor of JAK1 and JAK2. In isolated enzyme assays, it inhibited the activities of JAK1, JAK2, TYK2 and JAK3 with IC_{50} values of 5.9, 5.7, 53 and > 400 nM, respectively. The STAT3 transcription factor is directly phosphorylated (pSTAT3) by JAKs in response to cytokine stimulation. The sponsor developed an ex vivo assay method that measures cytokine stimulated pSTAT3 formation in human blood as a means of examining the primary PD effect of BAR.
- The primary PD effect of BAR is seen within 2 h of administration and recovers to Baseline by 24 h.
- Secondary haematopoietic effects of changes in haemoglobin were detectable by 1 week after commencement. Decreases in absolute neutrophil counts reached a nadir in 4 to 12 h after dosing and return to baseline by 24 h post-dose.
- No cardiac repolarisation, in particular QTc prolongation, occurred in doses up to 40 mg in normal healthy subjects.
- A direct drug concentration and change in pSTAT3 levels. Maximum pSTAT3 inhibition occurred near t_{max}, and returned toward baseline with drug clearance. PD effects were exposure rather than C_{max} related, and were dose proportional in the single or multiple once daily dosing. In multiple dose studies the pSTAT3 inhibition was similar on Day 1 and Day 10. Simulation showed once or twice daily dosing produced comparable efficacy and safety (anaemia and neutropaenia) endpoints, despite doubled C_{max}.
- Concomitant use of IL-6 inhibitors, for example, tocilizumab was not studied, but based on presumed cumulative risk co-administration of BAR and other bDMARD therapy is not recommended.
- The plateau of the exposure-response curve was at Week 12 for ACR20/50 but ACR70 and DAS28-hsCRP ≤ 3.2 and < 2.6 response continued to increase to Week 16. In the exposure-response relationship by quartiles the majority of $C_{avg,ss}$ values in the lowest quartile were from the 2 mg QD dose (71.8%) while the values in the upper 2 quartiles were from the 4 mg dose (95.8%). The ACR 20/50/70 and DAS20-hsCRP ≤ 3.2 and < 2.6 response rates were highest in the upper 3 quartiles compared to the lowest quartile. Patients that were dose adjusted for renal function were not included in the exposure-response by quartile analyses.

Efficacy

The dose for the Phase III studies was chosen from 3 Phase II studies (Studies JADN, JADA, and JADC) with 1, 2, 4, 7, 8, and 10 mg QD and 2 mg BD doses in RA patients in which the ACR20 was assessed at Week 12 [see Attachment 2 for study design]. The doses covered

the range of the dose-response curve. The 4 mg QD dose was on the plateau of the dose-response curve as higher doses offered no efficacy benefit (observed or modelled) and similar safety to the lower doses. Based on modelling the 2 mg QD dose was not predicted to perform as well as the 4 mg dose, although for some patients the 2 mg dose was on the plateau of the exposure response curve. BD dosing did not improve efficacy and was associated with more laboratory abnormalities in RA patients and patients with diabetic nephropathy.

The Phase III studies (Studies JADZ, JADV, JADX, and JADW) had similarities of design. All had a 3 to 42 days screening period followed by a double blind period and a 28 day follow-up. The common inclusion criteria were adults ACR/EULAR 2010 classification criteria of RA ≥ 6 tender and swollen (of the 68/66 joints examined) *and* hsCRP ≥ 1.2 times ULN (Study JADW was > ULN). Four broad exclusion categories included receipt of prohibited RA therapies (differed with each study), infection risk (infection ≤ 30 days prior to study entry including active/latent TB or other serious infections, symptomatic herpes zoster within 12 weeks or herpes zoster vaccination < 30 days from randomisation (other live vaccines < 12 weeks prior) or immunocompromised for any reason), laboratory abnormalities (aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin > 1.5 x ULN, CrCL < 40 mL/min, total white blood count (WBC) < 2.5 x 10^9/L, neutrophils < 1.2 x 10^9/L, lymphocytes < 0.75 x 10^9/L, platelets < 100 x 10^9/L and haemoglobin < 10 g/dL), *or* comorbidities such as current/prior lymphoproliferative disease, clinically significant malignancy in remission for < 5 years, pregnancy and lactation and Felty's syndrome. In all studies routine screening for hepatitis B, C and HIV and latent TB was undertaken. Low dose corticosteroids (prednisolone equivalent < 10 mg/day) for at least 6 weeks prior to study commencement had to continue to at least Week 24. Concomitant NSAIDs were permitted if the dose was stable for ≥ 6 weeks prior to randomisation. Statistical analyses were similar in all of the studies with categorical endpoints analysed using logistic regression with Non-Responder Imputation and major (gated) continuous variables analysed using ANCOVA with modified Baseline Observation Carried Forward (BOCF) imputation.

Study JADZ

Study JADZ (DMARD-naïve population) was a multicentre, multinational, randomised, double blind, placebo controlled study conducted over 52 weeks that treated 584 patients with active RA and up to 3 weeks MTX treatment (other cDMARD/bDMARD naïve). A single rescue opportunity occurred at Week 24 and all rescued patients were re-assigned or continued BAR 4 mg QD + MTX. Rescue therapy failures after ≥ 4 weeks were discontinued. The participants were mostly female (72.8%), Caucasian (59.8%) or Asian (28.3%) with a mean age of 49.9 years (range 18 to 80, 14.2% ≥ 65 years) and a median weight of 67.3 kg (range 35.1 to 151.3 kg). The mean duration of RA was 1.4 years (range 0.2 to 37.4 years). Most (79.7%) had DAS28-CRP scores > 5.1 at Baseline and mean CRP was 22.34 to 24.27 mg/L across the treatment groups. The prior cDMARD use in 8.7% was mostly (86%) low dose MTX. The three treatment arms comprised MTX only, BAR 4 mg QD only and BAR 4 mg QD+ MTX. BAR patients with a CrCL < 60 mL/min received 2 mg QD. MTX therapy commenced at 10 mg weekly and increased 5 mg every month to 20 mg weekly or where clinically justified the alternate lower dose regimen was 7.5 mg weekly increasing 2.5 mg monthly to 12.5 mg weekly. During the study the full dose MTX patients received a mean of 19 mg weekly and in the low dose subset 11.8 mg weekly. The sample size of 550 provided about 90% power for the non-inferiority based on a 12% margin for the ACR20 response at Week 24 between BAR only and MTX only, assuming ACR20 responses of 60% and 55% in the BAR and MTX arms, respectively. The sample size had about 80% power to detect superiority of BAR+MTX versus MTX only for the Week 24 ACR20 based on an estimate of 68.5% for BAR+MTX. About 89% completed the study, with withdrawals mostly due to lack of efficacy (4.8% of the MTX only arm and 0.6% of the BAR only arm) and the remainder consent withdrawal. Between Weeks 24 to 52

rescue-therapy occurred in 12.4%/4.4%/2.8% of the MTX/BAR/BAR+MTX groups. Protocol violations resulting in exclusion from the mITT population were for using prohibited medications (6.3%) and treatment compliance violations (4.3%).

Study JADV

Study JADV (MTX-IR, bDMARD-naïve population) was a multicentre, multinational, randomised, double blind, placebo controlled study conducted over 52 weeks in 1305 patients with active RA who had inadequate response or intolerance to ≥ 12 weeks MTX (7.5 to 25 mg weekly) and ≥ 3 joint erosions on X-ray in the hand/wrist/foot joints or ≥1 joint erosion on X-ray , rheumatoid factor (RF)/anti-cyclic citrullinated peptide (anti-CCP) antibody positive, on ≤ 1 cDMARD and bDMARD naive that compared placebo (PBO), adalimumab (ADAL) 40 mg SC Q2W and BAR 4 mg QD. BAR patients with a CrCL 40 to 60 mL/min received 2 mg QD. All non-responders according to pre-specified criteria at Week 14 to 16 at Week 16, or after Week 16 based on investigator discretion received rescue therapy and were re-assigned to or continued BAR 4 mg QD. Rescue therapy failures after ≥ 4 weeks were discontinued. The majority were 77.2% female, and either Caucasian (62.7%) or Asian (30.1%), with a mean age of 53.3 years (range 19 to 86 years, 18.5% ≥ 65 years) with a mean weight of 70 kg (range 32.4 to 144.3 kg). The mean duration of RA was 8.7 years (range 0.03-56.4 years), and the majority (84.4%) were seropositive for both RF and anti-CCP antibodies at Baseline. Most (74.3%) had a mean DAS28-CRP score > 5.1 at Baseline and the mean CRP across the treatment groups was 20.85 to 22.85 mg/L. The median baseline mTSS ranged from 21.5 to 25.5 sharp units across the treatment groups. At Baseline, 83.4% were taking 1 cDMARD (most MTX low dose) and 16.5% were taking 2 cDMARDs (MTX + 1 other). Corticosteroids were taken 58.7% at a median dose of 5.0 mg/day. The median weekly MTX dose was 15 mg in each group. A sample size of 1280 provided > 95% power to detect a difference of 60% versus 35% at Week 12, and a 94% power to detect a difference of 0.25 mTSS between BAR and PBO and a 93% power for the non-inferiority (margin 12%) of the ACR20 at Week 12 for BAR versus ADAL assuming a 60% response rate for each. About 92% completed the study. Prior to Week 24 the most common reason for discontinuation was adverse events in 3.3%/3.7%/2.1% of the PBO/BAR/ADAL groups followed by consent withdrawal in 3.3%/1.2%/3.9% and lack of efficacy in 3.3%/0.2%/0.9%. Up to Week 24 rescue therapy was provided for 25.6%/7.0%/11.8% and between Week 24 to 52 in 0.8%/1.6%/3.0%. Protocol violations resulting in exclusion from the mITT population were for treatment compliance violations (3.6%) and use of prohibited medications (1.5%).

Study JADX

Study JADX (cDMARD-IR, bDMARD-naïve population) was a multicentre, multinational, randomised, double blind, placebo-controlled study conducted over 24 weeks in 684 patients with active RA who had ≥ 12 weeks cDMARD treatment [see Attachment 2 for further details] and were bDMARD naïve, that compared PBO, BAR 2 mg QD and BAR 4 mg QD. BAR patients with a CrCL 40 to 60 mL/min received 2 mg QD. All non-responders according to pre-specified criteria at Week 14 to 16 were re-assigned to or continued BAR 4 mg QD at Week 16. At Week 20 rescue therapy was available based on investigator discretion. Rescue therapy failures after ≥ 4 weeks were discontinued. The participants were mostly female (81.9%) and either Caucasian (66.9%) or Asian (26.4%). The mean weight was 76 kg (range 31.6 to 181.5 kg). The median duration of disease was 3.5 years, range 0.07-52.8 years and 68.7% were seropositive for RF and anti-CCP antibodies at Baseline. About 67.8% had DAS28-CRP score > 5.1 at Baseline the mean CRP ranged from 14.2 to 18.2 mg/L. The median baseline mTSS ranged from 6.0 to 8.5 sharp units. At Baseline most 65.2% were taking 1 cDMARD, 24.9% were taking 2 cDMARDs, 2.9% were taking ≥ 3 DMARDs and 7% were taking no DMARD. For MTX users the median weekly dose was 15 mg weekly in each group. A sample size of 660 provided > 95% power to detect a difference at Week 12 of BAR 4 mg QD versus PBO (60% versus 35%), and >90%

power to detect a difference between BAR 2 mg QD versus PBO. About 92% completed the study to Week 24. Discontinuations prior to Week 24 were mostly due to adverse events (4.4%) and patient withdrawal (3.5%). Between Week 16 to 24 rescue therapy was received by 24.1%/9.2%/6.6% in the PBO/BAR 2 mg/BAR 4 mg. Protocol violations resulting in exclusion from the mITT population were for insufficient compliance 1.8% and prohibited change in corticosteroid therapy 1.0% and change in cDMARD treatment 0.7%.

Study JADW

Study JADW (TNFα -IR) was a multicentre, multinational, randomised, double blind, placebo controlled study conducted over 24 weeks in 527 patients with active RA on stable doses of cDMARDs and who had failed treatment (inadequate response or intolerance to) after ≥ 3 months of at least one TNF-α inhibitor treatment that compared PBO, BAR 2 mg QD and BAR 4 mg QD. bDMARDs had to be discontinued ≥ 28 days prior to randomisation (6 months for rituximab). All non-responders at Week 14 to 16 were re-assigned to or continued BAR 4 mg QD at Week 16. At Week 20 rescue therapy was available based on investigator discretion. Rescue therapy failures after ≥ 4 weeks were discontinued. Most 81.8% were female, Caucasian (83.0%) with a mean age of 55.7 years (range 21to 82 years, 22.0% ≥ 65 years). The mean weight was 81.9 kg (range 66 to 175 kg). The mean duration of disease was 14.0 years (range 0.88 to 50.7 years), and about 64.8% were seropositive for RF and anti-CCP at Baseline. About 82% had DAS-CRP score > 5.1 at Baseline and mean CRP ranges from 19.8-20.6 mg across the treatment groups. Previous bDMARDs use in 41.9% was 1 prior biologic, in 30.4% 2 bDMARD, and in 26.9% ≥ 3 bDMARDs. The prior DMARDs were etanercept (56.4%), adalimumab (44.4%) infliximab (28.7%), abatacept (20.3%, tocilizumab (19.4%) rituximab (17.1%) golimumab (11.0%), certolizumab (10.1%) and anakinra (1.3%). Most (88.6%) were taking 1 cDMARD, 10.4% taking 2 cDMARDs, 0.6% were taking ≥3 cDMARDs and 0.4% was no longer taking cDMARDS. The most common cDMARD was MTX taken at a median weekly dose of 15 mg. About 58% took low dose corticosteroids (median dose 5 mg daily). A sample size of 525 had 97% power to detect 4 mg QD versus PBO at Week 12 assuming 45% versus 25% responses for BAR 4 mg and PBO, respectively, and 80% power to detect a difference between BAR 2 mg QD and PBO assuming 39% versus 25% responses, respectively. About 87% completed to Week 24. The most common reasons for discontinuations before Week 24 were adverse events (4.6% and lack of efficacy (4.6%). Between Week 16 to 24 rescue therapy was received by 31.8/21.8%/18.6% in the PBO/BAR 2 mg/BAR 4 mg groups. Protocol violations resulting in exclusion from the mITT cohort were mostly for treatment noncompliance (3.4%) and change in cDMARD without a safety concern (1.9%).

Table 10, shown below, gives the primary and selected key secondary endpoints from the evaluated Phase III studies.

Table 10: Primary and selected key secondary endpoints Phase III studies

	Study JADZ (cDMARD naïve)	Study JADV (MTX-IR)	Study JADX (cDMARD-IR)	Study JADW (TNFα-IR)
Duration	52 weeks 52 weeks placebo controlled	52 weeks 24 weeks placebo or active controlled 24 weeks active controlled 28 day follow-up	24 weeks 24 weeks controlled 28 day follow-up	24 weeks 24 weeks controlled 28 day follow-up

	Study JADZ (cDMARD naïve)	Study JADV (MTX-IR)	Study JADX (cDMARD-IR)	Study JADW (TNFα-IR)
Treatment groups (mITT)	BAR 4 mg only (n = 160) MTX 20 mg only (n = 213) BAR 4 mg + MTX (n = 215)	BAR 4 mg (n = 488, 52 weeks) PBO (n = 489, all BAR after Week 24) ADAL 40 mg SC Q2W (n = 330, 52 weeks)	BAR 4 mg (n = 227) BAR 2 mg (n = 229) PBO (n = 228)	BAR 4 mg (n = 177) BAR 2 mg (n = 174) PBO (n = 176)
Primary endpoint ACR20	Week 24 mITT BAR only versus MTX 76.7% versus 61.9% Difference 14.8% (95%CI: 5.5%, 24.1%) $p_{(noninf)}$ = 0.001 $p_{(sup)}$ = 0.003	Week 12 mITT BAR versus PBO 69.6% versus 40.2% difference 29.4% (95% CI: 23.5%, 35.4%) p = 0.001	Week 12 mITT BAR 4 mg versus PBO 61.7% versus 39.5% Difference 22.2% (95%CI: 13.2%, 31.2%) p = 0.001	Week 12 mITT BAR 4 mg versus PBO 55.4% versus 27.3% Difference 28.1% (95% CI: 18.2%, 37.9%) p = 0.001
ACR20 (other groups)	Week 24 mITT BAR +MTX versus MTX 78.1% versus 61.9% Difference 16.2% (95%CI: 7.7%, 24.8%) p = 0.001	Week 12 mITT ADAL versus PBO 61.2% versus 40.2% Difference 21.0% (95%CI: 14.2%, 27.9%) p = 0.001 ADAL versus PBO Difference 21.0% (95% CI: 14.2%, 27.9%) p = 0.001 BAR versus ADAL 69.6% versus 61.2% Difference 8.4% (95%CI: 1.7%, 15.1%)*	Week 12 mITT BAR 2 mg versus PBO 65.9% versus 39.5% Difference 26.5% (95%CI: 17.6%, 35.3%) p = 0.001	Week 12 mITT BAR 2 mg versus PBO 48.9% versus 27.3% Difference 21.6% (95%CI: 11.7%, 31.5%) p = 0.001

	Study JADZ (cDMARD naïve)	Study JADV (MTX-IR)	Study JADX (cDMARD-IR)	Study JADW (TNFα-IR)
HAD-QI change from baseline (mBO COMPARED WITH)	Week 24 mITT BAR versus MTX LSMD -0.29 (95%CI:-0.41, -0.16) p = 0.001 BAR+MTX versus MTX LSMD -0.23 (95%CI: -0.35, -0.12)	Week 12 mITT BAR versus PBO LSMD -0.49 (95%CI: -0.73, -0.25) p = 0.001	Week 12 mITT BAR 4 mg versus PBO LSMD -0.2 (95%CI: -0.3, -0.1) p = 0.001 BAR 2 mg versus PBO LSMD -0.21 (95%CI: -0.3, -0.11) p = 0.001	Week 12 mITT BAR 4 mg versus PBO LSMD -0.23 (95%CI: -0.33, -0.13) p = 0.001 BAR2 mg versus PBO LSMD -0.2 (95%CI: -0.3, -0.1) p = 0.001
DAS28-hsCRP change from baseline	Week 24 mITT BAR only versus MTX only LSMD -0.69 (95% CI: -0.98, -0.40) p = 0.001 BAR+MTX versus MTX LSMD –0.78 (95%CI:-1.05, -0.51) p = 0.001	Week 12 mITT BAR versus PBO LSMD -1.23 (95%CI: -1.37, 1.09) p = 0.001	Week 12 mITT BAR 4 mg versus PBO LSMD -0.84 (95%CI: -0.97, -0.53) p = 0.001 BAR 2 mg versus PBO LSMD -0.75 (95%CI: -0.97, -0.53), p = 0.001	Week 12 mITT BAR 4 mg versus PBO LSMD -0.95 (95%CI: -1.22, -0.69) p = 0.001 BAR 2 mg versus PBO LSMD -0.66 (95%CI: -0.93, -0.39) p = 0.001
SDAI (≤3.3 response)	Week 24 mITT BAR only versus MTX only 22% versus 10.5% OR 2.5 (95%CI: 1.4, 4.4) p = 0.001 BAR+MTX versus MTX 22.8% versus 10.5% OR 2.6 (95%CI: 1.5, 4.5) p = 0.001	Week 12 mITT BAR versus PBO 8.4% versus 1.8%, p = 0.001 ADAL versus PBO 7.3% versus 1.8%, p = 0.001	Week 12 mITT BAR 4 mg 8.8% BAR 2 mg 9.2% PBO 0.9%	Week 12 mITT BAR 4 mg 5.1% BAR 2 mg 2.3% PBO 1.7% BAR 4 mg or 2 mg not statistically significantly different from placebo

	Study JADZ (cDMARD naïve)	Study JADV (MTX-IR)	Study JADX (cDMARD-IR)	Study JADW (TNFα-IR)
mTSS change from Baseline	Week 24 mITT BAR versus MTX LSMD -0.22 (95% CI: -0.52, -0.08) p = 0.158 BAR+MTX versus MTX LSMD -0.32 (95% CI: -0.6, -0.04) p = 0.026	Week 24 mITT BAR versus PBO LSMD -0.49 (95%CI: -0.73, -0.25) ADAL versus PBO LSMD-0.56 (95% CI: -0.83, -0.29) Week 52 mITT BAR versus PBO LSMD -1.10 (95% CI: -1.55, -0.64) ADAL versus PBO LSMD -1.20 (95%CI -1.71, -0.69)	Exploratory endpoint Week 24 BAR 4 mg versus PBO LSMD -0.55 (95%CI: -0.92, -0.19) BAR 2 mg versus PBO LSMD -0.38 (95%CI: -0.74, -0.01) No progression: BAR 4 mg 80.5% BAR 2 mg 71.3% PBO 73.2%	

*> 0% = pre-specified limit of superiority; for results of other endpoints, see Attachment 2.

Analyses by multiple baseline characteristics including age and weight for the 4 mg QD dose versus PBO and the 2 mg QD dose versus PBO showed consistent results.

Study JADY

Study JADY is an interim analysis of an extension study in 2539 patients who had participated in Study JADA/JAGS or any of Studies JADZ/JADV/JADX/JADW taking 0 to 2 background open label cDMARDs comparing BAR 2 mg QD with BAR 4 mg QD for up to 48 months to investigate the long term safety and tolerability of BAR. All patients receiving BAR at the commencement of Study JADY continued the same dose, and all who were randomised to a non-BAR comparator commenced 4 mg QD. As with the previous studies patients with eGFR of < 60 mL/min/1.73 m^2 at baseline in the index study were only eligible for 2 mg QD dosing. Efficacy was a secondary endpoint and was measured by the mean change from baseline (up to 48 weeks) in CDAI and SDAI as well as the rates of categorical clinical response over time with CDAI, SDAI, ACR20, ACR50 and ACR70 [see Attachment 2 for full secondary endpoint data]. In the study, 297 patients took 2 mg QD (180 from Study JADX, 117 from Study JADW), and 2242 took 4 mg QD (450 from Study JADZ, 975 from Study JADV, 403 from Study JADX, 331 from Study JADW, and 83 from Study JADA). In the interim analyses the overall trends were for improvement in ACR50/70 DAS28-CRP CDAI remission (≤ 2.8) or low disease activity (CDAI ≤ 10) and SDAI. Similar results over time were seen in HAD-QI scores, with a trend towards a lower % response in ACR20.

A secondary objective was to determine the efficacy of a 2 mg QD dose in a step-down regimen from 4 mg QD. Patients with a sustained response (CDAI ≤ 10 for patients from Studies JADV, JADX, JADW or JAGS or CDAI ≤ 2.8 for patients from Study JADZ) to 4 mg QD for at least 3 months after transitioning into Study JADY, at least 15 months of 4 mg QD treatment including the time in the index study and no rescue therapy in either study (n = 491) were randomised to either 2 mg QD (n = 244) or 4 mg QD (n = 247). A disease flare on the step-down dose could be treated with analgesics/NSAIDs. Ongoing failure to

maintain low dose activity or clinical remission they could return to 4 mg QD and/or received cDMARD or corticosteroid therapy. Step-down only occurred once in the study. Efficacy in the step-down sub-study was measured by low disease activity (CDAI ≤ 10) and remission (CDAI ≤ 2.8) 12 weeks after step-down and mean change from Baseline at 12 weeks in SDAI, DAS28 and components of the ACR criteria. At the cut off for the interim analysis of the study 9.8% had discontinued. Of the patients that did not enter the step-down 49% of the baseline 2 mg QD and 28% of the baseline 4 mg QD group received rescue therapy. In the step-down group at Week 12 after re-randomisation CDAI ≤ 10 and CDAI ≤ 2.8 was achieved by 92.5% and 38.8% of the 4 mg QD group and 84.2% and 37% of the 2 mg QD group but 3.6% of the 4 mg QD and 9.4% of the 2 mg QD groups needed rescue therapy. No meaningful rebound effect was seen in the 28 day follow up period in patients electing not to continue in open label extension studies.

Study JAGS

Study JAGS is an ongoing multicentre, multinational, randomised, double blind, placebo controlled study conducted over 52 weeks in 167 patients with active RA who had inadequate response or intolerance to MTX, on ≤ 1 cDMARD and bDMARD naive to compared placebo, and BAR 4 mg QD. Rescue therapy was offered after Week 16.

Safety

The safety set included the patients and healthy subjects from the RA study series and safety data from Study JADP in psoriasis and Study JAGQ in diabetic nephropathy. Using these data the sponsor undertook three analyses in the Integrated Safety Summary: a comparison of baricitinib 4 mg with placebo (primary analysis: n = 997 BAR, n = 1070 PBO), a comparison of baricitinib 4 mg and 2 mg QD doses (secondary analysis n = 479 each) and an analysis of safety from randomisation to the last available observation (extended BAR n = 958). Analyses were also undertaken of all patients in the clinical trial program, and by individual study for Studies JADZ and JADV (active comparators MTX and ADAL).

A total of 3822 patients were exposed to BAR in the clinical studies for any dose or indication. Of those 3464 had RA and represented 4214.1 patient years (PY). 2166 patients had ≥ 1 year treatment and 467 patients had ≥ 2 years treatment. 1508 had at least one dose ≥ 4 mg QD and 479 had 2 mg QD. A total of 979 had rescue therapy during the Phase III studies (including the analysis from Study JADY). Most also received concurrent MTX and more than half took low dose corticosteroids or NSAIDs.

Adverse events

In the placebo controlled safety analysis up to Week 16, the 10 most commonly reported AEs reported for BAR 4 mg QD for >2% and greater than placebo were nasopharyngitis, URTI, headache, urinary tract infection, bronchitis, nausea, pharyngitis and hypertension. A statistically greater proportion of events reported as an AE in the primary analysis were for CPK (12.0% versus 2.0%) and hypercholesterolaemia (9.6% versus 5.7%). Nausea was numerically more frequent with BAR 4 mg (9.5%) and more than half the events were reported in the first 2 weeks of treatment. Infections were more common with BAR notably acne (0.8% versus 0%) and herpes zoster infection (1.8% versus 0.4%). In the comparison of 4 mg QD and 2 mg QD dosing increased blood CPK (5.0% versus 2.3%) and increased AST (2.1% versus 0.4%) and hypercholesterolaemia (3.3% versus 1.5%) and RA (2.1% versus 1.0%). In the extended BAR 4 mg QD versus 2 mg QD set includes all time on the dose not just in the comparator period statistically significant treatment-emergent AEs (TEAEs) included increased blood CPK (7.7% versus 4.4%) increased AST (2.9% versus 0.8%) and hypercholesterolaemia (5.0% versus 2.5%). An odds ratio of ≥ 2.0 for BAR 4 mg versus 2 mg as found for falls (no temporal pattern and not clearly related) and alopecia (most of which occurred in the first 12 to 16 weeks of treatment). Fewer patients had

abdominal pain and rhinitis in the 4 mg QD versus 2 mg QD arms. The three most common types of AEs were Infections (about 50% of AEs) with Gastrointestinal and Musculoskeletal (25% each). In the extended treatment set, herpes zoster occurred in 3.8% versus 2.9%, and oral herpes and herpes simplex infection combined were in 2.7% versus 2.3%, of the 4 mg QD versus 2 mg QD doses, respectively. Hypertension occurred in 3.3%/3.1%/1.1% of the 2 mg/4 mg/PBO groups. No signal was raised for ophthalmic disorders.

Treatment related adverse events (adverse drug reactions)

From the integrated safety analysis acne, upper gastrointestinal (GI) symptoms (mostly nausea and discomfort), herpes simplex, herpes zoster, upper respiratory infection, elevated CPK, elevated lipids and triglycerides, AST/ALT elevated, neutropaenia and thrombocytosis were all identified potential adverse drug reactions. Significantly more patients in the BAR 4 mg QD group (1.4%) than PBO (0.4%) reported herpes zoster infections, but there was no statistical difference between the BAR 2 mg and BAR 4 mg groups. Of the 141 cases, 3 had an associated facial palsy and 7 were considered disseminated. Herpes simplex infections also showed this pattern of statistical difference for BAR versus PBO but not BAR 2 mg versus BAR 4 mg. There were 6 cases of pancytopaenia, of which 4 occurred in BAR patients with RA, 1 in another population and 1 with ADAL. All BAR patients took concomitant MTX but 1 missed folic acid doses, 1 in a Phase II study had 8 mg BAR doses and 1 had up-titrated from BAR 2 mg to BAR 4 mg, and 1 had a confounding medical history. Infections were more common with BAR 4 mg (14.2%) compared to adalimumab (10.0%) and PBO (9.4%), and in the same study BAR had a higher incidence of AEs from SOC of blood and lymphatic disorders (3.1% versus 1.8% and 1.6% with PBO). Abnormal investigations such as increase AST/ALT and CPK were seen with BAR (6.8%) versus ADAL 6.4% versus 1.6% PBO. In the Phase III studies up to 52 weeks duration the types of AEs were consistent across the study period.

In the safety data set to the data lock point of November 2015, 31 deaths were reported across all studies with baricitinib that included 5 MACE (2 of which occurred in screening) and 4 cancers but no clear pattern was identified. Of the SAEs more common in BAR patients were most commonly infection (3.6%) pneumonia and herpes zoster infection were most frequent. There were 9 events of pulmonary embolism (PE), 1 of which was fatal, 5 events of deep vein thrombosis (DVT), and 2 patients had concurrent events. Another fatal PE event occurred in a patient taking MTX only. The 5 cases of syncope and 3 of pre-syncope requiring hospitalisation did not result from primary cardiovascular or neurological causes. The two cases of gastrointestinal perforation occurred in patients taking corticosteroid and NSAIDS concomitantly. Permanent discontinuations from treatment due to AEs overall occurred in 7.4%, most commonly in the BAR groups from infection (2.9%, mostly herpes zoster), abnormal investigation results (0.9%) and blood and lymphatic disorders (0.8%). Discontinuations of BAR 2 mg QD and PBO occurred in similar proportions of patients (11.0% and 10.8%, respectively).

Up to Week 16, any elevation of CPK was common (31.0% versus 7.5% in the BAR 4 mg versus PBO comparison, 31.1% versus 18.4% in the BAR 4 mg versus BAR 2 mg comparison). An increased CPK of ≥ Grade 3 occurred in 0.7% of the BAR 4 mg group and 0.2% of the PBO group and 1.5 to 2.5% of the 4 mg QD and 0.8 to 1.0% of the 2 mg QD BAR patients. In Study JADV, 2.7% of the BAR group and 1.2% of the ADAL group had an elevated CPK and in Study JADZ it occurred in 4.8% of the BAR 4 mg +MTX group. Most were asymptomatic, only 0.2% discontinued and rapidly returned to Baseline. There were no confirmed cases of rhabdomyolysis, and one patient had the SAE of myositis, muscular weakness and myalgia. More than half of the reported cases with an increase in CPK to ≥ Grade 3 reported exercise or trauma at the time of the abnormality. Most events reached a plateau within the first few months of therapy and resolved quickly with discontinuation. CPK elevation has been reported with other JAK inhibitors.

Because BAR is a targeted synthetic bDMARD and not given parenterally it was not expected to cause hypersensitivity reactions, and no hypersensitivity reactions occurred with a likely causal relationship.

Infection was the most common AE with BAR in either dose and compared to any of the comparators. It was also the most common reason for BAR discontinuation. Herpes zoster and pneumonia were commonly reported. There were 6 cases of TB occurring after a latent period of 218 to 617 days, 2 were military. All cases occurred in countries which have endemic TB. Hepatitis B virus (HBV) DNA was found in 17 patients, 8 during the controlled period of the studies, 3 commenced antiviral therapy and one patient had clearly documented reactivation during Study JADX. One patient each had reactivation of cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Overall, in the all BAR RA group including the 12 month safety update, the EAIR for serious infections was 2.9 per 100 PY and 3.2 per 100 PY for herpes zoster.

Haematological suppression events were of particular interest because erythropoietin, G-CSF, GM-CSF and thrombopoietin signal through the JAK-STAT pathway. Haemoglobin < LLN was reported in 27.4% BAR 4 mg and 24.5% of PBO patients. The 4 mg QD BAR versus 2 mg QD dosing results were 26.4% versus 25.1% for haemoglobin < LLN, and in the extended cohort 35.0% versus 30.9%, respectively. In the all exposure BAR population a shift to Grade 3 or 4 lymphopaenia occurred in 1.9%, Grade 3 or 4 neutropaenia in 0.7% and thrombocytosis in 2.4%. There was no apparent dose relationship with BAR. In Study JADZ Grade 3 or 4 neutropaenia occurred in 0.6% BAR monotherapy, 0.5% MTX combination BAR and MTX and 0% MTX monotherapy. Thrombocytosis occurred in 2.4% of the all exposure BAR group and in the extended 4 mg QD versus 2 mg QD analysis in 3.4% versus 1.4%, respectively. 2.9% patients on methotrexate developed lymphopaenia. In the extended BAR 4 mg QD (that included patients on concomitant MTX) versus 2 mg QD compared with the BAR monotherapy group (7.6%).

BAR induced an elevated LDL-C ≥ 3.36 mmol/L in a dose dependent manner: 33.6% BAR 4 mg QD versus PBO, and at Week 16 in 28.5% for 4 mg QD versus 20.2% for 2 mg QD versus 11.6% PBO. By Week 24 in the Phase III studies a LDL ≥ 3.36 mmol/L was reported in 38.5 to 44.1% of the BAR 4 mg group, increasing to 53.4% in the all BAR 12 month safety update group. At Week 52 in Study JADV 53.8% of the BAR 4 mg group and 36.9% of the ADAL group had elevated LDL-C. No increased risk of MACE events beyond the background risk for RA was seen with BAR, and events were consistent over time based on 24 week exposure intervals.

Elevated AST and ALT were reported previously in JAK inhibitors and MTX therapy. No clear signal for increased risk versus PBO emerged from the integrated safety analysis and the incidence was similar in both BAR dose groups. Across the BAR trials 2.9% had ALT > 3 x ULN, 0.9% 5 x ULN and 0.2% 10 x ULN (none of these cases were considered probably related). There were no Hy's Law cases.

BAR was associated with small, dose-dependent increases in mean serum creatinine values that reached a plateau by Week 8 to 12.

Although weight gain was attributed to BAR (around 7% weight gain combined BAR) versus 2% PBO, the largest weight gain was in the group < 60 kg at baseline. Weight gain has previously been associated with improved disease control.

Prior to August 2015, 15 pregnancies had occurred during study participation, of which 12 were exposed to BAR. Five were full term or premature deliveries, 4 spontaneously terminated, 1 electively terminated and two were ongoing. No fetal abnormalities were reported in the delivered infants.

Analyses of specific groups: safety analyses by age (<65 years, ≥ 65 years, ≥ 75 years), gender, race, body weight (<60 kg, 60-100 kg and > 100 kg) did not reveal differences for these patient variables.

Venous thromboembolism (VTE) risk

Up to the data lock point of September 2016, a total of 31 cases reporting at total of 38 venous thromboembolism (VTE) events in BAR patients. One case was in the MTX monotherapy group, and no cases were reported in the PBO or ADAL comparator groups.

The number of events, EAIR, and VTEs reported as TEAEs or serious adverse events (SAE) by primary, secondary and extended safety analysis, specific analysis of Study JADV by comparator group and the total number of events in all the studies are presented in Table 11 (below).

The following was noted:

- In the randomised controlled period, 5 BAR cases had 3 PEs and 2 DVTs, 1 MTX case had a PE. Early events in the BAR group occurred in Studies JADX and JADV.
- 26 patients reported events after the controlled period (post rescue, or entry into the long-term extension Study JADY).
- 8 cases occurred after discontinuation of BAR, 6 occurred within 28 days.
- 12 permanently discontinued, 19 had ongoing exposure and 2 had recurrent events, 1 after discontinuing anticoagulant therapy. There were 3 VTE deaths (2 in the BAR group and 1 in the comparator group).
- Including cases after the data lock period, BAR RA patients had a total of 12 PEs and 19 DVTs were reported as separate events and an additional 7 patients had both a DVT and PE. One patient in a Phase II psoriasis study had both a DVT and PE.

Table 11: Number and exposure adjusted incidence rates (EAIR) of VTE events

	TEAE	SAE
BARI 4-mg RA PC Wk 0-24		
Placebo (N=1070)	0	0
BARI 4-mg (N=997)	5 [1.2]	2 [0.5]
BARI 2-mg vs 4-mg RA Wk 0-24		
Placebo (N=551)	0	0
BARI 2-mg (N=479)	0	0
BARI 4-mg (N=479)	2 [1.0]	2 [1.0]
BARI		
BARI		
Ext BARI 2-mg vs 4-mg (through 1 Sep 2016)		
BARI 2-mg (N=479)	3 [0.5]	3 [0.5]
BARI 4-mg (N=479)	4 [0.6]	3 [0.5]
Study JADZ Wk 0-52		
MTX (N=210)	1 [0.6]	1 [0.6]
BARI 4-mg (N=159)	0	0
BARI 4-mg + MTX (N = 215)	0	0
Study JADV Wk 0-24		
Placebo (N=488)	0	0
BARI 4-mg (N=487)	3 [1.4]	0
Adalimumab (N=330)	0	0
Study JADV Wk 0-52		
BARI 4-mg (N=487)	3 [0.7]	0
Adalimumab (N=330)	0	0
All BARI RA (through 1 Sep 2016)		
Phases 1-3 (N=3492)	31 [0.46]	21 [0.3]

Abbreviations: BARI = baricitinib; DVT = deep vein thrombosis; ICH = International Committee on Harmonisation; MTX = methotrexate; N = number of patients in the safety analysis set; n = number of patients in the specified category; PC = placebo-controlled; PE = pulmonary embolism; RA = rheumatoid arthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Including follow-up data where applicable. SAEs by ICH only.

Note: 2 patients with DVT/PE post study were not included in the table (JADV-963-29508 and JADV-570-19185).

Data as of Sep. 1, 2016, including post-treatment follow-up where applicable. Patients years are the sum of observation time without censoring except for All BARI RA set for which observation time is censored at event.

- The sponsor provided evidence from the literature that the VTE risk in RA patients is 0.29 to 0.74 per 100 PY based on observational studies but did not include a comparison event rate from Phase III RA clinical trials. The overall BAR EAIR was 0.46 per 100 PY, in the midrange of the 'real world' data. The DVT IR for the 2 mg QD and 4 mg QD doses as at September 2016 were 0.4 and 0.3 per 100 PY and the PE IR was 0.2 per 100 PY for both groups. The incidence in the MTX only group was 0.59 per 100 PY.
- No post-market VTE events were reported.
- As of September 2016 arterial thrombotic events occurred at an EAIR of 0.5 per 100 PY.
- Platelet counts tend to increase in the first few weeks of therapy and return toward baseline, and were similar in the groups that did and did not develop VTE. An increase in thrombopoietin resulting from JAK2 blockade is postulated as the cause. The sponsor has not discussed any alteration in platelet function or stickiness with baricitinib.
- Baseline risk factors were considered as a possible explanation for the observed of events. The sponsor presented a summary of these in Table 12, shown below.

Table 12: Characteristics of patients who reported VTE versus no VTE in the all baricitinib RA dataset at 1 September 2016

	Patients with DVT/PE (N=31)	Patients without event (N=3461)
Age: 18-49	3 (9.7)	1242 (35.9)
50-59	11 (35.5)	1110 (32.1)
>=60	17 (54.8)	1109 (32.0)
>=65	11 (35.5)	601 (17.4)
BMI: >=30 kg/m2	22 (71.0)	1048 (30.3)
>=35 kg/m2	17 (54.8)	457 (13.2)
>=40 kg/m2	8 (25.8)	171 (4.9)
Concurrent MTX	26 (83.9)	2675 (77.3)
Concurrent glucocorticoid	20 (64.5)	na
Concurrent OCP or SERM	2 (6.5)	213 (6.2)
Tobacco Use	2 (6.9)	571 (20.0)
Prior DVT/PE	4* (12.9)	30 (0.9)
Prior Malignancy	2 (6.5)	69 (2.0)
Preceding trauma, surgery, or decreased mobility	13 (41.9)	na
Evidence of thrombophilia	3 (9.7)	na
Platelets ≥400,000/L baseline	3 (9.7)	398 (11.5)
post-baseline	8 (25.8)	1242 (36.1)
Platelets ≥600,000/L baseline	0	18 (0.5)
post-baseline	2 (6.5)	114 (3.3)

Abbreviations: BARI = baricitinib; BMI = body mass index; DVT = deep vein thrombosis; MTX = methotrexate; na = not applicable; OCP = oral contraceptive pill; PE = pulmonary embolism; RA = rheumatoid arthritis; SERM = selective estrogen receptor modulator.

Data are n (% of N) as of 01 September 2016 for All BARI RA, including post-treatment follow-up where available.

Medication use is concurrent and baseline for the event and non-event groups, respectively.

*1 additional patient had prior DVT noted in the SAE summary, but not in the clinical database; total 5 with prior DVT/PE

- The true comparison period is the first approximately 16 weeks in Studies JADV, JADX and JADW and 24 weeks in Study JADZ. This is the period before rescue therapy could be offered and imbalances in the numbers of groups in each treatment arms emerged in the studies. Events were all in the BAR groups early. This has raised concern. The sponsor has provided an analysis of events in blocks of exposure. In the first 120 weeks and in 24 week intervals the numbers of events were 5, 1, 4, 2 and 0 group

randomised to BAR and 1, 4, 0, 1 and 5 for the group that switched from another arm to BAR either as rescue therapy or because of continuation to Study JADY. The events and EAIR are shown in Table 13 (see below) up to the 1 September 2016 data lock point. The EAIR is expressed in events per 100 patient years.

Table 13: VTE events and EAIR by 24 week time intervals

Time Block (Weeks)	All Patients in Time Block	Patients with Events	PYE	Exposure Adjusted Incidence Rate/ 100 PY[a]	CI[b]
0-24	3492	6	1534.1	0.39	0.14, 0.85
24-48	3160	8	1349.4	0.59	0.26, 1.17
48-72	2815	6	1201.8	0.50	0.18, 1.09
72-96	2371	3	1004.2	0.30	0.06, 0.87
96-120	1988	5	803.3	0.62	0.20, 1.45
120+	1420	3	832.7	0.36	0.07, 1.05
Overall	3492	31	6725.6	0.46	0.31, 0.65

Abbreviations: BARI = baricitinib; CI = confidence interval; DVT = deep vein thrombosis; IR = incidence rate; PE = pulmonary embolism; PYE = patient years of exposure; RA = rheumatoid arthritis. Data as of 1 September 2016 for All BARI RA, including post-treatment follow-up where available; a) IR is 100 times the number of patients experiencing the adverse event divided by the event-specific exposure to treatment (exposure time [on baricitinib] up to the event for patients with the event and exposure time up to the end of the period for patients without the event), in years; b) 95% CI for IR are based on Poisson distribution.

After the DLP, 5 additional cases with 2 PEs and 4 DVTs occurred on BAR in Study JADY, reducing the overall EAIR to 0.33 per 100 patient years.

The sponsor is of the view that a contraindication in high risk patients is unwarranted and this was supported by the clinical evaluator, and that the precautionary statement and advice to temporarily interrupt therapy and treat in the Olumiant PI is sufficient.

Clinical evaluator's recommendation

After three rounds of evaluation the clinical evaluator recommended approval of baricitinib for the amended indication:

> *Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to 1 or more disease modifying anti-rheumatic drugs (DMARDs) has been inadequate.*
>
> *Olumiant has been shown to reduce the symptoms and signs of RA and to improve physical function.*
>
> *Olumiant can be given as monotherapy or in combination with cDMARDs, including methotrexate.*
>
> *Therapy with Olumiant should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA*.

Risk management plan

The TGA has evaluated EU-RMP (version 1.6, dated 11 January 2017, DLP 1 January 2017) with ASA (version 0.2, dated 24 February 2017). Post-second round, the RMP team has noted the negotiated changes to the ASA to include a survey of the effectiveness of the healthcare education materials that form additional risk minimisation activities in Australia. The sponsor has undertaken to provide an updated RMP and ASA prior to launch of the product and this action is proposed for inclusion as a condition of registration.

Risk-benefit analysis

Delegate's considerations

Baricitinib is the second JAK inhibitor for rheumatoid arthritis for which registration is sought in Australia and the third in class overall. The proposed indication reflects current practice with cDMARD therapy preceding the use of a bDMARD, and although not first-line therapy for RA the sponsor's proposed indication allows for the use of baricitinib as a first-line DMARD.

The clinical efficacy and safety of baricitinib is supported by 4 Phase III and 3 Phase II studies. Adequate dose finding studies were conducted and a sound rationale has been provided for the 2 doses chosen for the main clinical studies. The 4 Phase III studies were well designed and had sufficient similarities for cross comparison. Four patient groups based on prior therapy were studied. This is an acceptable approach and represents typical patient groups for which JAK inhibitor therapy may be considered. An active bDMARD (adalimumab) has been included as a treatment arm in Study JADV, providing some comparison of baricitinib at the sponsor's preferred dose with a TNFα inhibitor. The efficacy of BAR monotherapy was demonstrated in MTX naïve patients (Study JADZ), with concomitant MTX in Study JADV and cDMARDs more generally in Studies JADX and JADW. Head to head comparisons of 2 mg QD and 4 mg QD doses were provided in patients with more refractory disease but not in early treatment and limiting the conclusions that can be drawn about the optimal dose for the initiation of therapy. The clinical evaluator commented that while consistent with current use of conventional therapy recent expert opinion may consider some of the mean and median doses of concomitant/background cDMARDs in the clinical studies suboptimal, and was concerned this may introduce bias in favour of BAR. Background therapies of NSAIDs and low dose corticosteroid were considered consistent with current Australian practices.

There are several issues with this submission: a signal for VTE events, a relative paucity of the safety data to support the 2 mg dose in patients not requiring dose adjustment because of CKD, some dose-related toxicity with the 4 mg dose, and whether the warnings about the use in pregnancy are sufficient.

A total of 3822 patients received at least one dose of baricitinib, 3464 with RA: 2166 were dosed for ≥ 1 year and 467 for ≥ 2 years, 1508 received at least one dose ≥ 4 mg QD, 1476 received 4 mg QD and 479 received 2 mg QD. Patient exposure was adequate for an initial safety assessment. Nausea was a common effect particularly in the first few weeks of therapy. CPK, elevated AST/ALT and hypercholesterolaemia were the most common laboratory abnormalities with baricitinib. Comparing the 2 mg and 4 mg doses increases in CPK, abnormalities of liver function and RA activation were more common in the 4 mg group. Infections were common in the studies. Up to 24 weeks of therapy URTI, herpes zoster and herpes simplex infections were the most common. Most were mild to moderate although complicated herpes zoster infections were reported in small numbers. Elderly patients were more at risk of herpes zoster infections with the 4 mg QD dose but had

lower disease activity with that dose. Although noted there was not a strong signal for TB reactivation, however patients were screened prior to enrolment. Deaths occurred in the studies and although reported MACE and malignancy events did not appear disproportionate given the age of the patients the timing of the events and the variety of tumour types. Elevated CPK has been noted with other JAK inhibitors and appeared dose dependent. Hypercholesterolaemia was very common and while there was no signal for MACE events the studies may not have been of sufficient duration or power to detect differences between baricitinib strengths and/or the comparators.

The VTE risk is a significant concern with the use of baricitinib, and has not been seen with other JAK inhibitors. Events in the baricitinib trials occurred in a disproportionately high number of baricitinib treated patients and notably only one patient in the comparator arm had an event. Although transient thrombocytosis was seen these patients were not those with the events. Five events in the BAR groups occurred in the first 6 months of exposure, all within the first 16 weeks (EAIRs 1/0/0 for BAR 4 mg/BAR 2 mg/PBO), but events continued throughout the clinical trial program. On switching to BAR from a comparator arm either as rescue therapy or in the open label studies there was no spike in events in the first 6 months of treatment. Of the patients with VTE events at least one underlying risk factor was identified. The event rate was similar to the background rate for RA patients in a number of studies. A predominance of events was seen in 4 mg dosing but this may reflect the numbers exposed rather than a true dose-response relationship. There were unexpectedly few events in the comparator arms of the studies.

The sponsor has identified a disproportionately high distribution of patients with underlying VTE risk factors in the 4 mg group. Although not stratified by VTE risk, randomisation would have been expected to account for at least some of this background risk and it is recognised that there is an increased VTE risk in RA patients. BMI was identified as a risk factor and it is noted there is a question about a reduction in baricitinib exposure with increasing BMI. The sponsor has argued that there is no clear dose-response with the VTE events. There is a relationship between psoriasis and higher BMI. One VTE event has been reported in a Phase II baricitinib psoriasis study. The sponsor is requested to analyse the VTE risk factors and review the safety data for further events in that study.

The overall EAIR for VTE baricitinib patients is in the mid-range of that observed in RA patients in other studies most of which were observational and some reliant on billing data, but this does not explain the reason for the very low VTE event rate in patients taking comparator medications. VTE risk factors were present in the comparator groups across the Phase III studies so it is unclear why such an imbalance is seen.

The sponsor proposes a precautionary statement to mitigate the risk, to align with the approach taken in the EU. The events in the US with the FDA issuing a complete response letter after its initial assessment of baricitinib, and Health Canada's issuing a Notice of Noncompliance that the sponsor states is to allow the provision of additional data are both noted. The clinical evaluator has reviewed the data provided by the sponsor in the initial submission and in several additional analyses in three rounds of evaluation and has concluded this risk can be managed with a precautionary statement. The Delegate is of the view that a stronger warning may be warranted. The advice of the Advisory Committee on Medicines (ACM) in this matter is sought about the signal and the risk mitigation strategies.

The sponsor has adopted a Pregnancy Category D;[16] based on the nonclinical evaluation identifying the transplacental transfer of baricitinib and abnormalities in animal pregnancies and fetal abnormalities. The small numbers of pregnant patients exposed to baricitinib limit the conclusions that can be drawn regarding its safety but no congenital abnormalities have been reported to date. It is noted that the EU Summary of Product Characteristics (SPC) for baricitinib has included pregnancy as a contraindication for use

of baricitinib, but to date the sponsor has not proposed this approach in Australia. The sponsor is asked for clarification and ACM will be asked for advice in this matter. It is recognised that many patients taking baricitinib could concomitantly use MTX which is contraindicated in pregnancy but baricitinib monotherapy is included in the proposed indication.

The safety of the 2 mg QD dose is less well characterised than the 4 mg dose. The dose exposure was 253 patients for 24 weeks and 172patients for 52 weeks; although considered sufficient for assessment by the clinical evaluator, it limits the conclusions that can be drawn about the safety of this dose. It is noted that 2 mg QD dosing was mostly with concomitant DMARDs, and with no direct evidence as monotherapy. CPK elevation, AST and cholesterol were elevated in a greater proportion of patients in the 4 mg QD dosing groups compared with 2 mg QD but there was no difference in SAEs, deaths, temporary interruption due to AEs or serious infections. Rheumatoid arthritis is a common disorder and additional data to support the safety of the 2 mg dose would have provided additional reassurance. The advice of the ACM is sought regarding the adequacy of the safety and efficacy data to support the sponsor's proposal for the 2 mg dose.

Indication

The clinical evaluator has agreed to the inclusion of a statement of efficacy claims in the indication. Although the efficacy claims are not disputed these outcomes do not a priori define the patient population for which evidence has been provided in support of the indication. Information about the efficacy of baricitinib can be included in other sections of the PI if it is approved. The approach of defining the indicated population by disease and response to previous therapy has been taken in the EU for baricitinib and it is consistent with the recommendations in the draft EU guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. It is agreed that if approved BAR should be initiated and supervised by a rheumatologist or specialist physician with experience in the management of patients with and that this statement should be located in the Dosage and Administration section of the PI. If the sponsor so choses a precautionary statement could also be included.

Dose

Baricitinib 4 mg QD was efficacious across the studies compared with placebo and adalimumab, demonstrated in ACR20 and DAS28-hsCRP assessments. Efficacy was also demonstrated indices of disease activity and function. Overall the onset of action was within weeks and a plateau in responses was seen at Week 12 for ACR20 and ACR50, with ongoing improvements in DAS28-hsCRP and ACR70 to Week 16. The treatment effect size was on the upper end of the range of responses expected with other bDMARDs.

The efficacy evidence supporting the 2 mg QD dose is less certain. The 2 mg QD dose was not investigated in MTX-IR patients and because rescue therapy was offered after 16 weeks in Phase III studies that included a 2 mg QD there are some limitations to the interpretation of the efficacy data. The responses to the 2 mg and 4 mg QD doses were similar in the cDMARD–IR study but 4 mg QD achieved a larger proportion of responders among TNFα-IR patients than 2 mg QD dosing. The time to onset was slower and the 2 mg dose had lower levels in response in the exposure quartile analyses. A statistically significant recrudescence of RA activity on dose reduction was seen when moving from a 4 mg to 2 mg dose in the JADY step-down sub-study, but about 9% compared with about 4% needing rescue therapy on step down and almost twice the number of patients needing rescue who stayed on a 2 mg QD dose from their index study compared with those that stayed on the 4 mg QD dose. No rebound effect was seen in with either dose in patients who discontinued therapy after the index study. Only 4 mg QD doses have been compared with ADAL and only in the MTX-IR population. While a benefit over ADAL is not essential for establishing efficacy of the 2 mg dose such information would have been

helpful to assist prescribers optimise therapy for their patients. The ACM is asked to comment on the efficacy evidence to support the 2 mg dose for its proposed use. The 2 mg dose was also used as a dose equivalent to 4 mg QD in patients with CKD, based on exposure equivalence. There is no concern regarding this approach per se however clarification is sought from the sponsor regarding its exclusion of patients with a CrCL < 40 mL/min but inclusion of these patients in the dosing instructions.

The clinical evaluator found the 4 mg dose had more clinical benefit and should be the typical dose. The sponsor has requested a 4 mg once daily dose for most patients with a dose reduction to 2 mg for patients with moderate to severe renal disease, those that exhibit fewer risk factors for destructive disease, and those who do not tolerate the 4 mg dose. The evidence to support dosing for this group is confined to Study JADX that included a lower proportion of patients with high levels of disease activity. There is uncertainty about the use of the 2 mg dose in other patient groups. Conversely safety risks such as risk of infection and the risk of laboratory abnormalities appear dose dependent and the 2 mg dose appears from the limited safety data to have a lower risk. The exposure response curve seems to have considerable individual variability and it is possible this dose may be suitable from an efficacy viewpoint but the ACM's advice is sought on this issue.

As previously noted dose reduction based on the PopPK analysis and the supportive clinical evidence in patients with a CrCL of 40 to 60 mL/min appears reasonable.

Data deficiencies

There are limited long term data, and this is of importance because increased risk of malignancy and MACE are potential concerns with biological DMARDs. There are no data to support the use of the 2 mg QD dose in MTX naïve and MTX inadequate response that are naïve to other cDMARDs. The data are limited to support the safety of the 2 mg QD dose.

Delegate's preliminary assessment

Baricitinib is a once daily oral medication for use in rheumatoid arthritis, a condition for which most widely used bDMARDs are delivered by SC injection, and this is factored into the considerations since it is likely to be used in a broader population than those exposed in the clinical trials. The sponsor has requested an indication for baricitinib as potentially a first-line bDMARD in patients with inadequate response to another DMARD. In most cases this DMARD will be MTX. In consideration the benefits and risks an important factor is the VTE signal. The lack of a demonstrated biologically plausible mechanism does not rule out a relationship between baricitinib and the observed events. Although the sponsor has argued an imbalance in the baseline risk factors a dominant factor the Delegate is not persuaded because of the low event rate in the comparator arms. There are questions about the optimal dose but a relative deficiency in the data to support the 2 mg dosing. At this time, because of the uncertainty, the Delegate is unable to provide a favourable assessment, noting the ACM's advice is sought on the issues of concern. The Delegate is also uncertain whether restriction of the indication to patients who have failed a bDMARD would be a group for which the efficacy would balance the increased risk and uncertainty.

Summary of issues

There is an apparent increased VTE risk. It is unclear whether it is an acceptable risk for the RA patient groups proposed in the indication that is, second-line therapy after at least 1 DMARD (first-line bDMARD therapy), or whether further restrictions such as refinement of the indicated population would result in an identifiable group in which the risk is acceptable. Given the uncertainties with the submission the issue is whether the benefits of baricitinib are sufficient to offset the risks and uncertainties in patients with an

inadequate response to bDMARDs. If there is a group with a favourable benefit risk profile, advice is sought on risk communication and mitigation.

The 4 mg dose is the sponsor's preferred starting dose and the emphasis in the clinical development program has been on this dose. Given there are dose-related safety signals for increased laboratory values and infections, such as herpes zoster, is it unclear whether this should be the starting dose. Conversely there are limited safety data provided to support the 2 mg dose, the 2 mg dose was only studied in 2 of the 4 Phase III studies and the comparative efficacy of the 2 mg and 4 mg doses differs in these two studies.

It is unclear whether there should be a weight based dose adjustment.

It is unclear whether the Pregnancy Category D is sufficient based on the risk from the nonclinical studies and the signal for VTE risk or whether pregnancy should be a contraindication for use.

Proposed action

The Delegate was not in a position to say at the time that the application for baricitinib should be approved for registration for the indication requested.

The advice of the ACM is sought on a number of issues regarding this application.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Has sufficient evidence of efficacy and safety been provided to support 4 mg once daily as the usual dose, or should the starting dose be 2 mg once daily?
2. A signal of increased risk of VTE was identified in the studies. Based on the information to hand can this be considered a real risk, or can the arguments regarding confounding from other patient characteristics be accepted? Following multiple analyses of the data the sponsor and the clinical evaluator each concluded the proposed precautionary statement is acceptable. Is the proposed warning sufficient to mitigate the risk? Are other strategies such as a patient alert card warranted?
3. In the PK-PD modelling analysis there was a 30% difference in response across the weight range. Can the committee comment on the influence of body weight on response to bDMARDs in general for patients with RA. Is weight based dose adjustment warranted for baricitinib?
4. The EU Summary of Product Characteristics (SmPC) contraindicates baricitinib in pregnancy, whereas the sponsor proposes Pregnancy Category D classification in Australia, without the contraindication. Can the committee comment on the approach proposed for Australia by the sponsor? Is a contraindication in pregnancy warranted, taking into account the nonclinical data and the safety of baricitinib?
5. Can the committee provide its view on the benefit-risk balance for baricitinib for the proposed indication? Would the benefit risk profile be more acceptable for a restricted population and is a refinement of the indication warranted?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions for the sponsor

1. Please provide a table showing EAIR for the first 16 weeks in each Phase II and Phase III study, and all studies combined by treatment, including BAR 2 mg and BAR 4 mg individually and combined BAR.

2. Please comment on the age of the batch of baricitinib given to patients with VTE events in the weeks prior to the VTE events. Could there be a relationship between the events and degradation products or other impurities?
3. Please explain the reason in some documents provided to the TGA discussing the VTE risk 4 case narratives are provided for the control period and in others there are 5.
4. Please also clarify the numbers of PE and DVT events used to calculate the EAIRs for these events for the 2 mg and 4 mg doses.
5. Tables 12 and 13 in this overview have been copied from responses to questions provided by the sponsor. Table 13 indicates there are 31 cases prior to the 1 September 2016 data lock in the BAR group. Table 12 would indicate there are 30. Please clarify. Are the two patients [patient ID redacted], excluded from Table 12 included in the VTE analyses including the EAIR calculations and the multivariate analysis?
6. Obesity was a significant covariate in the analysis of risk factors for VTE events. Psoriasis is more common in obese patients. For the psoriasis study please provide the mean BMI for the baricitinib and comparator groups, and the EAIR for VTE events in the baricitinib and control groups for that study.
7. Please provide a KM curve of the VTE events for the 4 mg and 2 mg doses. Please indicate how patients were censored in this analysis.
8. The sponsor has provided a comparison of largely observational studies to demonstrate the EAIR for VTE in RA patients. Please provide where possible the rates found for TNF α inhibitors, MTX and tofacitinib from publically available data sources for the pivotal clinical trials.
9. A contraindication is present in pregnancy in the SPC for BAR in the EU. The sponsor has proposed a precautionary statement about VTE risk, and rheumatoid arthritis and pregnancy are both have increased risks for VTE. Please provide the reasoning behind the different approach in Australia.
10. Simvastatin was investigated in the Drug Interactions studies. Given their potential interactions and their likely use to reduce LDL-C please explain the reasons drug interactions with atorvastatin and rosuvastatin were not undertaken.
11. A statement in the Dosing and Administration section has been inserted to inform prescribers that patients with a creatinine clearance of < 40 mL/min were excluded from the main studies. Please justify the inclusion of dosing instructions for patients that include an eGFR of 30 ≤ 60 mL/min/1.73 m^2.
12. The 2 mg QD dose as a starting dose is proposed for all patients with less active disease. Please summarise the data that support this approach.
13. Please provide an update on the progress of the submissions for baricitinib in the US and Canada.

Response from sponsor

Sponsor's response to Delegate's questions for the sponsor

Question 1

> *Please provide a table showing EAIR for the first 16 weeks in each Phase II and Phase III study, and all studies combined by treatment, including BAR 2 mg and BAR 4 mg individually and combined BAR.*

The number and exposure-adjusted incidence rate (EAIR; per 100 PY) of DVT/PE events during the controlled period up to Week 16 in each Phase II and III study are shown below in Table 14.

Table 14: Exposure adjusted incidence rate (EAIR) for VTE events during the first 16 weeks of each Phase II and III study, and all studies combined by treatment, including BAR 2 mg and BAR 4 mg; individually and combined BAR

n [EAIR]	PBO	1 mg	2 mg	4 mg	7 mg	8 mg	10 mg	Combined BAR	MTX Mono	ADA
JADC (N=125)	0	-	-	0	0	-	0	0	-	-
JADA (N=300)	0	0	0	0	-	0	-	0	-	-
JADN (N=145)	0	0	0	0	-	0	-	0	-	-
JADZ (N=584)	-	-	-	0	-	-	-	0	0	-
JADV (N=1305)	0	-	-	2[1.35]	-	-	-	2[1.35]	-	0
JADX (N=684)	0	-	0	2[[2.96][a]	-	-	-	2[1.47][a]	-	-
JADW (N=527)	0	-	0	0	-	-	-	0	-	-
All	0	0	0	4[1.34][a]	0	0	0	4 [0.66] [a]	0	0

Abbreviations: ADA = adalimumab; BAR = baricitinib; EAIR = exposure-adjusted incidence rate; Mono = monotherapy; MTX = methotrexate; PBO = placebo; VTE = venous thromboembolism.

[a] Includes 1 case with event occurring 4 weeks post last dose of baricitinib (reason for study drug discontinuation was adverse event of hypersensitivity).

Question 2

> *Please comment on the age of the batch of baricitinib given to patients with VTE events in the weeks prior to the VTE events. Could there be a relationship between the events and degradation products or other impurities?*

The commercial baricitinib drug product formulation and manufacturing process was utilised to supply Phase III clinical trial materials. The original Australian registration package provided representative baricitinib tablets 2 mg and 4 mg clinical trial stability data for up to 24 months stored at 30°C and 65% room humidity, and for 6 months stored at the accelerated 40°C/75% room humidity condition. In addition, 12 months of primary stability data were provided for baricitinib tablets 2 mg and 4 mg stored and tested at the long-term storage conditions of 30°C/65% room humidity for bottles and 2 mm polychlorotrifluoroethylene (PCTFE) blisters, and 30°C/75% room humidity for compared with aluminium foil blisters and stored for 6 months at the accelerated storage condition 40°C/75% room humidity for all packages. In addition, at this time, up to 36 months of primary stability data are available for all package configurations at their respective storage conditions.

These data consistently demonstrate that baricitinib tablets 2 mg and 4 mg at batch release and throughout stability contain no individual impurities or degradation products greater than the analytical method reporting limit (0.05%). These impurity/degradation product levels are significantly less than the ICH Q3 toxicology qualification threshold (that is, 0.15% for drug substance impurities or 1.0% for drug product degradation

products).[4,24] In addition, the purity analytical methodology used for release and stability testing are validated to ensure all potential drug product impurities and degradation products would be detected and quantified above 0.05%.

The sponsor has assessed the age of the baricitinib lots received by the 5 patients who experienced a VTE during the randomised, controlled portions of the Phase III studies. These lots were manufactured between 9 and 18 months prior to the VTE occurrences. Therefore, due to the high purity seen with baricitinib drug product for up to 36 months stored at 30°C/65% room humidity and for 6 months at the accelerated 40°C/75% room humidity condition, it is highly improbable that impurity or degradation products within drug product clinical materials are associated with the patient VTE reports.

Question 3

> *Please explain the reason in some documents provided to the TGA discussing the VTE risk 4 case narratives are provided for the control period and in others there are 5 case narratives.*

In the Phase III RA placebo-controlled studies, all patients receiving placebo were switched to baricitinib at Week 24. However the study design allowed rescue therapy to be provided at Week 16 and patients moved from their randomised group. As discussed in in Question 1 above, there were 4 patients who developed VTEs during 0 to 16 weeks in the randomised, controlled portion of the Phase II/III RA studies. However, responses that describe 5 patients with VTEs and/or provided 5 narratives refer to the entire Week 0 to 24 period of the randomised, controlled portion of the Phase II/III RA studies.

Please note that although the text and tables of the 26 April 2017 responses correctly describe the 5 VTEs that occurred during the randomised, controlled portions of the RA studies, the case listing in Appendix 1 inadvertently omitted one case narrative [narrative ID redacted]. This omission had been corrected in the EU Type II variation overview, which was provided to TGA in September 2017 and is reproduced in the response (table not included in this AusPAR).

Question 4

> *Please also clarify the numbers of PE and DVT events used to calculate the EAIRs for these events for the 2 mg and 4 mg doses.*

The numbers of PE and DVT events used to calculate the EAIRs for these events for the 2 mg and 4 mg once daily (QD) doses are shown in Table 15. Note that one 2 mg patient had both a DVT event and a PE event.

[24] ICH 3QB (R2): Guideline on impurities in new drug products (Step 5); 2 June 2006.

Table 15: Numbers of PE and DVT events used to calculate the EAIRs for 2 and 4 mg QD doses from the 12 month update

	Dose Comparison Extended 2 mg vs 4 mg[a]	
	Bari 2 mg (N=479) PYE=554.5 **n [EAIR]**	Bari 4 mg (N=479) PYE=604.1 **n [EAIR]**
DVT/PE TEAE	2 [0.4]	3 [0.5]
PE	1 [0.2]	1 [0.2]
DVT	2 [0.4]	2 [0.3]

Abbreviations: Bari = baricitinib; DVT = deep vein thrombosis; EAIR = exposure-adjusted incidence rate; PE = pulmonary embolism; PYE = patient years of exposure; QD = once daily; RA = rheumatoid arthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Dose comparison extended 2-mg vs 4-mg data set consisted of long-term exposure from 2 Phase 2 and 2 Phase 3 studies.

Question 5

> *Tables 12 and 13 in this overview have been copied from responses to questions provided by the sponsor. Table 13 indicates there are 31 cases prior to the 1 September 2016 data lock in the BAR group. Table 12 would indicate there are 30. Please clarify. Are the two patients [patient ID redacted], excluded from Table 12 included in the VTE analyses including the EAIR calculations and the multivariate analysis?*

As discussed in the TGA response from 26 April 2017, in the original submission did not describe post-treatment events. During the randomised controlled portion of Study JADX, 1 patient experienced a VTE approximately 1 month after discontinuing treatment with baricitinib. Therefore, analyses that include solely on-treatment events show 4 VTEs as having occurred in the randomised controlled portions of the Phase II/III RA studies and 30 patients having experienced VTEs in the All BARI RA dataset. However, analyses that include both on-treatment as well as post-treatment follow-up events (such as tables from the TGA response from 26 April 2017) show 5 VTEs as having occurred in the randomised controlled portion of the Phase II/III RA studies and 31 patients who experienced VTEs in the All BARI RA dataset.

The footnote to Table 12 in the Delegates Overview, which refers to two patients, applied only to the by-study analyses (which did not include post-treatment follow-up events) and not to the ALL BARI RA analysis. Therefore, we can confirm that both of these patients are included in the count of 31 patients and that they are included in the EAIR calculations and the multivariate analysis.

Question 6

> *Obesity was a significant covariate in the analysis of risk factors for VTE events. Psoriasis is more common in obese patients. For the psoriasis study please provide the mean BMI for the baricitinib and comparator groups, and the EAIR for VTE events in the baricitinib and control groups for that study.*

In Study JADP, mean BMI was 28.8 kg/m^2 in the placebo group and 31.0 kg/m^2 in the combined baricitinib group. One patient in the baricitinib group had a reported SAE of PE (0.9% of the 109 patients in the high dose group (10 mg) in Part B of this study); note that the investigator had also noted that Doppler revealed a DVT in the left leg, although only the PE was reported as an SAE. Underlying risk factors for this patient included obesity (BMI = 31 kg/m^2). There were no DVT/PE events for patients on placebo. The EAIR for

VTE in the baricitinib group was 0.35 per 100 patient-years. Similar EAIRs for VTEs in patients with psoriasis were seen in a recent population-based cohort study.[25]

Question 7

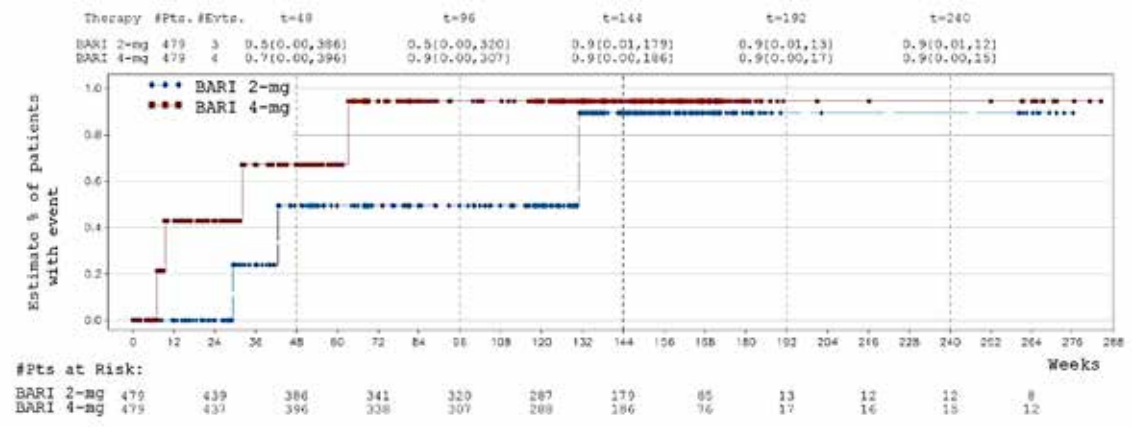
> *Please provide a Kaplan-Meier curve of the VTE events for the 4 mg and 2 mg doses. Please indicate how patients were censored in this analysis.*

The Kaplan-Meier curve of the DVT/PE events in the extended 2 versus 4 mg set is shown below (Figure 5). In this analysis, the data were censored at the event start date for patients with an event; for patients without event, data were censored at the last observation date or the data cut-off date.

Although at first glance there seems to be separation between the curves for the 4 and 2 mg doses over the earlier timeframe, this should be interpreted with caution because:

- over the long term, the 2 curves meet, indicating that event rates long term are comparable;
- there are relatively few VTEs (this is an uncommon event), especially over the earlier timeframe, the curves are informed by a limited number of data points and are therefore less accurate than the longer term comparisons.

Figure 5: Kaplan-Meier curve of the DVT/PE events in the extended 2 mg versus 4 mg set



Abbreviations: Evts=events; Pts=patients; SE=standard error.
Data as of September 1, 2016.
For patients with the event, data censored at the event start date; for patients without event, data censored at the last observation or data cutoff date.

Question 8

> *The sponsor has provided a comparison of largely observational studies to demonstrate the EAIR for VTE in RA patients. Please provide where possible the rates found for TNFα inhibitors, MTX and tofacitinib from publically available data sources for the pivotal clinical trials.*

The sponsor has looked for all available information on VTE incidence rates from clinical trial data, as these rates would provide the best comparator with the baricitinib VTE rates from the Phase III programme. However, older trials did not include information on VTE or, when it was included, only described counts without information on the exposure time. Without both a count of incident events and exposure (person-time), it is not possible to calculate the incidence rate of VTE from the trial or the confidence intervals around that estimate. Data provided here are for the most recently completed Phase III RA programme

[25] Ogdie A et al. Risk of venous thromboembolism in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a general population-based cohort study. *European Heart Journal. 2017;0:1 -7, doi:10.1093/eurheartj/ehx145.*

for an RA therapy approved in the US and EU sarilumab (an anti-IL-6 monoclonal antibody) and tofacitinib. Data for sarilumab and tofacitinib were only available for serious VTE events. It should be noted that the VTE occurrences for baricitinib described by Lilly in the original submission and subsequent responses include both serious and non-serious events. For example, 3 of the 5 VTEs reported in baricitinib treated patients during the randomised, controlled portion of the studies were non-serious, as were 11 of the remaining 26 VTEs reported in the rest of the baricitinib RA programme; this provides useful context when comparing to clinical trial data for approved therapies that report solely serious events. For this reason in the comparison below, only serious PE and DVT events for baricitinib are included in the comparison of EAIRs between drugs.

The sarilumab clinical trial programme describes an EAIR for serious PEs of 0.2 per 100 patient-years and a serious DVT EAIR of 0.2 (Sarilumab EU Summary of Clinical Safety (SPC)). In the baricitinib programme as of 1 September 2016, identical rates of serious PE and serious DVT to those in the sarilumab programme are observed (EAIR of 0.2/100 patient years for serious PE and EAIR of 0.2/100 patient years for serious DVT).

For the tofacitinib Phase III RA programme, there were 4 serious PEs (3 events on tofacitinib (2 in the controlled portion as well as one PE leading to death) and 1 event on placebo in the controlled portion), and no serious DVTs were reported in the active treatment arms (FDA Clinical Review, Tofacitinib for Rheumatoid Arthritis, September 2012). Although EAIRs were not provided, these data are very similar to the number of occurrences in the controlled portion of the baricitinib studies (2 serious PEs on baricitinib treatment, 1 PE on MTX treatment, no serious DVTs), which had controlled portions in the Phase III studies of similar duration.

The similarity of the sarilumab and baricitinib serious VTE incidence rates and the similarity in the number of occurrences in the tofacitinib and baricitinib controlled portions of the Phase III studies, support the assessment from observational studies that the VTE IR for baricitinib is within the background range expected for an RA patient population.

Question 9

> *A contraindication is present in pregnancy in the SmPC for BAR in the EU. The sponsor has proposed a precautionary statement about VTE risk and rheumatoid arthritis and pregnancy are both have increased risks for VTE. Please provide the reasoning behind the different approach in Australia.*

The core safety information for baricitinib, which represents the sponsor's assessment of all of the available data on baricitinib and is used as the core safety information for labels globally, does not contain a contraindication for pregnancy. The need or otherwise to contraindicate in light of the baricitinib non-clinical findings was carefully considered when developing the core safety information statement on pregnancy for baricitinib. The outcome of this evaluation with both non-clinical and clinical experts was that there may be circumstances, on an individual patient basis, when a clinician would determine that the benefits outweighed the putative risk associated with the findings observed in the offspring of rats and rabbits. The Use in pregnancy wording included in the core safety information formed the basis of what has been initially proposed in all labels globally, including the Australian PI and the European SmPC, and was intended to allow such an informed decision between the clinician and a patient who intends to become pregnant.

The CHMP request for a contraindication arose late in the procedure and thus was accepted by the sponsor as a condition of the approval, despite the fact this did not reflect the sponsor's assessment of the data. Given the available non-clinical data, a Pregnancy Category of D would seem appropriate and is aligned with other approved drugs in the same class, including tofacitinib for which very similar non-clinical findings were observed. The sponsor accepts that the risk of VTE is increased in pregnant women;

however, a caution on use in patients with risk factors for VTE is already contained within the proposed warning and precaution.

Question 10

> *Simvastatin was investigated in the Drug Interactions studies. Given their potential interactions and their likely use to reduce LDL-C please explain the reasons drug interactions with atorvastatin and rosuvastatin were not undertaken.*

The clinical drug interaction studies for baricitinib were designed primarily to assess mechanisms of drug-drug interactions (DDIs) such as inhibition of transporters/cytochrome P450s (CYPs). In this regard, the potential for baricitinib to specifically inhibit OATP1B1 and CYP3A was sufficiently investigated in the simvastatin study, where simvastatin was a sensitive probe substrate for both OATP1B1 and CYP3A. The results from the probe DDI study can then be extrapolated to other drugs that are substrates of OATP1B1 and/or CYP3A, such as other statins including atorvastatin (CYP3A and OATP1B1 substrate) and rosuvastatin (OATP1B1 substrate). Based on the simvastatin interaction clinical study and in vitro data, specific clinical DDI studies with baricitinib were not warranted with atorvastatin or rosuvastatin. Therefore, baricitinib can be safely co-administered with atorvastatin or rosuvastatin.

In vitro, the potential for baricitinib to inhibit OATP1B1 and inhibit/induce CYP enzymes was evaluated. In the transporter study, baricitinib did not inhibit OATP1B1 at concentrations up to 50 μM baricitinib. In the CYP inhibition study, at concentrations up to 20 μM baricitinib, none of the CYPs evaluated were sufficiently inhibited by baricitinib to determine half maximal inhibitory concentrations, and thus inhibition constants could not be determined. In the CYP induction study, baricitinib did not cause clinically relevant increases in CYP3A4 activity at concentrations of baricitinib up to 50 μM; however, statistically significant decreases in CYP3A messenger Ribonucleic acids (mRNA) and activity were observed at the higher concentration of 50 μM. Based on the combined in vitro data, the potential for baricitinib to cause clinically significant DDI via OATP1B1 and CYP3A is low.

Despite the low likelihood of a clinically relevant DDI with baricitinib and drugs that are substrates of OATP1B1 and/or CYP3A, the sponsor conducted a clinical pharmacology study evaluating the effect of baricitinib on the pharmacokinetics of simvastatin. The study was conducted to more fully investigate the potential of baricitinib to inhibit CYP3A based on the discrepancy of in vitro results observed at 20 μM versus 50 μM baricitinib. The clinical study results confirmed that baricitinib does not inhibit OATP1B1 or CYP3A in vivo and indicate that baricitinib can be safely co-administered with simvastatin. Therefore, baricitinib can also be safely co-administered with atorvastatin or rosuvastatin, as well as other drugs that are substrates for OATP1B1 and CYP3A.

Question 11

> *A statement in the Dosing and Administration section has been inserted to inform prescribers that patients with a creatinine clearance of < 40 mL/min were excluded from the main studies. Please justify the inclusion of dosing instructions for patients that include an eGFR of 30 to ≤ 60 mL/min/1.73 m².*

Although an estimated glomerular filtration rate (eGFR) < 40mL/min/1.73 m^2 was used as an exclusion criterion for the Phase III studies, once patients were enrolled into the trial, study drug was not interrupted unless eGFR fell below 30 mL/min/1.73 m^2 for those patients with documented renal impairment at baseline in order to avoid the situation in which a patient has an inconsequentially small drop in eGFR that requires immediate drug interruption.

Therefore, the dataset generated for the PopPK analysis was consistent with the dosing cut-off in the proposed labelling. The PopPK modelling which was used to inform the renal

dose recommendation was based on data pooled from 7 Phase II and Phase III studies where the minimum enrolment or screening eGFR was 28.8 mL/min/1.73 m^2. The simulation results supporting a lower cut-off value of 30 mL/min/1.73 m^2 are detailed under 'Renal Impairment' in the Clinical Pharmacology Summary. Moreover, analyses based on renal function classified as moderate renal impairment with an eGFR of 30 to < 60 mL/min/1.73 m^2 at study entry were available from the renal impairment Study JADL.

In summary, given the design of the Phase III studies and the data from PK analysis (based on the PopPK and Study JADL), the efficacy and safety conclusions are all supportive of the dosing cut-off of 30 to 60 mL/min/1.73 m^2 for dose adjustment for patients with moderate renal impairment as proposed in the label.

Question 12

> *The 2 mg QD dose as a starting dose is proposed for all patients with less active disease. Please summarise the data that support this approach.*

The sponsor proposes that 2 mg QD could be an appropriate starting dose for conventional disease-modifying anti-rheumatic drug-inadequate response (cDMARD-IR) patients *'...who have moderate disease severity, limited risks for progressive joint damage, and a low urgency to rapidly regain physical function.*' This approach is supported by the following data. Notwithstanding the differences in benefit/risk favouring the 4 mg dose over 2 mg dose, that is with respect to rapidity, consistency, and magnitude of benefit, baricitinib 2 mg demonstrated superior efficacy compared to placebo in 2 Phase III studies (Studies JADX and JADW) across multiple clinical endpoints. As proposed in labelling, patients with moderate disease activity may derive similar benefit from treatment with the 4 or 2 mg dose. In an integrated analysis of cDMARD-IR patients from 3 Phase II and Phase III studies, cDMARD-IR patients with moderate disease activity (defined as baseline Disease Activity Score 28 joints C-reactive protein (DAS28-CRP) of ≤5.1), no statistically significant difference in low disease activity (DAS28-CRP ≤ 3.2) response rates was seen for the 4 mg dose compared to the 2 mg dose after 12 weeks of treatment. In contrast, in cDMARD-IR patients with severe disease activity (defined as baseline DAS28-CRP of > 5.1), statistically significant improvements in low disease activity response rates were seen for the 4 mg dose compared to the 2 mg dose after 12 weeks of treatment.

Patients who are at risk of progressive joint damage are best treated with the 4 mg dose, as the 2 mg dose demonstrated less robust treatment effects than baricitinib 4 mg with respect to inhibition of progressive joint damage. Therefore, patients could be treated with the 2 mg dose if at limited risk of progressive joint damage. With respect to regaining physical function, patients who urgently require improvement are best treated with the 4 mg dose. In cDMARD-IR patients, a statistically significant change in Health Assessment Questionnaire Disability Index (HAQ-DI) from Baseline, compared to placebo, was first observed after 1 week of treatment with the 4 mg dose but only after 8 weeks of treatment with the 2 mg dose. The 2 mg dose could therefore be used in patients with low urgency to rapidly regain physical function.

Furthermore, the sponsor has generated data and proposed specific posology labelling for dose tapering (from 4 mg to 2 mg) after induction of disease control. This proposal is based on an extensive, blinded, randomised, dose-withdrawal study in Study JADY. Such a treatment strategy aligns with current professional guidelines for the management of RA;[26,27,28] which allow for the use of a lower, long-term maintenance dose once disease control has been established with the higher starting dose.

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

Given the current treatment algorithm in RA, it is common practise for physicians in the field to adjust the dose of RA treatments on an individual patient basis, taking into account the patient's disease severity and prognosis, comorbidities, concomitant treatments, treatment history, and resulting goals, as is being proposed for the dose taper approach.[26,27] While baricitinib 4 mg QD is the recommended dose for patients with moderately to severely active RA, a dose of 2 mg QD demonstrated efficacy compared to placebo in two Phase III studies and may be considered acceptable for some patients, such as those with moderate disease severity whose individual circumstances justify a lower-than- standard starting or maintenance dose, as assessed by their prescribing physician.

Question 13

> *Please provide an update on the progress of the submissions for baricitinib in the US and Canada.*

There is no further progress in terms of these pending applications over and above the status update provided in September 2017, other than we now anticipate the resubmission to the FDA by January 2018.

Advisory Committee Considerations[29]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM considered Olumiant film coated tablets containing 2 mg and 4 mg of baricitinib to have an overall positive benefit-risk profile for the indication, as amended by the sponsor:

> *'Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately, or who are intolerant to, one or more DMARDs (disease-modifying antirheumatic drugs).*
>
> *Olumiant can be taken as monotherapy or in combination with cDMARDs (conventional DMARDs), including MTX (methotrexate).*
>
> *Olumiant has been shown to improve physical function [and], reduce the signs and symptoms of RA'.*

In making this recommendation the ACM noted:

- that the extensive clinical program had shown:
  - baricitinib 4 mg daily reduced disease activity of patients with RA more than placebo;

[27] Singh JA et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016; 68(1):1-26.

[28] Lau C et al. Asia Pacific League of Associations for Rheumatology. APLAR rheumatoid arthritis treatment recommendations. *Int J Rheum Dis*. 2015; 18(7):685-713.

[29] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

  - efficacy in patients who are MTX naive, MTX inadequate responders and TNF inhibitor non responders; and
  - the efficacy of baricitinib to be similar to that of adalimumab.
- the safety profile of baricitinib is similar to that of other biologic DMARDs.
- that the increase in infections, cholesterol and venous thromboembolism (VTE) risk will need careful review.
- that two JAK inhibitors are already approved in Australia.

Proposed conditions of registration

The ACM advised the following:

Analysis from registry data (for example, from the US rheumatoid arthritis registry (Consortium of Rheumatoid Researchers of North America (Corrona)), relating to risks identified in the RMP, should be provided to the TGA in a timely fashion, in addition to routine pharmacovigilance reporting.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

1. Additional information on VTE risk should be included under *'Precautions'*. There should be consideration of anticoagulant prophylaxis for patients with risk factors for VTE. Patients with multiple risk factors for VTE should be closely monitored.
2. Medicines used for VTE prophylaxis (for example: aspirin, low molecular weight heparins) should be specifically addressed under *'interactions with other medicines'*.
3. Pregnancy Category D was the appropriate Use in Pregnancy category.[16]
4. The amendments under '*Use in pregnancy'* in the proposed PI (v0.40) were appropriate.
5. Pregnancy Category D and the statement in the PI to the effect that women of childbearing potential should take appropriate precautions to avoid becoming pregnant during treatment with Olumiant and for at least one week after the final treatment, should be accurately and adequately reflected in the relevant sections of the CMI. The advice to discuss a planned or actual pregnancy with the doctor was insufficient.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission.

> *1. Has sufficient evidence of efficacy and safety been provided to support 4 mg once daily as the usual dose, or should the starting dose be 2 mg once daily?*

The ACM noted that clinical efficacy has been more substantially examined at the 4 mg dose in Phase III studies, after the dose ranging Phase II studies that involved the 2 mg dose.

The 2 mg once daily dose produced improvement in the signs and symptoms of RA and physical function. However, baricitinib 4 mg consistently provided more rapid onset and a numerically higher response compared to placebo than the baricitinib 2 mg dose. Treatment with baricitinib 2 mg/day resulted in lower clinical response rates than treatment with baricitinib 4 mg/day.

The safety signals do not have a clear dose-response gradient. The ACM advised the 4 mg dose to be the usual dose.

The ACM noted that 2 mg is the recommended dose in patients with moderate renal impairment.

> *2. A signal of increased risk of venous thromboembolism (VTE) was identified in the studies. Based on the information to hand can this be considered a real risk, or can the arguments regarding confounding from other patient characteristics be accepted? Following multiple analyses of the data the sponsor and the clinical evaluator each concluded the proposed precautionary statement is acceptable. Is the proposed warning sufficient to mitigate the risk? Are other strategies such as a patient alert card warranted?*

While only 31 events had been reported in clinical trials, the ACM advised that the risk of VTE cannot be dismissed at this time as solely due to confounding factors.

VTE risks should be manageable in the patient population, if the PI is amended as suggested above.

The ACM advised that a patient alert card was warranted, as a condensed reminder of the VTE and other risks/precautions. Reliance on an initial provision (and intermittent resupply) of the CMI was insufficient to mitigate the risks.

> *3. In the pharmacokinetic-pharmacodynamic modelling analysis there was a 30% difference in response across the weight range. Can the committee comment on the influence of body weight on response to bDMARDs (biological DMARDs) in general for patients with RA. Is weight based dose adjustment warranted for baricitinib?*

The ACM agreed with the evaluator's conclusion that the pharmacokinetics of baricitinib does not appear to be substantially affected by body weight. The ACM advised the 4 mg dose to be the usual dose.

> *4. The European Summary of Product Characteristics contraindicates baricitinib in pregnancy, whereas the sponsor proposes Category D classification in Australia, without the contraindication. Can the committee comment on the approach proposed for Australia by the sponsor? Is a contraindication in pregnancy warranted, taking into account the nonclinical data and the safety of baricitinib?*

The ACM advised that Category D was reasonable given the available data.
A contraindication was not required. The formal definition of Category D includes that the medicine is not absolutely contraindicated during pregnancy.[16] A contraindication in the PI would be consistent with Category X, which was not warranted.

The ACM advised that use in pregnancy advice should be consistent with other available JAK inhibitors.

The ACM advised that there is no need for a protracted time after baricitinib is discontinued before planning a pregnancy.

> *5. Can the committee provide its view on the benefit-risk balance for baricitinib for the proposed indication? Would the benefit risk profile be more acceptable for a restricted population and is a refinement of the indication warranted?*

The ACM advised that the benefit-risk balance was favourable for the amended indication stated in the PI (v0.4).

Efficacy has been demonstrated in patients who are MTX naive, inadequate responders to MTX, and inadequate responders to TNF inhibitors.

The benefit-risk profile of baricitinib appeared similar to that of other biological DMARDs.

Major adverse cardiovascular events, particularly the risk of VTE, and cholesterol levels will need careful clinical monitoring.

Pharmacovigilance monitoring will also be required regarding the increase in serious infections, including opportunistic infections, herpes zoster, candidiasis and pneumocystis pneumonia.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of baricitinib.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Olumiant baricitinib 2 mg and 4 mg film-coated tablets, indicated for:

> '*Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately, or who are intolerant, to one or more DMARDs.*
>
> *Olumiant can be taken as monotherapy or in combination with cDMARDs, including methotrexate (MTX)*'.

Specific conditions of registration applying to these goods

- Olumiant (baricitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Olumiant must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The baricitinib EU-Risk Management Plan (RMP) (version 1.6, dated 11 January 2017, data lock point 1 January 2017), with Australian Specific Annex (version 0.2, dated 24 February 2017), included with Submission PM-2016-01468-1-3, to be revised to the satisfaction of the TGA, will be implemented in Australia.
- The following final study reports must be submitted to the TGA as soon as possible after completion, for evaluation for TGA evaluation:
  - Study JAGS
  - Study JADY.

Attachment 1. Product Information

The PI for Olumiant approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au