15 December 2016
EMA/13493/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Olumiant

International non-proprietary name: baricitinib

Procedure No. EMEA/H/C/004085/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Term	Definition
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
ACR20/50/70	20%, 50%, or 70% improvement in American College of Rheumatology criteria
ADA	adalimumab
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Apo-A1	apolipoprotein A1
Apo-B	apolipoprotein B
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
$AUC_{\tau,ss}$	area under the concentration versus time curve during one dosing interval at steady state
BARI	baricitinib
BCS	Biopharmaceutics Classification System
bDMARD	biologic disease-modifying antirheumatic drug
BID	twice daily
BMI	body mass index
$C_{av,ss}$	model-estimated average drug concentration under steady state conditions during multiple dosing
cDMARD	conventional disease-modifying antirheumatic drug
CDAI	Clinical Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use

CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
$C_{max,ss}$	mean maximum plasma baricitinib concentration at steady state
CPK	creatine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
CPP	critical process parameter
CQA	critical quality attribute
CYP	cytochrome
DAS28	Disease Activity Score based on 28 joints. Higher scores indicate increased disease activity.
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DoE	design of experiments
DSC	differential scanning calorimetry
EAIR	exposure adjusted incidence rate
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
EQ-5D-5L	European Quality of Life–5 Dimensions–5 Level
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
Ext	extended
EU	European Union
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue. Lower scores indicate greater fatigue.
FMECA	failure mode, effects and criticality analysis
FTIR	Fourier Transform Infrared Spectroscopy
GC	gas chromatography
G-CSF	granulocyte-colony stimulating factor

GI	gastrointenstinal
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage colony-stimulating factor
HAQ-DI	Health Assessment Questionnaire-Disability Index. Higher scores indicate greater disability.
Hb	haemoglobin
HBcAb	hepatitis B core antibody
HBV	hepatitis B viral
HDL-C	high-density lipoprotein cholesterol
HPLC	high performance liquid chromatography
hsCRP	high sensitivity C-reactive protein
ICH	International Council on Harmonisation
IC50	half maximal inhibitory concentration
ICP-MS	inductively coupled plasma mass spectrometry
IL	interleukin
IPC	in-process control
IR	inadequate response
IR	infrared
JAK	Janus kinase
LDA	low disease activity
LDL-C	low-density lipoprotein cholesterol
LLDPE	linear low density polyethylene
LLN	lower limit of normal
LOCF	last-observation-carried-forward
LSM	least squares mean
MACE	major adverse cardiovascular events
MATE1	multidrug and toxin extrusion protein 1
MATE2-K	multidrug and toxin extrusion protein 2

mBOCF	modified baseline observation carried forward
MDRD-eGFR	Modification of Diet in Renal Disease-estimated glomerular filtration rate
MJS	morning joint stiffness
MRI	magnetic resonance imaging
mTSS	modified Total Sharp Score
MTX	methotrexate
NCEP	National Cholesterol Education Program
NK	natural killer
NMR	nuclear magnetic resonance
NSAID	nonsteroidal anti-inflammatory drugs
NRI	nonresponder imputation
OAT3	organic anion transporter 3
OCT2	organic cation transporter 2
PD	pharmacodynamics
PI	prediction interval
PK	pharmacokinetics
PRO	patient-reported outcomes
PSD	particle size distribution
PSTAT	phosphorylated STAT
PYE	patient-years of exposure
Q2W	every 2 weeks
QbD	Quality by design
QD	once daily
QTc	corrected QT interval
RA	rheumatoid arthritis
RF	rheumatoid factor
RNA	ribonucleic acid
SAE	serious adverse event

SAP	statistical analysis plan
SDAI	Simplified Disease Activity Index
SF-36	Short Form (36) Health Survey
SOC	system organ class
STAT	signal transducers and activators of transcription
TB	tuberculosis
TEAE	treatment-emergent adverse event
$t_{1/2}$	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
t_{max}	time of maximum observed drug concentration
TNF	tumour necrosis factor
TTC	threshold of toxicological concern
TYK2	tyrosine kinase 2
ULN	upper limit of normal
URTI	upper respiratory tract infection
UV	ultraviolet
VAS	Visual Analogue Scale
WPAI-RA	Work Productivity and Activity Impairment Questionnaire: Rheumatoid arthritis
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 22 January 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Olumiant, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014.

The applicant applied for the following indication:

Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who are naïve to, have responded inadequately to, or who are intolerant to disease-modifying anti-rheumatic drugs (including conventional or biologic DMARDs). Olumiant may be used as monotherapy or in combination with non-biologic DMARDs.

Olumiant has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The applicant indicated that baricitinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0069/2013 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0069/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance baricitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 17 November 2011 and on 26 June 2014. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Bart Van der Schueren

- The application was received by the EMA on 22 January 2016.
- The procedure started on 25 February 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 May 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 May 2016.
- During the meeting on 23 June 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 June 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 September 2016.
- During the PRAC meeting on 29 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 4 October 2016.
- During the CHMP meeting on 13 October 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 November 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 November 2016 and on 9 December 2016.
- During the PRAC meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 1 December 2016.
- During the meeting on 15 December 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Olumiant.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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.

2.1.2. Epidemiology

The prevalence of RA is in the order of 0.5-1% of the population. It occurs about two to three times more commonly in women than in men, although this gender difference disappears in later life. Onset is maximal in the fifth-sixth decades.

2.1.3. Clinical presentation

Rheumatoid arthritis is characterised by chronic systemic inflammation that primarily affects diarthrodia joints, but can affect other organ systems. The disease has variable expression and outcome ranging from mild, limited disease to severe systemic disease associated with progressive joint destruction, significantly compromised quality of life, and reduced survival (Smolen and Steiner 2003; Colmegna et al. 2012). Patients with mild, limited RA usually have minimal joint destruction. Patients with moderately 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, infections, mental health disorders, and malignancies (CDC 2015). Within the joint, inflammation directly affects the synovial membrane and bone resulting in damage to the bone and articular cartilage. Importantly, while signs and symptoms are reversible with appropriate treatment, joint damage and the associated disability are permanent.

2.1.4. Management

Pharmaceutical treatment options in moderate-severe RA include conventional small molecule Disease Modifying Anti-Rheumatic Drugs (cDMARDs), and biologic DMARDs (bDMARDs). In addition, symptomatic treatment with conventional NSAIDs or selective COX-2 inhibitors is often required.

Conventional small-molecule DMARDs include, amongst others, methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Biologic DMARDs that are registered in Europe for the treatment of RA include Tumour Necrosis Factor inhibitors (TNF-I) adalimumab, etanercept, golimumab, infliximab, and certolizumab pegol, Interleukin-6 inhibitor tocilizumab, B-cell depletion therapy rituximab, T-cell co-stimulation modulator abatacept, and Interleukin-1 antagonist anakinra. The latter is not much used anymore in modern rheumatology practice.

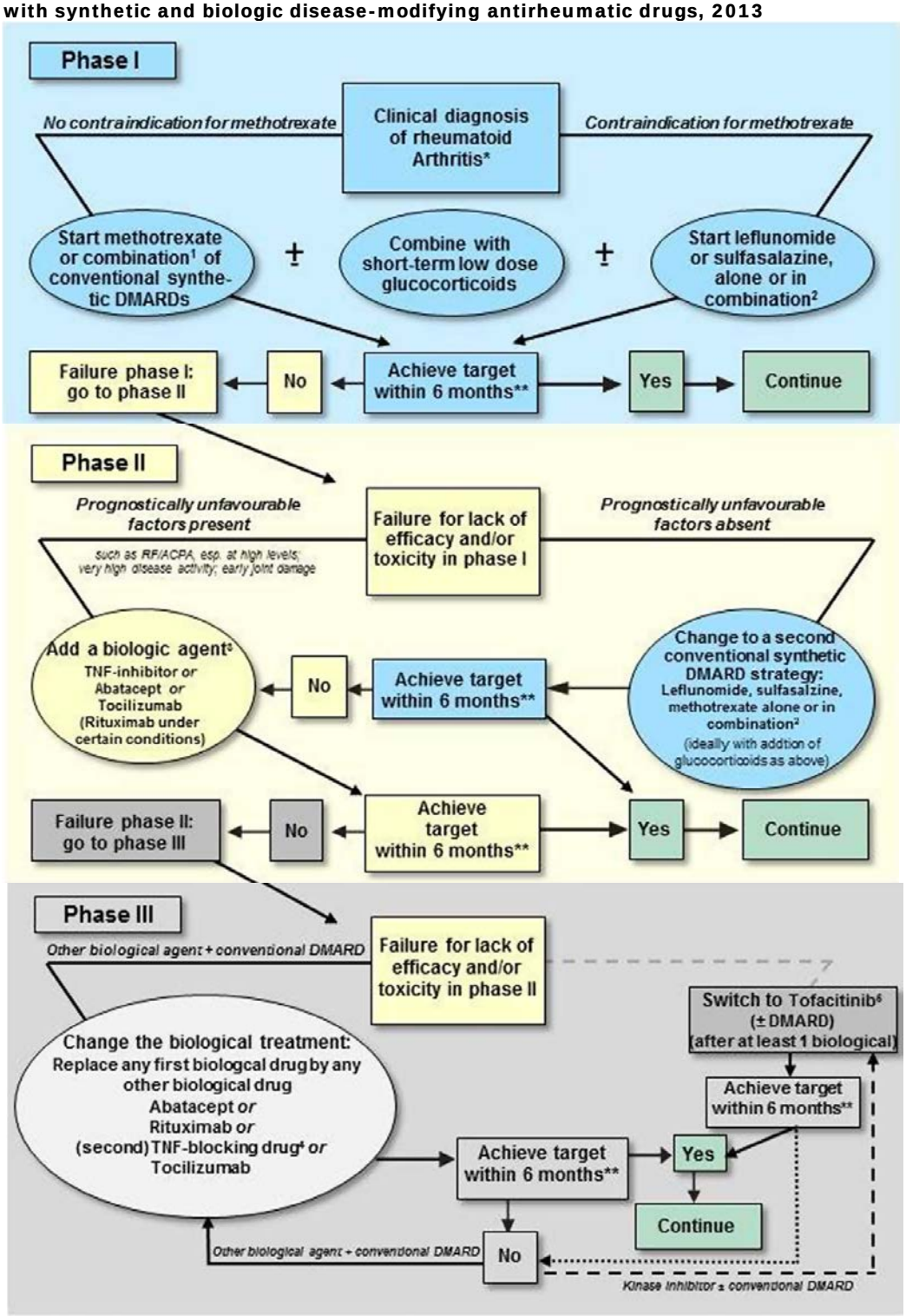
In DMARD-naive patients, the initial choice of DMARD is commonly methotrexate (MTX), used as monotherapy or in combination with other cDMARDs and/or low doses of corticosteroids. Tolerability issues are well-described for MTX; approximately 40% of patients receiving MTX experience gastrointestinal symptoms (nausea, vomiting, and abdominal pain, while hepatotoxicity is observed frequently and pulmonary toxicity is observed occasionally. Patients responding insufficiently to MTX or other cDMARDs commonly begin treatment with a bDMARD along with MTX.

Therapeutic strategies employing more intensive intervention with DMARDs in early disease phase, often using combinations of non-biologic and biologic DMARDs, have shown a faster onset of action and more profound clinical responses than traditional step-up approaches. As recommended by the EULAR (European League against Rheumatism), treat-to-target strategies are now employed, meaning that the treatment goal is Remission, or at least Low Disease Activity (LDA) in advanced patients (see outline EULAR recommendations, Smolen JS, Landewé R, Breedveld FC, et al. Ann Rheum Dis doi:10.1136/annrheumdis-2013-204573, see also figure below). Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 to 6 months.

Even with the most effective treatments available, such as bDMARDs, more than half of patients do not achieve a substantial response defined as achievement of low disease activity (Rubbert-Roth and Finckh 2009; Villeneuve and Haraoui 2010). In addition, some patients treated with bDMARDS may lose efficacy due to the development of anti-drug antibodies. The risk of bDMARDs include injection or infusion site reactions, increased frequency of infections, reactivation of tuberculosis or viral infections, pneumonia, gastrointestinal perforations, other autoimmune conditions, and -possibly- an increased incidence of malignancy.

In conclusion, despite the availability of a number of agents for the treatment of RA with various methods of action, many patients fail to respond to initial treatment, do not tolerate treatment, or lose response over time. For patients with an inadequate response to cDMARDs, only parenteral biological DMARDs are available thus far. Thus, there is a need for alternative oral treatment options.

Figure 1. Scheduled of EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs, 2013



*2010 ACR-EULAR classification criteria can support early diagnosis; **The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed, if no improvement is seen after 3 months. [1]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychroquine; [2]Combinations of sulfasalazine or leflunomide except with methotrexate have not been well studied, but may include combining these two and also with antimalarials; [3]these circumstances are detailed in the text; [4]Adalimumab, certolizumab, etanercept, golimumab, infliximab or respective well studied and FDA/EMA approved biosimilars; [5]where licensed.

Lines: Full black line, recommended; as shown; grey interrupted line: recommended for use after biologics failure (ideally two failed biologics); interrupted black line: recommended after two biologics failed, but efficacy and safety after failure of abatacept, rituximab and tocilizumab not sufficiently studied; black dotted line: possibly recommended, but efficacy and safety of biological use after tofacitnib failure unknown at the time of developing the 2013 update of the recommendations.

About the product

Baricitinib (Olumiant) is a Janus Kinase inhibitor with selectivity for JAK2 and JAK1, and less potency for JAK3 or TYK2. The JAKs and their associated signal transducers and activators of transcription (STATs) are the major intracellular pathway that controls the magnitude and duration of signalling for cytokines that bind to Type I and Type II cytokine receptors. These receptors lack intrinsic enzymatic activity capable of mediating signal transduction; so receptor-associated STATs are instead phosphorylated by JAKs, resulting in STAT activation. Activated STATs are active transcription factors and drive the expression of multiple genes important for cell activation, localisation, survival, and proliferation. Several of the pro-inflammatory cytokines implicated in the pathogenesis of RA, including IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF), and interferons signal via the JAK-STAT pathway. Thus, inhibition of JAK1 and JAK2 signalling targets multiple RA-associated cytokine pathways, and thereby may reduce inflammation, cellular activation, and proliferation of key immune cells.

Baricitinib has a low potency for JAK3. JAK3 may be more associated with the common gamma chain receptor, than the other JAKS. The common gamma chain cytokines include IL-15 and IL-21, which regulate lymphocyte activation, function, and proliferation.

The originally proposed indication was:

"*Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who are naïve to, have responded inadequately to, or who are intolerant to disease-modifying anti-rheumatic drugs (including conventional synthetic or biologic DMARDs). Olumiant may be used as monotherapy or in combination with conventional synthetic DMARDs.*

Olumiant has been shown to reduce the rate of progression of joint damage as measured by X-ray."

The approved indication is:

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

The recommended dose of Olumiant is 4 mg once daily. A dose of 2 mg once daily is appropriate for patients such as those aged ≥75 years and may be appropriate for patients with a history of chronic or recurrent infections. A dose of 2 mg once daily may also be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.

Treatment should not be initiated in patients with an absolute lymphocyte count (ALC) less than 0.5×10^9 cells/L, an absolute neutrophil count (ANC) less than 1×10^9 cells/L, or who have a haemoglobin value less than 8 g/dL. Treatment may be initiated once values have improved above these limits.

Type of Application and aspects on development

Legal basis: Article 8 (3), Directive 2001/83/EC, full application.

Scientific Advice obtained from the CHMP in November 2011 (EMA/CHMP/SAWP/868023/2011) and in June 2014 (EMA/CHMP/SAWP/343853/2014).

The clinical advice sought was primarily related to the design of the studies in support of indications in different RA sub-populations (first line in DMARD-naïve patients, and second line in MTX-IR patients and bDMARD-IR patients).

In general, the proposed design for a 52-week, randomized, double-blind, placebo- and active-controlled study in DMARD-naïve patients was supported by the SAWP. ACR20 response rate at Week 12 was proposed as the primary efficacy endpoint. The CHMP agreed with the design and endpoints, but noted that comparison with MTX beyond 12 weeks could be also included in the list of key endpoints. The primary endpoint was adapted to 24 weeks based on this advice. In addition, the CHMP considered that based on safety grounds, further restriction of the patient population might become necessary at the time of MAA.

There were a few deviations from the study plans that were provided for the Scientific Advice in 2011.

CHMP also pointed out recent approvals at the time for Cimzia, Simponi and Orencia which had used co-primary endpoints on the improvement of physical function and/or prevention of structural damage to include such claims in the label. However, the draft EMA guideline on RA and the EMA guideline on the SmPC points out that separate endpoints like structural damage and function are not considered as separate claims in the indication.

In relation to the second-line indication of RA patients who have had an insufficient response or intolerance to previous therapy with 1 or more cDMARDs (including MTX), a 52-week, randomized, double-blind, placebo- and active-controlled (with a TNF-I) trial was proposed.

The Applicant requested Scientific Advice in November 2011 before the revision process of the current RA Guideline had been initiated. In the draft guideline of 2015, different primary endpoints than ACR20 are proposed (see discussion B/R section).

Overall, the Applicant implemented the SAWP/CHMP advice adequately. Several changes were made in the design of the trials afterwards, without consulting the SAWP. E.g. in contrast to the original proposal, no placebo was included in the study on the “first-line’ indication in DMARD-naïve patients, for ethical considerations. This hampers the assessment of assay sensitivity. Retrospectively, assay sensitivity could be assumed in this study as the response to baricitinib 4 mg deviated from active control MTX. The omission of the placebo comparator may therefore be acceptable. See comments under Clinical Efficacy and the Benefit-Risk assessment.

Furthermore, no active comparator has been included in the study in bDMARD-inadequate responders, for practical considerations as the alternative treatment options required IV infusion and prior treatment of corticosteroids to avoid infusion reactions. As an active comparator –TNF-inhibitor adalimumab- has been included in another study in RA patients irresponsive to MTX alone, this may provide sufficient information regarding the position of baricitinib towards bDMARDs.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 2 mg or 4 mg of baricitinib as active substance.

Other ingredients of the tablet core are: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and mannitol. Ingredients of the film-coating are: iron oxide red (E172), lecithin (soya) (E322), macrogol, polyvinyl alcohol, talc and titanium dioxide (E171).

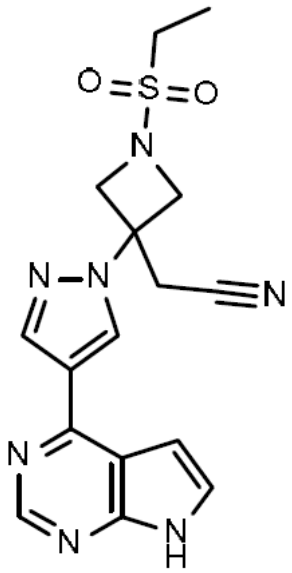
The product is available in polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium blisters and polyvinylchloride/aluminium/oriented polyamide - aluminium perforated unit dose blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of baricitinib is 2-(3-(4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile corresponding to the molecular formula $C_{16}H_{17}N_7O_2S$. It has a relative molecular mass of 371.42 and has the following structure:

Figure 2. Structural formula of baricitinib



The structure of baricitinib was confirmed using a combination of mass spectrometry, FTIR spectroscopy, Raman spectroscopy, UV spectroscopy, ^{1}H-NMR and ^{13}C-NMR spectroscopy, DSC, X-ray crystallography and elemental analysis.

The active substance is a non-hygroscopic, white to practically white to light pink powder, slightly soluble in 0.1 N HCl and practically insoluble in water. It is very slightly soluble in ethanol and sparingly soluble in acetone and tetrahydrofuran. It is classified as a BCS Class III substance.

Baricitinib has a non-chiral molecular structure.

Several crystalline forms of baricitinib free base were observed during a comprehensive polymorph screen. Crystalline form I of baricitinib free base, a thermodynamically stable anhydrous form, was selected for commercial development.

Baricitinib is considered to be a new active substance. The applicant demonstrated that neither it, nor its derivatives and salts have ever been active substances in products authorised in Europe.

Manufacture, characterisation and process controls

A single manufacturer carries out the entire process. Baricitinib is synthesized using a convergent synthesis, consisting of three sequential coupling reactions of the starting materials, with requisite protection and deprotection steps to ensure proper connectivity. The final step involves a deprotection reaction to form the active substance. Designation of the staring materials is in line with the scientific advice sought from the CHMP prior to submission of the dossier. Additional data requested at the time of the scientific advice procedure has been provided and it was considered acceptable.

The development of the manufacturing process for baricitinib included the use of Quality by Design (QbD) principles and linking of elements of risk and risk management to scientific understanding. Prior process knowledge and a combination of conventional univariate and bracketing studies, multivariate studies and statistical models were the basis of the proposed PARs and design spaces for three unit operations.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of active substances. A comprehensive discussion on potential and actual impurities is provided, including process impurities, genotoxic impurities and fate and purge studies. Impurities have been evaluated using a combination of *in silico* toxicity predictions, visual alerts, external databases, and *in vitro* assessments as needed. These evaluations took into account all starting materials, intermediates, reagents, reaction conditions in the route as well as potential impurities and degradation products. The evaluation of genotoxic impurities utilized an assessment for alerting structures as well as *in silico* toxicity predictions in compliance with ICH M7 guidance. *In silico* toxicity assessments flagged several impurities as positive and two impurities analysed were positive in the Ames test. Genotoxic impurities are controlled below the TTC.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. It includes three minor changes from the process used to manufacture batches for primary stability studies and clinical trials (including Phase 3 trials). Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in a linear low density polyethylene (LLDPE) primary liner which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. The liner contains an additive that provides antistatic protection. The LLDPE liner is placed in a laminated foil liner and may be placed in an appropriate container such as a corrugated container, fibre drum, polyethylene drum or metal drum.

Specification

The active substance specification includes tests for identity (IR or Raman), crystal form (XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), palladium (ICP-MS), description (visual), particle size distribution (laser light diffraction), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.) and microbiological testing (Ph. Eur.).

The active substance specifications are based on the active substance critical quality attributes (CQA). The CQAs identified are identity, potency, purity and particle size.

The omission of tests for elemental impurities (except palladium) has been justified based on the risk-assessment performed in line with ICH Q3D and batch analysis data.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Analysis data from 29 commercial and pilot scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Supportive stability data were also provided from a pilot scale and a commercial scale batch using earlier development processes for up to 48 months at 25 ºC / 60% RH and for up to 6 months at 40 ºC / 75% RH, respectively.

The following parameters were tested: identity (IR), crystal form, assay, impurities, description, package characteristics, particle size distribution and loss on drying. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. No significant changes or trends were observed in any of the parameters tested through 24 months and 6 months of storage at 25 °C / 60% RH and 40 °C / 75% RH, respectively, compared to the initial values.

Photostability testing following the ICH guideline Q1B was performed on one batch. The study confirmed that baricitinib is not sensitive to light.

Data following exposure to the following stressed conditions were provided for the active substance in the solid state: heat, light, heat and humidity. Data was also provided for the active substance in a solution or a suspension: under a wide range of pH conditions at elevated temperatures, light, oxidative conditions and the presence of radical initiator and metal salts.

Baricitinib active substance in solid state did not exhibit any detectable degradation under the stressed conditions of heat, heat and humidity, or simulated sunlight.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with no special storage conditions in the proposed container, LLDPE primary liner. The LLDPE liner is placed in a laminated foil liner and may be placed in an appropriate container such as a corrugated container, fibre drum, polyethylene drum or metal drum.

Comparability exercise for Active Substance

Not applicable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as immediate release film-coated tablets. The 2 mg strength is a light pink, oblong tablet, 9.0 mm by 7.5 mm in size and debossed with “Lilly” on one side and “2” on the other. The 4 mg strength is a medium pink, round tablet, 8.5 mm in diameter and debossed with “Lilly” on one side and “4” on the other. The different strengths of the film-coated tablets are distinguishable by their colour, shape, size, and debossing.

Pharmaceutical development of the finished product contains QbD elements.

The critical quality attributes identified were description, identification, potency, purity, content uniformity, and release throughout the finished product shelf-life.

The formulation and manufacturing development were evaluated through the use of risk assessment and laboratory experiments to identify the product critical quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect and criticality analysis (FMECA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or the EU legislation. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. Excipient compatibility studies, prior experience from other roller compaction projects, and scientific knowledge were utilized to select tablet excipients with appropriate functionality to manufacture an acceptable finished product. The good compatibility was further demonstrated with stability data as no degradation products were observed with commercial tablet formulations placed on stability through 6 months of accelerated and 24 months of long-term conditions.

An overview of the formulations used to support Phase 1, 2 and 3 trials has been provided. The commercial finished product formulation and manufacturing process were used throughout the Phase 3 clinical program and for the primary stability program. The *in vivo* equivalence of the 4 mg commercial tablet and the 4 mg Phase 2 tablet was confirmed in a relative bioavailability study.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium blisters and polyvinylchloride/aluminium/oriented polyamide - aluminium perforated unit dose blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: blending steps, roller compaction, sizing, final blending, tablet compression, film-coating and packaging steps. The process is considered to be a non-standard manufacturing process due to the low active substance content in the finished product.

Major steps of the manufacturing process have been validated by a number of studies. Validation data was provided for 2 consecutive and 1 additional commercial scale batch for 2 mg film-coated tablets and 3 consecutive commercial scale batches for 4 mg film-coated tablets and were found acceptable by the CHMP. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Proven acceptable ranges have been established based on multivariate. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: identity (IR), assay (HPLC), degradation products (HPLC), description (visual), uniformity of dosage units (HPLC), dissolution (HPLC), dye identity (chemical reaction).

The omission of several tests from the finished product specifications has been appropriately justified. Dimensions of the tablets are controlled by the process parameters (tooling) and a test is therefore not required in the specifications of the finished product as part of the visual description test. The omission of tests for elemental impurities has been justified based on the risk-assessment performed in line with ICH Q3D and batch analysis data. Omission of moisture (water content) has been justified based on the type of the manufacturing process (dry roller compaction and the removal of water at the end of the coating process) and stability data. Microbial testing was omitted based on batch analysis data and adequate controls for manufacturing, components of the finished product and packaging.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 44 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Supportive batch analysis results of 78 batches of different sizes of earlier development formulations were also provided.

The finished product is released on to the market based on the above release specifications, through traditional final product release testing.

Stability of the product

A matrix design for all strengths and packaging for the long-term storage conditions is proposed. The testing schedule employed a “one third reduction” i. e. 2 out of 3 batches of each strength were tested at the 3, 6, 9, and 12 month time points. All batches were tested at 18, 24, and 36 months. For accelerated conditions, the reduction concerns the number of batches and type of packaging tested at the 1 and 3 month time points, i.e. 1 or 2 batches per strength and packaging configuration were tested at each time point. All batches and packaging configurations were tested at the initial and 6 month time point. The reduction in the design is proposed based on the similarity of the composition and manufacturing process of the tablets, physical and chemical stability data exhibited during development and clinical stability studies, and it was found to be acceptable.

Stability data from 3 commercial scale batches of each strength of the film-coated tablets packaged in the polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium blister packs stored under long term conditions for up to 24 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Stability data from 3 commercial scale batches of each strength of the film-coated tablets packaged in the polyvinylchloride/aluminium/oriented polyamide - aluminium blister packs stored under long term conditions for 24 months at 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were also provided.

The batches of medicinal product are identical to those proposed for marketing.

Additional supportive stability data from six batches of the finished product manufactured by a process representative of the commercial process that were used in the clinical trials and data on the finished product packaged in the 3 different bottle presentations was provided.

Samples were tested for physical appearance, package characteristics, assay, impurities, dissolution, water activity and microbial quality. The analytical procedures used are stability indicating.

No significant changes to any parameters were observed and results remained within the proposed specifications under both long term and accelerated testing conditions.

Stress testing studies were conducted on the finished product in order to gain an understanding of the degradation chemistry of baricitinib when formulated as a solid oral product. Both strengths of baricitinib film-coated tablets were stressed. A minor increase in impurity levels was noticed. The low levels of degradation products detected in the stress testing study of the finished product suggest that it is anticipated to demonstrate good stability under typical storage conditions.

In addition, a commercial scale batch of each tablet strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed no significant change to any of the measured parameters and the finished product is thus considered photostable.

Based on available stability data, the proposed shelf-life of 24 months with no special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Comparability exercise for finished medicinal drug product

Not applicable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is of vegetal origin.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing processes. Design spaces have been proposed for three steps in the manufacture of the active substance and have been adequately verified. Only PARs are claimed for the finished product manufacturing process.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal safety pharmacology and toxicology studies were performed in compliance with GLP.

Scientific advice was obtained from the CHMP in November 2011 and June 2014. In 2011, the non-clinical package was considered in general appropriate, with as point of attention that the safety margin in the chronic studies in dogs can be regarded as very low.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In enzyme inhibition assays, baricitinib demonstrated selective and balanced potency against JAK 1 (IC50 5.9 nM) and JAK2 (5.7 nM) with less potency for TYK2 (53 nM) and far less potency for JAK3 (>400 nM). Baricitinib inhibited the phosphorylation of JAK2, STAT3 and STAT5 in activated PBMCs, which were stimulated by IL-2. Also, baricitinib inhibited IL-2 induced T cell proliferation with an IC50 of 29 nM, indicating the inhibition of JAK1 and the JAK/STAT3/5 pathway by baricitinib.

Functional inhibition of the JAK-STAT pathway has been demonstrated in multiple cell-based assay systems using physiologically relevant immune activators. In human IL-23 stimulated T cells baricitinib inhibited the JAK/STAT pathway by inhibiting both phosphorylation of STAT3 and production of the cytokines IL-17 and IL-22, with IC50s of 20-57 nM. Baricitinib also inhibited the JAK/STAT pathway in response to IL-12 stimulation

by inhibiting STAT3 phosphorilation (IC50 = 60 nM) and production of IFN-γ in human T cells (IC50 = 5.8 µM). In PBMCs, baricitinib inhibited the JAK/STAT pathway in response to IL-6 stimulation, resulting in decreased MCP-1 production. Baricitinib blocked IL-6 induced STAT3 phosphorylation in whole blood from humans, dogs and rats, with IC50 of 104, 49 and 128 nM respectively, confirming the species cross-reactivity of the compound. Also, ex vivo IL-6 stimulation of blood samples from the 4-week beagle dog toxicology study demonstrated that all dose levels were pharmacologically active, exhibiting inhibition of STAT3 phosphorylation that was dose- and time- dependent.

Baricitinib improved clinical and histological signs in several rodent arthritic related models of disease in a dose dependent manner. In a mouse delayed type hypersensitivity model, the animals were sensitized with dinitrofluorobenzene and then challenged with the same on the ear. Baricitinib at 10 mg/kg twice daily reduced significantly the magnitude of the swelling by 48%, suggesting that baricitinib is able to inhibit delayed type hypersensitivity cellular responses which may contribute to the overall efficacy observed in the rodent models which reflect certain aspects of rheumatoid arthritis.

In the murine collagen-induced arthritis (CIA) model, oral baricitinib ≥3 mg/kg bid showed efficacy which may be dependent on the impact of both T and B cell function by modulating the signalling of cytokines involved in the adaptive immune response. In a murine anti-collagen antibody induced arthritis model, baricitinib at 10 mg/kg bid improved clinical and histological signs without inhibiting the generation of autoantibodies and without a detectable reduction in peripheral leukocyte or erythroid cellular components.

In a rat adjuvant arthritis (rAIA) model, baricitinib (IV, 1 – 6 mg/kg/day for 2 weeks) reduced inflammation 50 – 100% as measured by redness and swelling of the paws, and histological comparison. Plasma levels were 53 – 480 nM, which compares well with the IC50 of 128 nM in the IL-6 induced STAT3 phosphorylation rat whole blood assay. In a similar model with oral dosing of 3 and 10 mg/kg/day baricitinib, clinical and histological signs were reduced by 39-82% at predicted AUC-values of 2 – 6.7 µM.h. Also in the rAIA model, oral baricitinib 10 mg/kg/day for 2 weeks reduces elevated cytokine mRNA levels from lymph nodes.

While greater than 90% inhibition of IL-6 induced STAT3 phosphorylation was observed at the 3 and 10 mg/kg doses at 1 hour in the rAIA model, only modest inhibition (13%), was observed at 3 mg/kg by 4 hours, and by 24 hours, no inhibition was detected at any of the doses. These data demonstrate that baricitinib is efficacious in a preclinical model relevant to RA without requiring complete or continuous inhibition of JAK/STAT signalling. The inhibition is reversible, as it is less at 4 hours post dose and no longer apparent by 24 hours.

Secondary pharmacodynamic studies

Baricitinib was screened for binding to a panel of kinases, and in addition to JAK1 and JAK2, baricitinib showed moderate binding affinity for CaMK2d and CaMK2g (IC50:170 nM and 150 nM, respectively). The relevance of binding to these kinases at the doses studied in humans is unknown, but the values are relatively high compared to the expected human free fraction Cmax of ca. 70 nM. Baricitinib did not show any additional significant binding to 250 other kinases.

Safety pharmacology programme

Baricitinib inhibited the hERG channel at a concentration 1400x the unbound Cmax at MRHD. In dog, baricitinib slightly increased heart rate and decreased systolic, diastolic and arterial blood pressure, with a safety factor of 1.2 fold the MRHD.

Baricitinib induced effects on the CNS and respiratory system which were observed at relatively high exposures of 17-80 fold exposure at the MRHD. Effects observed included red flush of the skin and mucous membranes, drooping eyelids, absence of pupillary response, decreases in body temperature and a lower respiratory frequency.

Pharmacodynamic drug interactions

Only human studies were conducted to examine pharmacodynamic drug interactions. Please see Clinical section of the report.

2.3.3. Pharmacokinetics

The nonclinical absorption, distribution, metabolism and excretion (ADME) studies have been conducted in the same species and generally in the same strains as used in the toxicology studies. The pharmacokinetics (PK) of baricitinib has been investigated upon single dose intravenous (IV) or oral (PO) administration in mouse, rat, dog and monkey. Multiple dose toxicokinetics (TK) was examined upon daily oral administration, which is the intended clinical route, in the CD-1 mouse, Tg-rasH2 mouse, Sprague Dawley (SD) rat, beagle dog and (pregnant) rabbit. The formulations used in the disposition studies were generally the same as those used in the pivotal toxicity studies although radiolabelled drug was incorporated when appropriate.

The Applicant provided validation reports for the analytical methods used, demonstrating the suitability of the methods, storage and handling for the purpose of analysis of baricitinib. Specific and sensitive bioanalytical assays have been developed and validated for the quantitative determination of baricitinib in mouse, rat, rabbit and dog plasma.

Baricitinib is a lipophilic compound (Mw 371.4), with very low solubility in aqueous solutions at neutral pH. The intended clinical route of baricitinib is by PO administration, which was also the route of administration for the pivotal toxicity studies. Several oral single dose studies were discussed to evaluate the absorption and pharmacokinetics of baricitinib in mice, rats and dogs but these studies only measured PK parameters of ([^{14}C]-baricitinib related) radioactivity upon the [^{14}C]-baricitinib phosphate administration to mice, rats, and dogs. These studies indicate that absorption in mouse, rat and dog was fast with Cmax at the first time point measured (1 h). In addition, the single dose oral pharmacokinetic profile of baricitinib and the intravenous pharmacokinetics, upon a short infusion, were examined in male Sprague Dawley rats, male dogs, male monkeys and humans. The IV pharmacokinetics was characterized by moderate plasma clearance values in rat (1.3 – 4.4 L/hr.kg) with lower values in dog (0.40 L/hr.kg), monkey (0.36 L/hr.kg) and human (0.21 L/hr.kg). The volume of distribution (Vss) was moderate in all species, with values ranging from 1.1 L/kg (monkey and human), 1.4 L/kg in dog to 2.1 - 6.2 L/kg in rat. The apparent elimination half-life ranged from 1 - 3 hrs in rat, 3 – 6 hrs in monkey and 4 - 5 hrs in dog. Oral bioavailability from a 0.5% methylcellulose aqueous solution formulation was high and ranged from 48% and 54% in dog and rat, 47 – 68% in monkey and 79% in human. Oral absorption was relatively fast in all species with peak concentrations occurring about 0.6, 1.0 and 1.6 hours after dosing in rats, dogs and monkeys, respectively. In humans, following single oral dosing, oral absorption was moderately fast with a T_{max} of baricitinib in plasma of 1.0 hour and a terminal elimination half-life of 8.6 h was found.

Single and repeat dose pharmacokinetic studies were conducted to evaluate the relative bioavailability of baricitinib in the free base versus phosphate salt forms. In both mice and rats multiple dose studies no

meaningful difference in the exposure to baricitinib were found following the administration of the free base or phosphate salt forms.

The repeated dose pharmacokinetic profile of baricitinib was obtained from toxicokinetic studies and determined in rat, mice, rabbits and dogs following daily oral administration for up to 9 months of treatment. Mouse (wildtype and Tg-rasH2), SD rat and dog have been selected as the animal species for pivotal repeat dose studies to assess the systemic toxicity of baricitinib. Generally, on multiple dosing, over all dose ranges examined an approximately dose proportional increase (less than 2-fold difference with the increase in dose) in plasma Cmax concentrations and exposure was found. The uptake of baricitinib was relatively fast and there was evidence of only limited decrease or accumulation (<2-fold) following multiple daily dosing in mice, rats and dogs, which is in line with human data. No apparent gender differences in Cmax or exposure were noted in dogs and rats while in mice Cmax and exposure values were slightly, but less than 2-fold, higher in female than in males.

Distribution

Plasma protein binding (PPB) of baricitinib was moderate across all preclinical species examined (45% - 56%). PPB was concentration independent from 0.32 – 10.7 µg/ml (ex vivo rat/dog). Baricitinib was also approximately 50% unbound in human plasma.

Blood to plasma (B/P) ratio of [^{14}C]-baricitinib was 0.83 in mice, 0.93 in rats and 1.04 in dogs at Cmax (1 hour postdose) This indicates that baricitinib was evenly distributed over the blood cell and the plasma compartment, with depending on species, about 45% – 50% binding to blood cells. In humans, the B/P ratio was 1.14 at Cmax (range 1.12 - 1.26), indicating a comparable binding to blood cells.

Quantitative whole-body autoradiographic (QWBA) techniques were used to determine the tissue distribution of baricitinib. Following an oral administration of [^{14}C]-baricitinib to male albino rats and male and female Long Evans rats, the ^{14}C-radioactivity was distributed into almost all tissues at the first time point, 2 hr post-dose. This was also the Tmax for these tissues, except for the alimentary canal. Distribution was extensive with the highest concentrations of radioactivity being found in alimentary canal contents, bile, and urine. Distribution of [^{14}C]-baricitinib related radioactivity was similar in pigmented and non-pigmented rats, with the exception of the pigmented skin and uveal tract of the eye in pigmented rats, suggesting binding to melanin-containing tissues.

Elimination was nearly complete by 168 hours post-dose in non-pigmented rats and complete by 672 hours post-dose in pigmented rats, except for some levels of radioactivity detectable in the dorsal caudal nerve, aorta, and in uveal tract of pigmented rats. In pigmented skin, [14C]-baricitinib related radioactivity was present up to 336 hours post dose. The highest total tissue exposure of drug-related radioactivity over plasma exposure ratio (AUC_{0-672} T/P) was observed in the dorsal caudal nerve (174-fold), the aorta (117-fold) and the uveal tract of the eye (94-fold). In toxicology studies, including phototoxicity, however, no toxicological findings were reported for these tissues suggesting that prolonged baricitinib exposure or melanin binding apparently has no toxicological consequences. Concentrations of radioactivity in the eye lens, spinal cord and non-circumventricular central nervous system (CNS) tissues (cerebellum, cerebrum, and medulla) were below measurable levels throughout the course of this study. No sex-dependent differences in tissue distribution of 14C-radioactivity were observed. In a separate experiment, the brain, cerebrospinal fluid (CSF) and plasma concentrations of baricitinib were determined in rats after IV dosing. Total brain concentration of baricitinib to total plasma concentration was 7.5% and the CSF concentration was ~1% of the total plasma concentrations. The results suggest that baricitinib has minimal penetration across the rat blood brain barrier.

Following a single oral 25-mg/kg dose of [^{14}C]-baricitinib to timed-pregnant female rats on Day 18 of gestation, radioactivity, as measured by QWBA, was widely distributed to maternal tissues, crossed the placenta, and was quickly distributed to fetal tissues. Fetal blood levels of [^{14}C]-baricitinib were about 2.2 fold lower than in maternal blood. In maternal tissues, the distribution of [^{14}C]-baricitinib-related radioactivity was comparable to previous studies. Most maternal and all fetal tissues reached their highest concentrations at 0.5 hours post-dose. Placental transfer and subsequent fetal exposure to [^{14}C]-baricitinib-related radioactivity occurred at moderate to low levels (up to 5080 ng eq [^{14}C]-baricitinib/g) through 8 hours post-dose. Highest levels were found in amniotic sac, placenta, fetal gastrointestinal tract and fetal adrenal gland. All fetal tissue radioactivity concentrations were maximal 3-fold fetal blood levels and were below the limit of quantitation or not detectable by the final sampling time at 24 hours post-dose.

Following a single oral 25 mg/kg dose of [^{14}C]-baricitinib to lactating dams, [^{14}C]-baricitinib-related radioactivity was highly excreted into the milk. Peak concentrations of radioactivity were observed at 4 hours postdose in milk (33600 ng eq. [^{14}C]-baricitinib/g) and 1 hour postdose for plasma (1900 ng eq. [^{14}C]-baricitinib/g) and declined similarly to low levels by 24 hours postdose. Exposure to [^{14}C]-baricitinib-related radioactivity was approximately 39- and 18-fold greater in milk than in plasma based on AUC0-∞ and Cmax values, respectively. The elimination half-lives of radioactivity in plasma and milk were similar (2.6 and 2.7 hours, respectively) (see SmPC section 5.3).

Metabolism

Multiple nonclinical studies were conducted in mice, rats, rabbits, and dogs to evaluate the in vivo metabolism of baricitinib throughout the development of the molecule. These studies indicate that following a single oral dose of [^{14}C]-baricitinib, the in vivo metabolism was minimal and that the parent compound was the primary circulating entity in plasma and also the major component excreted in both urine and feces in all species, including human.

Biotransformation of baricitinib in nonclinical species (CD1-mouse, Sprague-Dawley rat, New Zealand white rabbit, Beagle dog) and human were represented by mono-oxidation (M9, M10) and bis-oxidation (M22) on either the pyrazole or pyrimidine ring, oxidative ring opening of the pyrrole ring (M13, M3, M12) and glucuronidation (M6). In addition, several minor oxidative metabolites were also identified in these species.

In plasma of nonclinical species, baricitinib was the primary drug-related component in mice (81 - 92%), rats (79% - 93%), rabbits (95%) and dogs (84% - 96%). In human plasma, no detectable circulating metabolites were found but only baricitinib (96%) was present. In addition, in plasma from nonclinical species about nine metabolites were identified, which were each less than 10%. These metabolites were found in mouse (M3, M6, M9, M10, M22), rat (M13), rabbit (M7, M17) and dog (M2).

Excreta: After a single oral dose in CD-1 mice, drug-related radioactivity was mainly eliminated unchanged in urine (15% of the dose) and feces (39%). In urine, about 8% is excreted as metabolites of which M10 (3%) was largest. In feces ~23% is excreted as thirteen metabolites of which the highest (7%) is an unknown radioactive peak.

In both intact and bile duct cannulated (BDC) rats, parent drug and nine metabolites were quantified in rat urine, feces and bile following a single oral or intravenous dose of [^{14}C]-baricitinib phosphate. After an oral dose, drug-related radioactivity was mainly eliminated in feces (40% - 65% of dose) of which 40% was baricitinib and 0%-16% were metabolites and with ~29% of dose in urine (17%-20% as parent and <10% as metabolites), while bile only consisted of ~18% of the dose (~2% as parent). A majority of the intravenous dose (49%), however, was excreted in urine as unchanged baricitinib (35% of the dose), with several small amounts of metabolites. Feces of BDC rats, only contained unchanged baricitinib (11%) upon IV administration suggesting intestinal secretion. Bile excretion was 21% of the dose and contained twenty metabolites including 2% as unchanged parent. The metabolite profiles in BDC rats indicated that that biliary excretion and metabolism was a minor clearance route of baricitinib in rats.

In dog, a majority of the single oral dose of [^{14}C]-baricitinib phosphate was excreted as unchanged parent in urine (24% - 34% of the dose) and feces (9% - 20%), or as metabolites M2, M13, M3, M4 and M10 (all <10% in urine/feces).

In humans, unchanged parent and a total of four minor metabolites were identified in urine (M22, M3, M10) and feces (M12) from six healthy male subjects administered a single 10 mg dose. In urine, unchanged parent drug was the most abundant radioactive peak (69% of the dose). Metabolite M22 was the most abundant metabolite in urine (2% - 5%), while metabolites M3 and M10 each accounted for ~1% of the dose excreted in urine. In human feces parent drug (15%) was also the major component and M12 was ~1%.

Excretion

The route of excretion of [^{14}C]-baricitinib-derived radioactivity was determined in mice, rats (intact and BDC), and dogs. In all species, the total recoveries of radioactivity ranged from approximately 88% to 99%. In mice, upon oral administration, feces (62%) was the predominant route of elimination, while 24% was excreted by urine. In dogs, upon oral administration, the routes of elimination were similar in urine (39%) and feces (45%). In both intact and BDC rats similar excretion profile was found upon oral administration, where 29% was excreted in urine and 53% - 65% in feces (or feces and bile combined). Following a single IV dose, however, urine was the predominant route of elimination (50%) whereas 21% was excreted in bile and 12% in feces, which suggests a low level of intestinal secretion in rats.

In healthy male humans, urine and feces analysis following a single 10 mg oral dose showed that urine (75%) is the major route of elimination, while about 20% of radioactivity was recovered from feces.

2.3.4. Toxicology

Single dose toxicity

Table 10. Single dose toxicity studies with baricitinib

Study ID	Species / Sex / Number / Group	Dose / Route (mg/kg)	Approx. lethal dose / observed max non-lethal dose	Major findings
T08-05-05	Mouse 10/sex/group + 6-24/sex/group TK	0, 100, 300, 600 Oral gavage	>600 / 600	600: cool to touch, urogenital staining
T08-07-05	Mouse 10/sex/group + 6-24/sex/group TK	0, 600, 900, 1200 Oral gavage	>1200 / 1200	≥600: pink coloration of urine ≥900: urogenital staining
T07-06-09	Rat 4-6/sex/group	0, 50, 100, 200, 400 Oral gavage	>400 / 400	≥100: redness of ears, paws and testes ≥200: F: hair loss 400: M: hair loss
T07-06-12	Rat 6/sex/group	0, 200, 600 Oral gavage	>600 / 600	≥200: redness of ears 600: staining on face, forelimbs, urogenital area
T07-08-03	Dog 1/sex/group	2, 10 Oral gavage	>10 / 10	2: F: protrusion of nictitating membrane
T07-07-09	Dog 1/sex/group	5, 10, 20, 40 Oral gavage	>40 / 40	≥5: protrusion of nictitating membrane, activity↓, emesis, eye swollen/lacrimation ≥10: soft feces ≥20: redness of ears 40: ataxia, tremors

No mortality was observed after oral administration of baricitinib up to 1200 mg/kg to mice, 600 mg/kg to rats and 40 mg/kg to dogs. Baricitinib was tolerated well in mice and rats with mostly non-adverse observations such as pink coloration of urine and urogenital staining in mice and redness of ears, paws and testes and staining on face, forelimbs and urogenital area in rats. In some rats at ≥200 mg/kg, hair loss was observed. In dogs, baricitinib was less well tolerated, with temporary protrusion of the nictitating membrane, swelling and/or lacrimation of eyes, decreased activity, emesis, soft feces, and at 40 mg/kg in one animal ataxia and tremors.

Repeat dose toxicity

Repeat-dose toxicity studies were performed in mice (CD-1), rats (Sprague-Dawley) and Beagle dogs. In addition, a study was performed in CByB6F1-Tg (RasH2 wild type) mice for the dose selection for the 6-month carcinogenicity study in RasH2 mice. Study duration was up to 3 months in mice, 6 months in rats and 9 months in dogs. The pivotal dog studies included ECG measurements, which were performed prior to dosing, on day 1 of dosing (28-day study only), during the last week of dose administration and during the recovery phase. Immunophenotyping was performed in the 6-month and 9-month dog studies, by flow cytometry. In the 28-day mouse study (T08-07-08), no histopathology was performed.

The results of the repeat-dose toxicity studies are shown in table 11.

Table 10. Repeat-dose toxicity studies with baricitinib

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOAEL (mg/kg/day)	Noteworthy findings
Pivotal studies					
T08-07-08	Mouse 10/sex/group + 13-46/sex/group TK	0, 10, 75, 250, 500 Oral gavage	28 days	75 (NOAEL)	**≥250:** Hematology: lym↓, platelets↑, F: ret↓ **500:** Mortality: 1M, 4F Clinical chemistry: F: BUN↑ Organs/tissues: F: kidney: pale and/or small
8268827	RasH2 wild type mouse 10/sex/group + 6-45/sex/group TK	0, 75, 150, 300 Oral gavage	28 days	300 mg/kg (M), 150 mg/kg (F)	**≥75:** Hematology: lym↓, M: ret↓, WBC↓ Organs/tissues: bone marrow: hypocellularity, spleen + thymus: lym↓, M: epididymis: cellular debris in lumen **≥150:** Hematology: RBC↓, hb↓, ht↓, M: neut↑ **300:** Hematology: eos↓, F: ret↓, neut↑, platelets↑ Clinical chemistry: F: BUN↑ Organs/tissues: M: testis: degeneration seminiferous tubule, F: kidney: tubule degeneration/necrosis, dilatation, mineralization, lymph node: lym↓, uterus: atrophy, ovary: decreased corpora lutea
T08-09-01	Mouse 10/sex/group + 13-40/sex/group TK	0, 10, 75, 150 Oral gavage	3 months	10	**≥75:** Hematology: lym↓, M: RBC↓, platelets↑ **150:** Mortality: 1M, 1F Clinical signs: M: hypoactivity Clinical chemistry: M: ALT↑, AST↑ Organs/tissues: bone marrow: hypocellularity, F: mammary gland: glandular dilatation, kidneys: infarct
T07-11-01	Rat 15/sex/group including 5/sex/group recovery, + 4-10/sex/group TK	0, 2, 10, 40 Oral gavage	4 weeks + 4 weeks recovery	10 mg/kg	**≥2:** Hematology: F: WBC↓, lym↓, bas↓ **≥10:** Body weight: M: bw gain↓ Hematology: eos↓, ret↓, M: WBC↓, lym↓, bas↓ Organs/tissues: lymph node: histiocytosis, F: bone marrow: mixed depletion **40:** Body weight: , F: bw gain↓ Hematology: neut↓ Clinical chemistry: M: BUN↑, creatinine↑, glucose↑ Organs/tissues: spleen + thymus: lymphoid depletion, M: bone marrow: mixed depletion, kidneys: chronic progressive nephropathy

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOAEL (mg/kg/day)	Noteworthy findings
T08-04-05	Rat 23/sex/group including 8/sex/group recovery, + 5-11/sex/group TK	0, 0.5, 5, 25, 100/60[a] Oral gavage	6 months + 6 weeks recovery	5 mg/kg	**≥0.5:** Organs/tissues: M: bone marrow: mixed depletion **≥5:** Body weight: M: bw gain↓ Hematology: WBC↓, lym↓, bas↓, F: ret↓, eos↓ Organs/tissues: F: bone marrow: mixed depletion, spleen: lymphoid depletion **≥25:** Mortality: 1M, 1F Clinical signs: red skin Body weight: M: food cons.↓ Hematology: monocytes↓, M: eos↓ Organs/tissues: Peyer's patch: lymphoid depletion, M: spleen: lymphoid depletion **100/60:** Mortality: 7M Clinical signs: M: soft feces, Body weight: F: bw gain↓ Hematology: RBC↓, hb↓, ht↓, platelets↑ Clinical chemistry: M: BUN↑, ALP↑ Urinalysis: urinary volume↑ Organs/tissues: lymph node + thymus: lymphoid depletion, kidneys: intraluminar crystals and tubular degeneration, M: heart: cardiomyopathy, liver: inflammation, hepatocel. necrosis, hyperplasia, F: tongue: inflammation
T07-12-03	Dog 6/sex/group including 2/sex/group recovery	0, 0.15, 0.45, 3 Oral gavage	4 weeks + 4 weeks recovery	0.45	**3:** Clinical signs: M: injected sclera Hematology: RBC↓, hb↓, ht↓, ret↓ Organs/tissues: bone marrow: hypocellularity, lymph node + Peyer's patch + spleen + thymus: lymphoid depletion

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOAEL (mg/kg/day)	Noteworthy findings
T08-04-04	Dog 7/sex/group including 2/sex/group recovery	0, 0.25, 1/0.75[b], 5/2.5[c], 20/15/5[d] Oral gavage	6 months + 6 weeks recovery	M: 1/0.75 F: <0.25	**≥0.25:** Hematology: eos↓, F: CD8+ T-cells↓ **≥1/0.75:** Clinical signs: F: Demodex infection **≥5/2.5:** Mortality: 1M, 2F Clinical signs: red feces, soft feces, protrusion of nictitating membrane, M: Demodex infection Body weight: bw gain↓, food cons↓ Hematology: RBC↓, hb↓, ht↓, ret↓ Organs/tissues: lymph nodes: enlarged, Peyer's patch + thymus: lymphoid depletion, liver: periportal inflammation, F: lungs: perivascular inflammation **20/15/5:** Mortality: 2M, 1F Clinical signs: soft feces, emesis, M: limb function impaired, heart rate↑ Organs/tissues: small intestine + stomach: inflammation mucosa, M: skin: benign squamous cell papilloma (1M), F: spleen: lymphoid depletion
8221785	Dog 7/sex/group including 2/sex/group recovery	0, 0.25, 0.5, 3, 9/6[e] Oral gavage	9 months + 6 weeks recovery	0.5 mg/kg	**≥0.25:** Clinical signs: liquid feces Body weight: bw gain↓ Hematology: eos↓ **≥0.5:** Clinical signs: M: Demodex infection Body weight: food cons↓ **≥3:** Clinical signs: conjunctivitis, F: Demodex infection Hematology: T-cells↓, CD4+ T-cells↓, RBC↓, hb↓, ht↓ Clinical chemistry: F: ALP↑ Organs/tissues: lymph node: inflammation, lymphoblasts↑, macrophages↑, lym↓, spleen: lymphoid depletion, bone: degeneration sternal growth plate, M: prostate: atrophy, F: liver: periportal inflammation, bile duct hyperplasia **9/6:** Mortality: 2M, 1F Clinical signs: hypoactivity, dehydration, diarrhea Hematology: F: lym↓ Clinical chemistry: AST↑, M: ALP↑, F: ALT↑ Organs/tissues: Peyer's patch: lymphoid depletion, bone marrow: myeloid hyperplasia, GI tract: mononuclear cell infiltrates, M: liver: periportal inflammation, bile duct hyperplasia

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOAEL (mg/kg/day)	Noteworthy findings
Non-pivotal studies					
T08-05-10	Mouse 10/sex/group	0, 100, 250, 500 Oral gavage	8 days	500 mg/kg	**500:** Mortality: 1M
T07-10-10	Rat 6/sex/group	0, 10, 30, 100, 300 Oral gavage	10 days	<10	**≥10:** Hematology: F: ret↓ Organs/tissues: bone marrow: hypocellularity **≥30:** Hematology: M: ret↓ Coagulation: fib↓, APTT↑ Organs/tissues: thymus: hypocellularity, M: adrenal gland wt↓, spleen: hypocellularity **≥100:** Hematology: M: WBC↓, lym↓ Clinical chemistry: M: glucose↑ Organs/tissues: mes.lymph node: hypocellularity, F: spleen: hypocellularity **300:** Mortality: 1M, 4F Clinical signs: M: dehydration Body weight: M: bw loss, F: bw gain↓, food cons↓ Hematology: platelets↓, M: RBC↓, hb↓, ht↓, F: WBC↓, lym↓ Coagulation: F: PT↓ Clinical chemistry: P↓, M: BUN↑, AST↑, ALT↑, ALP↑, tg↑ Urinalysis: urinary volume↑ Organs/tissues: heart: cardiomyopathy, M: liver: degeneration and necrosis
T07-10-09	Dog 2/sex/group	0, 3, 10, 30 Oral gavage	7 days	<3	**≥3:** Hematology: ret↓ Organs/tissues: bone marrow: hypocellularity **≥10:** Clinical signs: protrusion of nictitating membrane, periocular swelling, injected sclera, soft feces Clinical chemistry: BUN↑ **30:** Mortality: 2M Clinical signs: activity↓, M: conjunctivitis, labored breathing Body weight: bw loss, food cons↓ Hematology: WBC↓, lym↓ Clinical chemistry: Ca↓, SDH↑, BUN↑ Organs/tissues: spleen + thymus + lymph node + Peyer's patches: hypocellularity, intestines: inflammation submucosa

TK=toxicokinetics; wt=weight; bw=body weight; ret=reticulocytes; lym=lymphocytes; bas=basophils; neut=neutrophils; eos=eosinophils; WBC=white blood cells; RBC=red blood cells; hb=haemoglobin; ht=haematocrit; fib=fibrinogen; tg=triglycerides; SDH=sorbitol dehydrogenase; mes=mesenteric

[a] Males were administered 100 mg/kg for the duration of the study. Females were administered 100 mg/kg for 22-23 consecutive doses, followed by a dosing holiday of 3-4 days and administered 60 mg/kg for remainder of study.

[b] Starting on Day 17, the administered dosage was decreased to 0.75 mg/kg/day for the remainder of the study.

[c] Starting on Day 17, the administered dosage was decreased to 2.5 mg/kg/day for the remainder of the study.

[d] The dose level of 20 mg/kg was administered on Days 1-3, followed by 3-day dosing holiday. A dose level of 15 mg/kg was administered on Days 7-11 followed by a 10-day dosing holiday. Dosing resumed at a dose level of 5 mg/kg on Day 22 and continued for the remainder of the study.

[e] Dogs were administered 9 mg/kg from Day 1-50, given a dosing holiday from Day 51-57 and administered 6 mg/kg for the remainder of the study.

Significant immune suppression was observed in mice, rats and dogs. In all species, decreases in lymphocytes, eosinophils and basophils were observed as well as lymphoid depletion in organs/tissues of the immune system such as spleen, thymus, Peyer's patch, and lymph nodes and mixed depletion in bone marrow (see SmPC section 5.3). Opportunistic infections with the Demodex mite were observed in dogs (see SmPC section 5.3). Immunophenotyping revealed decreased cytotoxic T-cells in female dogs at low dose in the 6-month study and decreased T-helper cells in the 9-month dog study at 6-9 times the human exposure. Decreased lymphocytes, eosinophils and basophils and mixed depletion of bone marrow in rats and decreased eosinophils and CD8+ T-cells in dogs were observed at exposures similar to the human therapeutic exposure or slightly above (based on AUC). Demodex infections in dogs started to occur at exposures similar to the human therapeutic exposure with dose-dependent increases in severity of symptoms. Symptoms at higher doses became so severe that several animals were sacrificed in moribund condition (starting at 2.5-5 mg/kg/day and 9-17-fold the human exposure). In mice, evidence of immune suppression occurred at higher exposures (starting at 18-fold the human exposure). Haematologic changes in mice, rats and dogs were partially or completely reversed. There was still evidence of lymphocyte depletion in the lymphoid organs at the end of the recovery period.

Decreases in red blood cell parameters were observed in mice, rats and dogs. In rats, decreases in reticulocytes were observed at exposures slightly higher than the human exposure (2-6 times the human exposure). Decreases in red blood cells, haemoglobin and haematocrit were observed in mice, rats and dogs at higher exposures (starting at 6-9 times the human exposure in dogs) (see SmPC section 5.3).

Effects on the liver were observed in mice, rats and dogs. Effects in mice (increased ALT and AST) and rats (inflammation, hepatocellular necrosis, hyperplasia and increased ALP in males) in the repeated dose studies were observed at very high exposures only. In the 2-year carcinogenicity study in rats, evidence of focal fatty changes was observed in the liver at 5-8 times the human exposure. Effects in dogs consisted of periportal inflammation and bile duct hyperplasia as well as increases in transaminases (from 6-9 times the human exposure). The effects in dogs were likely related to the infections that occurred in dogs. Periportal inflammation may have been part of a systemic inflammatory state as a result of the serious infections. Bile duct hyperplasia and liver enzyme increases were observed only in a 9-month study in which the dogs were treated with ivermectin and thus it is likely that these effects were mainly due to ivermectin treatment.

Renal toxicity (kidney infarct and tubule degeneration/necrosis in mice and chronic progressive nephropathy and crystal formation accompanied by tubular degeneration in rats) and cardiomyopathy in rats were observed at high exposures (at least 22 times the human exposure).

Some effects were observed on male and female genitals, mainly at high exposures. In RasH2 wild type mice, degeneration of the seminiferous tubule in the testis was observed at 300 mg/kg/day (at least 50x human exposure). In dogs, prostate atrophy was observed at lower exposures (3 mg/kg/day, 6-7x human exposure), but this was not accompanied by changes in the spermatogenesis. Uterus atrophy and decreased

corpora lutea in the ovary were observed in RasH2 wild type mice, at very high exposures only (at 300 mg/kg/day, 65-169x human exposure). In rats, no effects were observed on the reproductive organs, but in rat fertility studies, decreased fertility was observed (see Reproductive and developmental toxicity).

Degeneration/necrosis of the sternal growth plate was observed in several dogs treated for 9 months, at low incidence but with a dose-effect relationship in number and severity of the observations. The fact that this effect was observed only in the 9-month study and mostly in the recovery phase indicates an effect which only occurs after long-term treatment (see SmPC section 5.3).

- Toxicokinetics

The main toxicokinetic results are shown in the table below. Animal:human exposure multiples are based on the human AUC in patients with rheumatoid arthritis after multiple 4 mg once daily dosing during the dosing interval at steady state ($AUC_{T,ss}$) of 477.6 ng*hr/mL (from the Phase 2/3 PopPK Analysis).

Table 11. Toxicokinetics of baricitinib in repeated dose studies

Study ID	Daily Dose (mg/kg)	Study day	Animal Cmax (ng/ml)		Animal AUC_{0-24h} (ng.h/ml)		Animal:Human AUC_{0-24h} Exposure Multiple	
			♂	♀	♂	♀	♂	♀
Mouse								
T08-07-08	75	1	11254	9843	26037	16825	55	35
		28	9360	12331	18014	17865	38	37
T08-07-08	500	1	22917	23845	82455	80598	173	169
		28	18200	17382	70941	79855	149	167
8268827	75	1	2553	8673	8482	15951	18	33
		28	4857	11300	14765	21755	31	46
8268827	150	1	5053	8727	17846	18764	37	39
		28	8483	13187	21793	22664	46	47
8268827	300	1	7620	10080	28831	80700	60	169
		28	9323	12543	24030	31271	50	65
T08-09-01	10	1	1668	1311	3194	2834	6.7	5.9
		91	1241	1025	2838	2411	5.9	5.0
T08-09-01	75	1	12145	15265	22694	27077	48	57
		91	10585	10437	20057	18497	42	39
T08-09-01	150	1	17717	18905	57199	52370	120	110
		91	13780	13408	49399	35768	103	75
Rat								
T07-11-01	2	1	120	103	354	435	0.7	0.9
		28	148	129	461	498	1.0	1.0
T07-11-01	40	1	3673	4828	10363	13445	22	28
		28	4123	6834	12814	17754	27	37
T08-04-05	0.5	1	19.0	29.8	81.0	120	0.2	0.3
		28	18.2	29.6	78.0	104	0.2	0.2
		181	39.0	73.5	178	264	0.4	0.6
T08-04-05	25	1	2113	2830	4977	10028	10	21
		28	1623	2630	6983	7577	15	16
		181	4234	5274	10363	14151	22	30
T08-04-05	100/60[a]	1	6574	11625	29974	38999	63	82
		28	10697	9397	47542	69456	100	145
		181	11848	8877	42342	35396	89	74
Dog								
T07-12-03	0.45	1	138	131	557	557	1.2	1.2
		27	118	131	542	553	1.1	1.2
T07-12-03	3	1	1010	1029	4606	5014	9.6	10
		27	858	947	3974	4754	8.3	10

Study ID	Daily Dose (mg/kg)	Study day	Animal Cmax (ng/ml)		Animal AUC_{0-24h} (ng.h/ml)		Animal:Human AUC_{0-24h} Exposure Multiple	
		1	76.1	70.9	333	349	0.7	0.7
T08-04-04	0.25	29	73.2	83.2	409	479	0.9	1.0
		182	72.8	79.1	363	401	0.8	0.8
		1	369	320	1574	1523	3.3	3.2
T08-04-04	1/0.75[b]	29	276	220	1389	1241	2.9	2.6
		182	264	240	1374	1259	2.9	2.6
		1	1456	1664	6686	8246	14	17
T08-04-04	5/2.5[c]	29	802	977	4457	5720	9	12
		154	962	1293	5608	7168	12	15
		1	4271	3825	31088	23437	65	49
T08-04-04	20/15/5[d]	29	1266	1527	7094	7280	15	15
		154	2173	1920	12851	11477	27	24
		1	49.8	52.0	242	234	0.5	0.5
8221785	0.25	28	47.8	44.9	238	250	0.5	0.5
		269	48.0	45.3	285	261	0.6	0.5
		1	687	680	2964	2997	6.2	6.3
8221785	3	28	657	657	2900	3049	6.1	6.4
		231	631	735	3246	4085	6.8	8.6
		1	1909	1946	9620	9657	20	20
8221785	9/6[e]	28	2893	2159	19165	12257	40	26
		231	1909	1586	9211	8283	19	17

[a] Males were administered 100 mg/kg for the duration of the study. Females were administered 100 mg/kg for 22-23 consecutive doses, followed by a dosing holiday of 3-4 days and administered 60 mg/kg for remainder of study.

[b] Starting on Day 17, the administered dosage was decreased to 0.75 mg/kg/day for the remainder of the study.

[c] Starting on Day 17, the administered dosage was decreased to 2.5 mg/kg/day for the remainder of the study.

[d] The dose level of 20 mg/kg was administered on Days 1-3, followed by 3-day dosing holiday. A dose level of 15 mg/kg was administered on Days 7-11 followed by a 10-day dosing holiday. Dosing resumed at a dose level of 5 mg/kg on Day 22 and continued for the remainder of the study.

[e] Dogs were administered 9 mg/kg from Day 1-50, given a dosing holiday from Day 51-57 and administered 6 mg/kg for the remainder of the study.

Genotoxicity

The genotoxicity studies carried out for barcitinib are described in table 13.

Table 12. Genotoxicity studies with baricitinib

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria/T08-01-02/GLP	Salmonella strains TA1535, TA1537, TA98, TA100, E.coli strain WP2uvrA	0, 1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate +/- S9	Negative
Gene mutations in bacteria/T07-07-03/non-GLP	Salmonella strains TA98, TA100	0, 1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate +/- S9	Negative
In vitro chromosome aberration assay/T08-01-01/GLP	Human peripheral blood lymphocytes	4 hr exposure: 0, 75, 150, 300 µg/ml 20 hr exposure: 0, 5, 10, 25 µg/ml +/- S9	Cytotoxicity: mitotic inhibition at highest concentration 51-61% Genotoxicity: Negative

Chromosomal aberrations in vivo/T08-01-05/GLP	Rat, micronuclei in bone marrow (5/sex/group + 3/sex/group toxicokinetics)	0, 200, 400, 800 mg/kg oral gavage single dose sampling 24 or 48 h	Toxicity: at 800 mg/kg: lethargy, piloerection, females after 48 h: PCEs/CEs ↓ * Genotoxicity: Negative

* PCEs=polychromatic erythrocytes; CEs=total erythrocytes

Baricitinib was not genotoxic in the Ames test, an *in vitro* chromosome aberration assay and an *in vivo* rat micronucleus assay.

Carcinogenicity

Long-term studies

A 6-month study was performed in RasH2 mice and a 2-year study in Fischer 344 rats. In the mouse study, hemizygous RasH2 mice were used for the toxicology animals and wild type RasH2 mice for the toxicokinetics animals. In the mouse study, a positive control group was added (10/sex/group) which received one intraperitoneal dose of 75 mg/kg N-methyl-N-nitrosourea. The results are shown in the table below.

Table 13. Carcinogenicity studies with baricitinib

Study ID /GLP	Dose (mg/kg)/ Route	Exposure (AUC_{0-24h}, ng.h/ml)	Species/No. of animals	Major findings
8291245/ GLP	M: 0, 15, 40, 300 F: 0, 10, 30, 150 Oral gavage	At max dose: M: 26400 F : 37200 See further table 4.4.1.3	RasH2 mouse 25/sex/group + 9/sex/group or 48/sex/group TK control and treated animals resp. 6-month study	**≥10/15**: Body weight: F: food cons↓ Hematology: hb↓, WBC↓, lym↓, M: RBC↓ Organs/tissues: spleen: wt↓ **≥30/40:** Hematology: F: RBC↓ Clinical chemistry: M: BUN↑ **150/300:** Body weight: F: bw gain↓ Hematology: ht↓, platelets↑, M: eos↓ Clinical chemistry: F: BUN↑ Organs/tissues: bone marrow: adipocytes↑, M: liver: necrosis, F: bone marrow: hypocellularity
8253534/ GLP	M: 0, 1, 3, 8 F: 0, 3, 8, 25 Oral gavage	At max dose: M: 2874 F : 12964 See further table 4.4.1.3	Rat 60/sex/group + 6-12/sex/group TK 2-year study	**≥3/8:** Organs/tissues: Peyer's patch: lym↓, F: lung: alveolar lipoproteinosis, liver: clear cell foci↑ **8/25:** Clinical signs: scabs↑ Body weight: bw gain↓, food cons↓ Organs/tissues: bone marrow: decreased cellularity, F: ovary: cysts, spleen: lym↓, decreased extramedullary hematopoiesis, liver: basophilic foci↓

TK=toxicokinetics; bw=body weight; wt=weight; RBC=red blood cells; hb=haemoglobin; ht=haematocrit; WBC=white blood cells; lym=lymphocytes; eos=eosinophils

Mouse

The maximum dose was selected as 300 mg/kg/day for males based on >50% suppression of lymphocyte counts in the 1-month study in RasH2 mice. The maximum dose was 150 mg/kg/day for females based on adverse kidney findings at 300 mg/kg/day.

Unscheduled deaths/sacrifices were 2, 1, 2, 3 males at 0, 15, 40, 300 mg/kg/day and 3, 4, 3, 5 females at 0, 10, 30, 150 mg/kg/day. These mortalities were considered not treatment-related.

No baricitinib-related neoplastic changes were observed. In the positive control group, a robust carcinogenic response was observed with occurrence of a high incidence of neoplasms, most often hematopoietic (lymphosarcoma), vascular (hemangiosarcoma), nonglandular stomach (squamous cell), and skin/subcutaneous tissue (squamous cell) neoplasms.

Rat

A maximum dose of 8 mg/kg/day for males was based on a substantial decrease in body weight gain in the 6-month study. The high dose for females was 25 mg/kg based on immunosuppression observed at that dose.

Unscheduled deaths/sacrifices were 42, 37, 32, 29 males at 0, 1, 3, 8 mg/kg/day and 40, 35, 34, 28 females at 0, 3, 8, 25 mg/kg/day. A dose-related increase in survival was observed which was ascribed to the lower body weights in treated animals. Body weights were slightly lower in treated animals than in control animals but only at the high dose, significantly decreased body weight gain was observed, which was more obvious in males than in females. Due to low survival in the control animals, the study was terminated after Week 94 for the males and during Week 91 for the females.

No baricitinib-related increased incidence in tumors was observed.

Toxicokinetics

Table 14. Toxicokinetics in carcinogenicity studies

Study ID	Daily Dose (mg/kg)	Study day	Animal Cmax (ng/ml)		Animal AUC_{0-24h} (ng.h/ml)		Animal:Human AUC_{0-24h} Exposure Multiple	
			♂	♀	♂	♀	♂	♀
Mouse								
8291245	M : 15 F : 10	1 176	1590 320	943 753	3560 1340	1810 2470	7.5 2.8	3.8 5.2
8291245	M : 40 F : 30	1 176	7370 768	3640 3780	11600 2030	6680 9160	24 4.3	14 19
8291245	M : 300 F : 150	1 176	12700 5280	13800 12300	25500 26400	23500 37200	53 55	49 78
Rat								
8253534	M : 1 F : 3	1 176	66.8 99.9	217 371	278 410	964 1188	0.6 0.9	2.0 2.5
8253534	M : 3 F : 8	1 176	172 279	594 1052	845 1161	2544 3801	1.8 2.4	5.3 8.0
8253534	M : 8 F : 25	1 176	495 678	2073 2610	1999 2874	9048 12964	4.2 6.0	19 27

Reproduction Toxicity

Reproductive/development toxicity studies are shown in table 16.

Table 15. Reproductive and developmental toxicity studies with baricitinib

Study type / Study ID / GLP	Species; Number / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg & AUC)
Male fertility WIL-353240M GLP	Rat M/12	Oral gavage 0, 5, 15, 50	10 weeks (4 wks pre-mating to 6 wks post-mating)	≥5: bw ↓ , bw gain ↓, epididymis weight↓ 50: reddened forelimbs, copulation index↓, prostate and testes weight↓, males that mated without litter↑	General: <5 Fertility: 15 AUC at 15: 5859 ng.h/mL
Female fertility WIL-353240F GLP	Rat F/12	Oral gavage 0, 5, 25, 100	2 wks pre-mating through GD6	≥25: post implantation loss↑, early resorptions↑, live foetuses/litter↓ 100: reddened forelimbs, lacrimation, droopy eyelids, fc↑ (pre-mating), fc↓ (post-mating), bw gain↓ post-treatment (due to increased early resorptions), number of non-gravid females↑, copulation index↓, mean absolute number of corpora lutea and implantation sites↓, pre-implantation loss↑,	Maternal tox: 25 Fertility: 5 AUC at 5: 1972 ng.h/mL
Embryo-fœtal development Dose range finding study T08-05-02 Non-GLP	Rat F/8	Oral Gavage 0, 25, 75, 150, 300	GD6 through GD17	≥ 25: flushed skin 25 and 75: foetal weight↓ 75: , bw (gain)↓, post-implantation loss↑ ≥150 mg/kg: 7 found dead or euthanized (GD 11 - 15), hypoactivity, lethargy, pale, cool to touch, reddish material on body surface and discharge, fc↓. No foetal examination performed	F0 25 F1 <25 AUC at 25 16946 ng.h/mL
Embryo-fœtal development T08-07-01 GLP	Rat F/25	Oral Gavage 0, 2, 10, 40	GD6 through GD17	F0 40: lacrimation, body flushed, bw gain (GD6-18)↓ F1 ≥10: bent limb↑, rib anomalies↑, 40: foetal weight↓, bent rib, 7th cervical rib,	F0 10 F1 2 AUC at 2 1092 ng.h/mL
Embryo-fœtal development Dose range finding study T08-05-03	Rabbit F/6	Oral Gavage 0, 20, 40, 60, 80	GD7 through GD20	F0: ≥40: bw (gain)↓, fc↓ F0: ≥40: bw↓, fc↓ ≥60: death, prostration, hypoactivity, labored breathing, gasping, respiration↓	F0 20 F0 20 F1 20

Study type / Study ID / GLP	Species; Number / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg & AUC)
Non-GLP				F1: 40: Postimplantation loss↑, foetal weight↓ ≥60: no foetal examination due to mortality of F0	AUC at 20 12062 ng.h/mL
Embryo-fœtal development T08-07-02 GLP	Rabbit F/23	Oral gavage 0, 3, 10, 30	GD7 through GD20	F0: 30: mortality (2F, with fc ↓ , bw gain↓, defecation↓, red material in cage pan). Gravid uterine weight↓ F1: 10: vertebral anomalies (n=1) 30: postimplantation loss↑, early and late resorptions↑, viable foetuses↓, foetal weight↓, vertebral anomalies (n=2)	F0 10 F1 3 AUC at 3 1096 ng.h/mL
Peri & postnatal WIL-353280 GLP	Rat F0 F/30 F1 F+M/30	Oral gavage F0 0, 2, 5, 25	GD6 through LD20	F0: No adverse effects F1: 5: pre-weaning pup body weights (gain) ↓ 25: postnatal survival↓, malrotated forelimbs, delayed balanepreutial separation, delayed vaginal patency, forelimb and hindlimp strength↓, Cytotoxic Tcells↓ at day 35 (F), helper T-cells↑ at day 65 F2: No adverse effects	F0 25 F1 2 F2 25 F0 AUC at 2 mg/kg: 840 ng.h/mL

Bw=body weight; fc=food consumption

In rat, male and female fertility and copulation/conception indices were decreased at 50 and 100 mg/kg/day baricitinib, respectively. Furthermore, early resorptions were increased in females at 25 mg/kg/day and at 100 mg/kg/day number of corpora lutea and implantation sites were lowered and pre-implantation loss was higher. The fertility study was a combined male and female fertility assessment, and therefore it is not certain whether male, female or both were responsible for the decreased fertility. However, due to a decreased number of corpora lutea and intrauterine survival, the female reproductive process was affected by baricitinib. Also no compound-related effects were observed on sperm motility or concentration and sperm morphology for males at any dose level (see SmPC section 5.3). At the NOAEL the safety margin compared to the MRHD was 12 and 4 fold for male and female fertility, respectively.

Baricitinib reduced foetal weight at 40 mg/kg/day in presence of maternal toxicity and increased the incidence of limb bone and rib anomalies in rats from 10 mg/kg/day in absence of maternal toxicity (see SmPC section 5.3). In rabbit, baricitinib reduced foetal weight and induced post-implantation loss, with a concurrent reduction in viable foetuses at 30 mg/kg/day. At this dose, two maternal animals died, but in other maternal animals in this dose group no adverse effects were observed. A low number of foetuses with vertebral anomalies was observed in rabbit foetuses. At the NOAELs in rat and rabbit, the safety margin compared to MRHD was 2-fold in both species.

Baricitinib reduced postnatal survival and mean pup body weight prior to and following weaning at 25 mg/kg/day (see SmPC section 5.3). Additionally, an increased incidence of malrotated forelimbs was observed in this group. Comparable effects were noted in the rat embryo-foetal development study; therefore, this effect must have developed during the period of organogenesis. Furthermore, baricitinib-related effects were observed on forelimb/hindlimb grip strength at this dosage level. In F1 females, cytotoxic T-cells were decreased at PDN35 and T helper cells were increased at PND 65. No effects on reproductive parameters in the F1 group or on survival of the F2 group were noted. The NOAEL for the F1 generation was 2 mg/kg/day, corresponding to a safety margin of 1.5 fold compared to exposure at the MRHD.

Local Tolerance

Not applicable for the oral route of administration.

Other toxicity studies

Phototoxicity

Baricitinib was not phototoxic in the neutral red uptake phototoxicity assay in Balb/c 3T3 mouse fibroblasts.

2.3.5. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): baricitinib			
CAS-number (if available): 1187594-09-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.4 (pH 5) 1.4 (pH 7) 1.5 (pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.4 (pH 5) 1.4 (pH 7) 1.5 (pH 9)	not B
	DT50	DT_{50} water: 22.8/50.7 d DT_{50} system 349/279 d	Results obtained in two river systems; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	3.1 mg/L 2.1 mg/L 0.6 mg/L	not T
	CMR	toxicity to reproduction observed	potentially T
PBT-statement :	baricitinib is not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	0.02	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 16 952 L/kg (soil) K_{oc} = 13 250 L/kg (soil) K_{oc} = 36 083 L/kg (soil) K_{oc} = 371 L/kg (sludge) K_{oc} = 276 L/kg (sludge)	Geomean used in risk assessment: $K_{oc,soil}$ of 20 087 L/kg, and $K_{oc,sludge}$ of 320 L/kg.
Ready Biodegradability Test	OECD 301		Not available, but can be waived because OECD 308 is submitted.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} water: 10.8/24.0 d DT_{50} system 165/132 d	Results obtained in two river systems;

		Compound shifts to sediment, 38-47% over the duration of the test			sediment risk assessment triggered
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchenriella subcapitata*	OECD 201	NOEC	3100	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	2100	µg/L	mortality and reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	600	µg/L	growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	$\geq 10^6$	µg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	≥2570	mg/kg	normalised to 10% o.c.

Baricitinib is neither PBT nor vPvB.

Considering the above data and the environmental risk assessment, baricitinib is not expected to pose a risk to the surface water and groundwater compartment and the sewage treatment plant.

2.3.6. Discussion on non-clinical aspects

Baricitinib is a selective and balanced inhibitor against JAK 1 and JAK2 with less potency for TYK2 and far less potency for JAK3. Baricitinib improved clinical and histological signs in several rodent arthritic related models of disease. In the rat adjuvant arthritis model, baricitinib reduced inflammation at plasma levels between 53 and 480 nM, which compares well with the in *vitro* assays. However, the oral human Cmax is about 144 nM (4 mg/day, 53,4 ng/ml), which is in the neighbourhood of the IC50, but only during the peaks. In a similar model with oral dosing of 3 and 10 mg/kg/day baricitinib, clinical and histological signs were reduced by 39-82% at predicted AUC-values of 2 – 6.7 µM.h. With a human AUC of about 1.3 µM (478 ng h/ml) at 4 mg/day the effects may be suboptimal in humans.

Baricitinib is not expected to produce effects related to secondary pharmacology at clinical doses due to the specificity of baricitinib for the JAK1/2 target.

The PK / ADME data submitted were considered to be sufficient and in accordance with legal requirements and available guidelines. The nonclinical absorption, distribution, metabolism and excretion (ADME) studies have been conducted, IV and PO, in the same species as used in the toxicology studies (PO in mouse, rat, dog and rabbit).

Baricitinib is a lipophilic compound with very low solubility in aqueous solutions at neutral pH. Oral absorption was, as in humans, relatively fast. Oral bioavailability was high. The relative bioavailability of baricitinib in the free base versus phosphate salt forms was similar. The pharmacokinetics was further characterized by a moderate to low plasma clearance and volume of distribution. There was evidence of only limited decrease or accumulation (<2-fold) following multiple daily dosing in mice, rats and dogs, which is in line with human data. No apparent gender differences in Cmax or exposure were noted. More than 10-fold exposure multiples as compared to human exposure was achieved in the mouse, rat and dog.

The *in vivo* tissue distribution in rat was fast and showed that baricitinib related radioactivity was distributed into most tissues through 2 hr post-dose, with the alimentary canal contents, bile, and urine having the highest exposure. Lowest exposure was found in eye lens, spinal cord and non-circumventricular central nervous system tissues. Placental transfer and subsequent fetal exposure to [^{14}C]-baricitinib-related radioactivity occurred at moderate to low levels. Exposure of [^{14}C]-baricitinib-related radioactivity was approximately 39-fold greater in milk than in plasma. A warning has been included in section 4.6 to alert that Olumiant should not be used during breast-feeding, due to the immunosuppressive action of barcitinib.

Drug-derived radioactivity was found to be below quantifiable limits (BQL) at all time points in pigmented rats, while in non-pigmented male rats low levels of radioactivity were detected in the brain at 2 hours postdose, but were BQL at all other time points out to 168 hours. Considering the fact that low levels were only detected at the 2 hour time point and that baricitinib is a substrate of the drug-efflux transporter, ABCB1 (MDR1/Pgp) which is expressed in the blood brain barrier, this is unlikely to result from direct transport to the brain. Most likely, low levels of radioactivity were from the vascular system resulting from the exsanguination performed prior to animal preparation for imaging.

Plasma protein binding (PPB) of baricitinib is moderate across all preclinical species examined and in human plasma (~50%) meaning that free baricitinib levels are about half of the measured plasma concentration in mouse, rat, rabbit, dog and in humans. The blood to plasma (B/P) ratio of [^{14}C]-baricitinib indicates that baricitinib was evenly distributed over the blood cell and the plasma compartment, with depending on species, including human, about 50% binding to blood cells.

The metabolism data indicate that biotransformation is low and that there are no major differences in circulating or excreted metabolites across species. In addition, the minor metabolites observed in human excreta are also observed in at least one biological matrix.

Baricitinib was primarily cleared via renal excretion in human, and by faecal elimination in the mouse and rat, while in dogs elimination was comparable in urine and faeces. This indicates that there are species differences in the primary routes of elimination of baricitinib.

Baricitinib induced significant immune suppression in animals, visible as decreases in white blood cell parameters and lymphoid depletion in organs and the occurrence of opportunistic infections in dogs. Partly these effects also occurred at human therapeutic exposures. An increased risk of infections can therefore be expected when Olumiant is used. A decrease in red blood cell parameters was also observed in mice, rat and dogs.

Degeneration/necrosis of the sternal growth plate in dogs and skeletal malformations in the embryofoetal development study in rats indicate that baricitinib may have the potential to have an adverse effect on the growth of bone. In rat and rabbit reproductive toxicology studies, barcitinib was shown to reduce foetal growth/weight and produce skeletal malformations. In view of the preclinical data showing teratogenicity of baricitinib in rats and rabbits and the observed adverse effect on the growth of bone, CHMP decided to adopt a formal contra-indication for the use of barcitinib during pregnancy (see SmPC section 4.3).

Kidney toxicity and cardiomyopathy in mice and rats were observed at sufficiently high exposures and are therefore considered likely not clinically relevant.

Baricitinib had adverse effects on female and male fertility, embryonic development and pre- and post-natal development. The safety margin for skeletal anomalies in rats was low. A low number of foetuses with vertebral anomalies were observed in rabbit foetuses which were not statistically significant, but considering

the fact that skeletal malformations were observed in rats as well, this may be considered biologically relevant (see SmPC section 5.3).

Baricitinib was not genotoxic in the Ames test, an *in vitro* chromosome aberration assay and an *in vivo* rat micronucleus assay. No increases in tumours were observed in a 6-month study in RasH2 mice and in a 2-year study in rats.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data is considered acceptable.

2.4. Clinical aspects

2.4.1. Introduction

The applicant has submitted 26 completed clinical studies comprising 19 clinical pharmacology studies, and 3 Phase 2 studies (Studies I4V-MC-JADC [JADC], I4V-MC-JADA [JADA] and I4V-MC-JADN [JADN]) and 4 Phase 3 studies in RA patients (Studies I4V-MC-JADZ [JADZ], I4V-MC-JADV [JADV], I4V-MC-JADX [JADX] and I4V-MC-JADW [JADW]). In addition deblinded data from an ongoing long-term extension study (Study I4V-MC-JADY [JADY]) is also included.

As of 10 August 2015, a total of 513 subjects were exposed to baricitinib in the completed clinical pharmacology trials, and 3822 patients were exposed to baricitinib in a completed Phase 1 study in RA patients, the completed Phase 2 and 3 studies in RA patients, and two Phase 2 studies in psoriasis and diabetic nephropathy patients.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The following PK studies were performed in healthy volunteers or patients:

Table 18 - Clinical Pharmacology studies

Study	Description	Population	Dosing regimen
PK studies in healthy subjects			
JADF	Single dose safety and tolerability, PK, PD	Healthy subjects	Fasted: 1, 2, 5, and 10 mg Fed: 5 mg
JADE	Multiple dose safety, PK, PD	Healthy subjects	Part 1: dosed for 10 days once daily with 2, 5 or 10 mg or twice daily with 5 mg* Part 2: dosed for 28 days once daily with 10 mg or twice daily with 5 mg Part 3: once 20 mg at Day 1 and from Day 8 to 18 20 mg once daily
JADO	safety, tolerability,	Healthy subjects	Single oral dose of 20, 30, or 40 mg

	and PK of supra-therapeutic doses		
JADG	^{14}C-baricitinib disposition	Healthy subjects	unlabelled and ^{14}C labelled drug substance containing 10 mg baricitinib and 100 µCi radioactivity
JAGM	Absolute bioavailability and PK	Healthy subjects	Single oral 4 mg dose simultaneously with IV infusion of 4 µg [$^{13}C_4D_3{}^{15}N$]-baricitinib
JADM	Single- and multiple-dose safety, PK	Healthy Japanese subjects	Single dose: 2, 5, 10, or 14 mg Multiple dose(10 days): 10 or 14 mg (once daily)
PK studies in special populations			
JADL	Effect of renal impairment on PK, PD, safety and tolerability	Subjects with normal or impaired renal function	Single oral dose Healthy/Mild/Moderate: 10 mg Severe: 5 mg ESRD: 5 mg in 2 study periods separated by a 2-week washout
JAGC	Effect of hepatic impairment on PK, safety, and tolerability	Subjects with normal or impaired hepatic function	single oral 4 mg dose
JADP	Efficacy and safety of baricitinib to placebo	Subjects with moderate-to-severe psoriasis	Oral dose of 2, 4, 8, or 10 mg
JAGQ	Efficacy and safety of baricitinib to placebo	Subjects with diabetic kidney disease	Oral dose of 0.5, 0.75, 1, 1.5, 2.75, or 4 mg once daily or 0.5 or 0.75 mg twice daily
Food effect study			
JADF	Single dose safety and tolerability, PK, PD	Healthy subjects	Fasted: 1, 2, 5, and 10 mg Fed: 5 mg
JADH	PK and relative bioavailability	Healthy subjects	Each subject received the following 4 treatments: 2 x 4 mg phosphate salt capsules (fasted) 1 x 8 mg free-base tablet with particle size 1 (fasted) 1 x 8 mg free-base tablet with particle size 2 (fasted) 1 x 8 mg free-base tablet with particle size 3 (high fat meal)
JAGO	Relative bioavailability of Commercial Tablet to Phase 2 Tablet and food effect on Commercial Tablet	Healthy Japanese subjects	Each subject received the following 5 treatments: • 2 × 4 mg Commercial Tablets (fasted) • 1 × 4 mg Commercial Tablet (fasted) • 1 × 4 mg Commercial Tablet (low-fat meal) • 1 × 8 mg Phase 2 Tablet (fasted) • 1 × 4 mg Phase 2 Tablet (fasted)

Table 19 - Summary of Phase II exploratory trials

Phase II, dose finding							
Study	**Study Design**	**RA Population**	**N sites**	**Country**	**Treatment Arms/ Duration**	**Subjs by arm entered/ completed**	**PE**

I4V-MC-JADC	RCT, DB, PC, dose-ranging, parallel-group study	inadequate response to DMARDs, including biologics	41	US, CZ	BARI 4-, 7-, 10-mg QD for up to 24 wks	127/106	ACR20 Week 12
I4V-MC-JADA	RCT, DB, PC, dose-ranging, parallel-group study	background MTX therapy	69	US, PL, Ukr, Rom, CZ, Hun, Cro, India, Mex	Part A: PBO or BARI 1, 2, 4, 8 mg QD for 12 wks. Part B: BARI 2mg BID, 2mg QD, 4mg QD, 8mg QD for 12 wks. Part C: BARI 4mg QD, 8mg QD for 52 wks. Part D: BARI 4mg QD for 52 wks	Part A : entered 98: PBO, 49: 1mg QD, 52: 2mg QD, 52: 4mg QD, 50: 8mg QD Part B: 276 re-randomized: (63: 2mg BID, 63: 4mg QD, Continued; 52: 2mg QD, 50: 4mg QD, 50: 8mg QD). Part C: 201 (108: 4/4mg QD, 61: 4/8mg , 32:8/8mg QD). Part D entered: 144 (79: 4/4mg, 47: 4,8/4mg, 18: 8/4mg). Completed: 133 (76 in 4/4mg QD, 40 in 4:8/4mg QD, 17 in 8/4mg QD).	ACR20 Week 12
I4V-JE-JADN	RCT, DB, PC, dose-ranging, parallel-group study	Japanese patients with active RA	25	Japan	Part A: PBO or BARI 1, 2, 4, 8 mg QD for 12 wks. Part B: BARI 4mg QD or 8mg QD[a] for 52 wks (single-blind extension)	Randomized Part A: 145 (49 PBO, 24 each to 1-, 2-, 4-, 8-mg) Completed Part A 142 (48 PBO, 23 1mg, 24 BARI 2-mg, 23 BARI 4-mg, 24 BARI 8-mg) Re-randomized Part B: 142 (71 BARI 4mg, 71 BARI 8mg) Completed Parts A and B: 109 (55: 4mg, 54: 8mg)	ACR20 at Week 12

Table 20. Summary of Phase III confirmatory trials

Phase III, confirmatory trials							
Study	**Study Design**	**RA Population**	**N sites**	**Country**	**Treatment Arms/ Duration**	**Subjs by arm entered/ completed**	**PE**

RA-BEGIN (JADZ)	RCT, DB, AC (non-inferiority)	MTX-naive (1st line)	198	Europe, N- & S-America Asia Russia, South-Africa[1]	MTX mono-therapy / BARI 4mg QD mono-therapy / BARI 4mg QD + MTX combination	Randomized: 588 (213 MTX mono-therapy, 160 BARI mono-therapy, 215 BARI + MTX) Completed Wk 24: 519 Completed Wk 52: 470	ACR20 Wk 24
RA-BEAM (JADV)	RCT, DB, PC, AC (add-on to MTX)	MTX-IR (2nd line)	335	Europe, N- & S-America Asia South-Africa[2]	BARI 4mg QD 52 W ADA 40mg SC biweekly 52 W PBO (24 wks)	Entered: 2949 Randomized: 1307 (487 BARI, 330 ADA, 488 PBO) Completed through Wk 24: 1199 Completed through Wk 52: 717	ACR20 Wk 12
RA-BUILD (JADX)	RCT, DB, PC (add-on)	cDMARDs –IR (2nd line)	182	Europe, N- & S-America Asia[3]	BARI 2mg or 4mg QD 24 weeks PBO 24 weeks	Entered: 1241 Randomized: 684 (227: 4mg, 229: 2mg, 228:PBO) Completed: 611	ACR20 Wk 12
RA-BEACON (JADW)	RCT, DB, PC (add-on to cDMARDs)	TNF-IR (3rd line)	140	Europe, N- & S-America Asia[4]	BARI 2mg or 4mg QD 24 weeks PBO 24 weeks	Entered: 959 Randomized: 527 (177: 4mg QD, 174: 2mg QD, 176: PBO) Completed: 459	ACR20 Wk 12

AC=active controlled, ADA=adalimumab, cDMARD-IR =irresponsive to conventional DMARDs, MTX-IR= methotrexate irresponsive, PBO=placebo, PC=placebo controlled, RCT=randomised controlled trial, TNF-IR= irresponsive to TNF-Inhibitors, [1]Argentina, Austria, Belgium, Brazil, Canada, Germany, Greece, India, Italy, Japan, Mexico, Portugal, Russia, South Africa, South Korea, Sweden, UK, US, [2]Argentina, Belgium, Canada, China, Croatia, Czech Republic, France, Germany, Greece, Hungary, Japan, Latvia, Lithuania, Mexico, Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, South Africa, South Korea, Spain, Switzerland, Taiwan, UK, US, [3]US (including Puerto Rico), Canada, Argentina, Mexico, Croatia, Czech Republic, Hungary, Poland, Romania, Slovakia, Belgium, Germany, Italy, Portugal, Spain, UK, Japan, South Korea, Taiwan, Australia, India, Russia, [4]Argentina, Australia, Austria, Belgium, Canada, Denmark, France, Germany, Greece, Israel, Italy, Japan, South Korea, Mexico, Netherlands, Poland, Spain, Switzerland, Turkey, UK, US

Table 21. Long-term extension study

Study	Study Design / Duration	Patient Population	Treatment Arms	Number of Patients / Subjects	Primary Objective
JADY	Long-term extension study, 48 months, open-label	Patients who completed a Phase II/III Study were eligible	BARI 2 or 4mg QD	Entered as of data cutoff (10 August 2015): 2539 Completed: 0 patients have completed the 48-month treatment period (at 10 August 2015).	Long-term efficacy and safety

2.4.2. Pharmacokinetics

Absorption

After oral administration of baricitinib, Cmax levels are reached ~1h after dosing (0.5-3.0 h). The absolute bioavailability after oral administration of baricitinib from the commercial tablet is ~79% (CV=3.94%). At the clinical dose of 4 mg, the Cmax is ~112 nM and the AUC0-∞ is 740 nM × h in healthy volunteers. The intra-individual variability in AUC and Cmax is low (<14%) and the inter-individual variability moderate (17-26%).

In subjects with Rheumatoid Arthritis, the Cmax (~135 nM) and AUCT (~1200 nM × h) are higher compared to healthy volunteers. In addition, CL/F is ~46% lower and t½ ~25% lower in Rheumatoid Arthritis patients relative to that in heathy subjects. Furthermore, the inter-individual variability in Rheumatoid Arthritis patients is higher compared to healthy subjects (41% versus ~22%).

Capsule formulations were initially developed for use in early clinical studies. An immediate-release tablet formulation (referred to as Phase 2 Tablet) containing baricitinib free base was developed prior to commercial development. The final Commercial Tablet formulation containing baricitinib free base was developed and used for all the Phase 3 studies in RA patients. The Commercial Tablet and the Phase 2 Tablet have similar unit formulas.

Two relative bioavailability studies were conducted: study JADH (comparing capsules to Phase 2 tablet) and study JAGO (comparing Phase 2 tablets to Commercial tablets).

In study JAGO, a relative bioavailability study was conducted between the 4 mg Phase 2 tablet and the 4 mg Commercial tablet under fasted conditions. The C_{max} ratio was 0.955 (90% CI is 0.876-1.04). The $AUC_{0-\infty}$ ratio was 0.986 (90% CI is 0.950-1.02). The 90% CIs fell within the traditional bioequivalence boundaries of 0.8 to 1.25 and there was no difference in t_{max} between the 2 formulations in the fasted state.

In study JADH, a relative bioavailability study was conducted between the 8 mg Phase 2b capsule (phosphate salt) and the 8 mg Phase 2 tablet (free base) under fasted conditions. The C_{max} ratio was 0.962 (90% CI is 0.852-1.08). The $AUC_{0-\infty}$ ratio was 1.02 (90% CI is 0.947-1.09). The 90% CIs fell within the traditional bioequivalence boundaries of 0.8 to 1.25 and there was no difference in t_{max} between the 2 formulations in the fasted state.

A low-fat meal led to a 14% decrease in AUC0-∞ and an 11% decrease in Cmax, which did not lead to a significant effect in the pharmacokinetics of bariticinib. A high-fat meal decreased the AUC with 4-11% and the Cmax with 10-18%. The decrease in Cmax and AUC were considered to be clinically not relevant.

Distribution

Plasma protein binding

The protein binding of baricitinib (10 µM) was determined *in vitro* using an equilibrium dialysis method in human plasma and serum (study DMB-08-14-1). The protein binding of baricitinib in plasma was 49% at 10 µM and 50% at 1 µM, with an overall mean fraction unbound of 50 ± 2% in plasma. The protein binding of baricitinib in serum was 53% at 10 µM, 55% at 3 µM and 57% at 1 µM, with an overall mean fraction unbound of 55±3% in serum.

Blood-to-plasma ratio

The blood-to-plasma ratio of baricitinib was not investigated *in vitro*. Clinical study JADG showed that the mean ratios of AUC_{0-12} and C_{max} for total radioactivity in whole blood to plasma were slightly greater than one (1.14 for AUC and C_{max}).

In vivo distribution

The *in vivo* human distribution of baricitinib was investigated in study JAGM after IV infustion of 4 µg ($^{13}C_4D_3{}^{15}N$)-baricitinib for approximately 1.5 hours. Mean volume of distribution (V_d) was 75.7 L (21% CV), suggesting distribution of baricitinib into tissues. The mean body weight was 70 kg, resulting in a V_d of 1.08 L/kg.

The plasma protein binding of baricitinib is ~50% and was independent of the concentration (including clinically relevant concentrations). The blood-to-plasma ratio is 1.14 and the volume of distribution is ~1.1 L/kg.

Elimination

Only baricitinib was detected circulating in human plasma. Metabolites accounted for 4-7% of the dose in urine and ~1% in faeces. In addition, baricitinib is metabolised to a limited extent *in vitro.*

In vitro studies indicate that baricitinib is a substrate for P-glycoprotein, BCRP, OAT3 and MATE2-K. Baricitnib is not a substrate for OATP1B1, OATP1B3, OAT1, OCT1, OCT2, and MATE1.

The elimination half-life of baricitinib is ~8 h in healthy volunteers. Baricitinib is mainly excreted via urine and predominately as parent compound. Around 20% of the dose is excreted via faeces. The total clearance is ~17 L/h and the renal clearance is ~13.4 L/h in healthy subjects.

Dose proportionality and time dependencies

The Cmax and AUC0-∞ increases dose-proportional in healthy subjects, over a single dose range of 1 to 30 mg (slightly more over the dose range 30 to 40 mg). However, the Phase 1,2a capsules and the Phase 2 tablets were used for determination of the dose-proportionately.

The kinetics of baricitinib from the commercial tablet was dose proportional over 2 to 4 mg. After multiple once-daily dosing, steady state was reached between the second and third dose. Accumulation after repeated dose administration of baricitinib is minimal; the accumulation ratio ranged from 0.89-1.25-fold and 1.02-1.24-fold based on Cmax and AUC, respectively.

The pharmacokinetics of baricitinib was predictable from single dose data, suggesting that baricitinib possesses linear pharmacokinetics with respect to time.

Special populations

The effect on the pharmacokinetics of baricitinib of renal function, hepatic function, age, weight, race, gender, and Erythrocyte Sedimentation Rate were investigated, including PopPK Analysis.

Moderate hepatic impairment, age (age range of 19 to 83 years) and Erythrocyte Sedimentation Rate (measure of disease state) did not have a clinically significant effect on the exposure to baricitinib.

A reduction in baricitinib renal clearance and an increase in the AUC were observed with increased severity of renal impairment.

The effect of renal impairment on the PK of baricitinib was evaluated in the clinical pharmacology Study I4V-MC-JADL (JADL) and subsequent Phase 2 and Phase 3 studies.

JADL was a Phase 1, Open-Label, Single-Dose, Pharmacokinetic, Pharmacodynamic and Safety Study of INCB028050 (10 and 5 mg) administered to Subjects with various degrees of renal impairment (mild, moderate, severe renal impairment or end-stage renal disease [ESRD] requiring hemodialysis [HD]).

The pharmacokinetics of INCB028050 was significantly affected by renal function.

The INCB028050 pharmacokinetic parameters and geometric mean ratios (reference=healthy cohort) are presented in table 22 below by cohort.

Table 22. Summary of INCB028050 Plasma Pharmacokinetic Parameters and Geometric Mean Ratios (Reference=Healthy Cohort) (PK Population)

Cohort	C_{max} (nM)	t_{max}[a] (h)	$t_{1/2}$ (h)	AUC_{0-t} (nM·h)	$AUC_{0-\infty}$ (nM·h)	Cl/F (L/h)	Vz/F (L)
Mean ± SD and Geometric Mean							
Healthy Cohort INCB028050 10 mg (n=10)	231 ± 54.4 222	1.0 (1.0–3.0)	8.4 ± 2.4 8.1	1540 ± 324 1510	1560 ± 327 1530	18.0 ± 3.69 17.6	215 ± 64.4 207
Mild Cohort INCB028050 10 mg (n=10)	275 ± 106 258	1.5 (1.0–4.0)	10 ± 3.5 9.5	2200 ± 556 2140	2230 ± 561 2160	12.8 ± 3.45 12.5	197 ± 124 171
Moderate Cohort INCB028050 10 mg (n=10)	330 ± 58.2 326	1.3 (1.0–1.5)	12 ± 3.7 11	3510 ± 1180 3340	3590 ± 1270 3400	8.35 ± 2.79 7.93	129 ± 24.3 127
Severe Cohort INCB028050 5 mg (n=8)	164 ± 50.5 157	1.5 (1.0–2.0)	19 ± 4.6 18	2930 ± 531 2880	3150 ± 649 3090	4.43 ± 0.88 4.35	116 ± 26.6 113
ESRD Cohort INCB028050 5 mg (Day 1; HD postdose) (n=8)	105 ± 39.1 98.5	2.0 (1.0–3.0)	19 ± 4.6 18	1780 ± 513 1720	1920 ± 570 1840	7.67 ± 2.63 7.31	199 ± 55.9 192
ESRD Cohort INCB028050 5 mg (Day 15; HD predose) (n=8)	125 ± 29.0 122	1.8 (1.0–4.0)	18 ± 6.7 18	2360 ± 670 2280	2520 ± 729 2430	5.75 ± 1.65 5.55	150 ± 58.7 140
P-Values from a 1-Factor ANOVA of Log-Transformed Data[b]							
Healthy, Mild, Moderate, Severe, and ESRD (Day 1)							
Overall p-value	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	0.003
Healthy, Mild, Moderate, Severe, and ESRD (Day 15)							
Overall p-value	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	0.006
Ratio of Dose-Normalized Geometric Mean Plasma Exposure and 90% Confidence Interval (Reference=Healthy Cohort)[b]							
Mild (n=10)	116% 92-145%	--	--	141% 116-172%	141% 115-174%	--	--
Moderate (n=10)	146% 117-183%	--	--	220% 181-269%	222% 181-273%	--	--
Severe (n=8)	140% 111-178%	--	--	381% 309-470%	405% 325-503%	--	--
ESRD (Day 1) (n=8)	88% 70-112%	--	--	226% 184-279%	241% 194-300%	--	--
ESRD (Day 15) (n=8)	110% 86-139%	--	--	301% 244-371%	318% 256-395%	--	--

Abbreviations: ANOVA=analysis of variance; ESRD=end-stage renal disease receiving dialysis; HD=hemodialysis; Healthy=normal renal function; Mild=mild renal impairment; Moderate=moderate renal impairment; SD=standard deviation; Severe=severe renal impairment.

[a] median (minimum-maximum) are reported.

[b] Dose-dependent parameters (C_{max} and AUC) were dose normalized prior to statistical comparisons.

In patients with Rheumatoid Arthritis, a less pronounced effect of the renal function on the exposure of baricitinib was observed.

Cmax decreased with increasing body weight. However, the effect of body weight on baricitinib PK is not considered clinically relevant.

Gender and race (American versus Japanese) were shown to have an effect on the PK of baricitinib but were considered to not be clinically relevant.

No clinical studies with baricitinib were performed in patients with severe hepatic impairment.

	Age <65 (subjects number/total number)	**Age 65-74 (Older subjects number/total number)**	**Age 75-84 (Older subjects number/total number)**	**Age 85+ (Older subjects number/total number)**
Phase 1 [a]	539 / 557 (96.8%)	14 / 557 (2.5%)	4 / 557 (0.7%)	0 / 557 (0.0%)
Controlled Trials: Phase 2 dose-ranging studies (JADC, JADA, JADN) (N=571)	485 / 571 (84.9%)	76 / 571 (13.3%)	10 / 571 (1.8%)	0 / 571 (0.0%)
Controlled Trials: Completed Phase 3 studies (JADZ, JADV, JADX, JADW) (N=3100)	2563 / 3100 (82.7%)	466 / 3100 (15.0%)	70 / 3100 (2.3%)	1 / 3100 (<0.1%)
Noncontrolled Trials: (JADY) (N=2534)	2058 / 2534 (81.2%)	413 / 2534 (16.3%)	62 / 2534 (2.4%)	1 / 2534 (<0.1%)

Pharmacokinetic interaction studies

Baricitinib is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5 3A5 at clinically relevant concentrations. In addition, baricitinib is not an inducer via AhR, PXR and CAR at clinically relevant maximal plasma concentrations, portal vein concentrations and maximal intestinal concentrations.

Furthermore, baricitinib is not an inhibitor of the transporters P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE-1 and MATE2-K at clinically relevant concentrations. Baricitinib may be an inhibitor of OCT1 at maximal portal vein concentrations.

In clinical DDI studies, the potential of baricitinib to affect the PK of oral contraceptives (via CYP3A), simvastatin (via CYP3A and OATP1B1), and digoxin (via P-glycoprotein) was investigated. The clinical DDI studies confirm the in vitro data that baricitinib is not an inhibitor or inducer of CYP3A and not an inhibitor of P-glycoprotein. Concomitant administration with simvastatin led to a (not clinically significant) decrease in AUC and Cmax of simvastatin. The underlying mechanism of action is unknown. Furthermore, baricitinib does not have an effect on the PK of methotrexate, a commonly concomitant prescribed drug, in Rheumatoid Arthritis patients.

In the clinical safety studies, an effect on the creatinine clearance was observed (decrease in creatinine clearance). Creatinine is cleared by the following transporters OCT2, OAT2, MATE1 and MATE2-K. Baricitinib was not an inhibitor of OCT2, MATE1 and MATE2-K at clinically relevant concentrations.

In vitro and *in vivo* data indicate that >10% of the baricitinib dose is metabolised. Baricitinib is actively excreted by the transporters P-glycoprotein, BCRP, OAT3 and MATE2-K. In clinical DDI studies, the potential of other drugs to affect the PK of baricitinib was investigated. A clinically significant interaction was observed when baricitinib was co-administered with probenecid (a strong OAT3 inhibitor). No other clinical DDI studies have been conducted with OAT3 inhibitors with less inhibition potential. The prodrug leflunomide, which rapidly converts to teriflunomide and teriflunomide, is an inhibitor of OAT3 (furosemide exposure was increased in patients concomitantly taking teriflunomide and furosemide).

Co-administration of ketoconazole (strong CYP3A inhibition), fluconazole (strong CYP2C19 inhibition and moderate CYP2C9 and 3A inhibition), rifampicin (inducer via CAR/PXR of among others CYP3A and P-glycoprotein) and cyclosporine (P-glycoprotein inhibition) with baricitinib did not have a clinically relevant effect on the pharmacokinetics of baricitinib.

No *in vivo* studies were performed for inhibition of BCRP and MATE2-K. Increase in gastric pH does not affect the overall exposure to baricitinib.

2.4.3. Pharmacodynamics

Mechanism of action

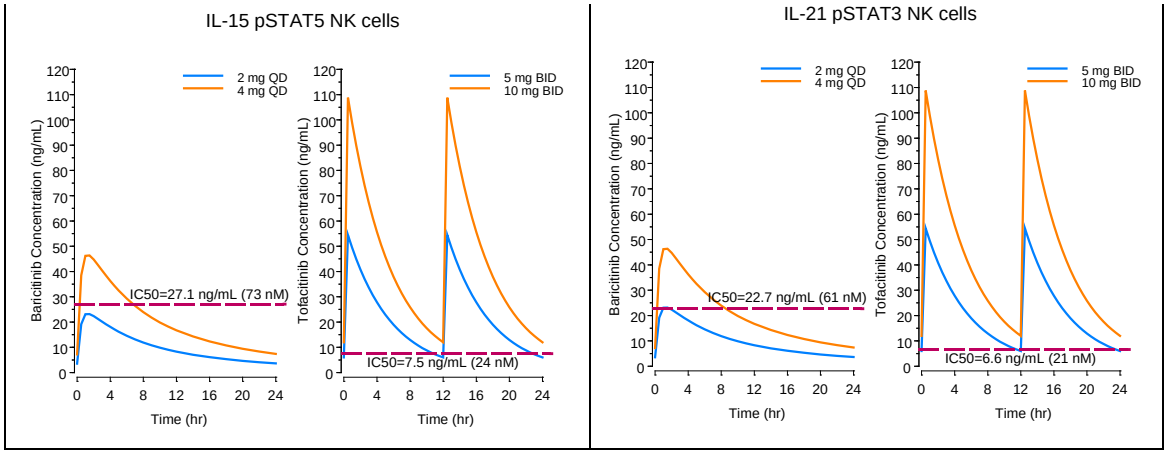
Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, Tyrosine Kinase 2 and JAK3 with IC_{50} values of 5.9, 5.7, 53 and > 400 nM, respectively.

Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation and immune function. Within the intracellular signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.

Primary and Secondary pharmacology

According to the data provided, the duration of exposure over the IC50 for signalling mediated by the common gamma-chain cytokines that use the JAK1/JAK3 heterodimer, including IL-15 and IL-21, is shorter for baricitinib than reported for tofacitinib, based on *in vitro* experiment with peripheral blood mononuclear cell preparations from healthy donors. To be noted, barcitinib is dosed once daily, whereas the regular tofacitinib dose is 5 mg *twice* daily, in RA.

Figure 9. Inhibition of cytokine IL-15 and IL-21 signaling by baricitinib and tofacitinib: duration of exposure over calculated IC50 values in NK cells

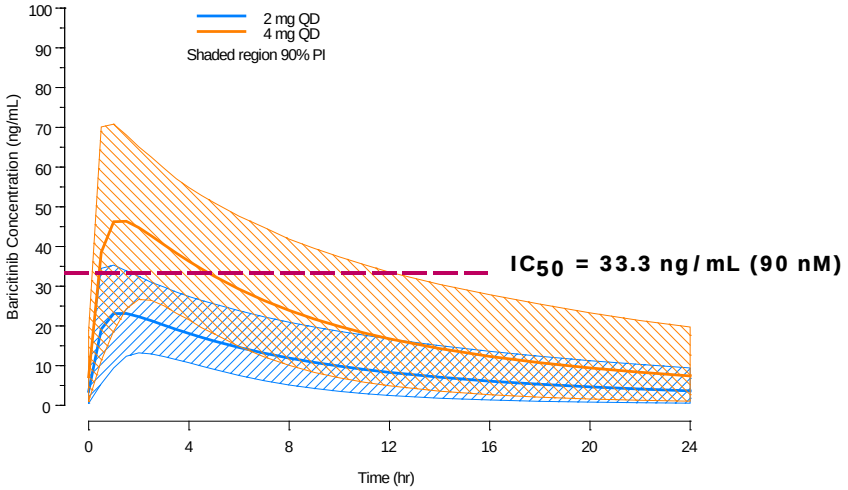


Left figure in each panel: baricitinib 2/4 mg,. Right figures in the panels: tofacitinib. Abbreviations: IC50 = half maximal inhibitory concentration; IL-15= interleukin-15; IL-21= interleukin-21; JAK = Janus kinase; NK = natural killer; PK = pharmacokinetics; pSTAT3 = phospho-STAT3; pSTAT5 = phospho-STAT5; STAT = signal transducers and activators of transcription. Note: The IC50 value is the geometric mean from the 6 donors. Signaling of IL-15 and IL-21 is via JAK1/3. The PK profiles of tofacitinib were simulated using a one-compartment model with zero-order absorption . Parameter Estimates from CP690,550 Final Population Pharmacokinetic Model (Run 502) in the "Clinical Pharmacology Biopharmaceutics Review(s)" of tofacitinib (FDA website)

Interleukin IL6 study

As baricitinib is a JAK1/JAK2 inhibitor and IL-6 signals via a JAK1/JAK2 heterodimer, an IL-6 stimulated pSTAT assay was developed. Pharmacokinetic modeling indicates that for baricitinib 4 mg once-daily, there will be a 12-hour period during the 24 h dosing interval when the baricitinib serum concentration is below the 50% inhibitory threshold for IL-6 stimulated STAT phosphorylation (figure 10 below).

Figure 10. Plasma concentration time profiles of once-daily dosing of baricitinib over a dosing interval at 2-mg and 4-mg doses compared to the IC_{50} for IL-6 stimulated pSTAT3 formation estimated from Phase 1 studies (JADF and JADE)



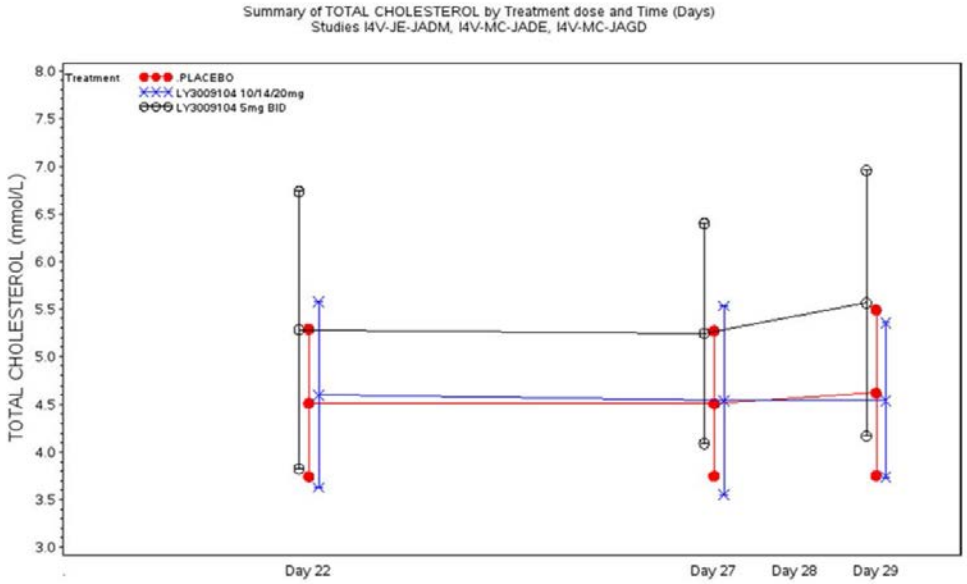
Abbreviations: IC_{50} = half maximal inhibitory concentration; IL-6 = interleukin-6; PI = prediction interval; QD = once daily.

Baricitinib inhibits CK-induced JAK-mediated phosphorylation of STAT3 (P-STAT3) in a dose-dependent manner. Maximum inhibition of STAT3 phosphorylation occurs at 1-2 hr post dose and concurs with Cmax. P-STAT3 levels return to normal at about 24 hrs following single or multiple doses, even when dosed for 10 days.

Secondary pharmacodynamics

In healthy volunteers, baricitinib had no relevant effect on total cholesterol in healthy volunteers. A modest increment was observed after a supratherapeutic dose, with wide confidence intervals.

Figure 11. Total cholesterol in healthy volunteers receiving baricitinib at supratherapeutic doses



Immunoglobulins

Mean absolute lymphocyte count increased by 1 week after starting treatment with barcitinib, returned to baseline after week 24, and then remained stable through at least 104 weeks. For most patients, changes in lymphocyte count occurred within normal reference range.

Lymphocytes

Mean absolute lymphocyte count increased by 1 week after starting treatment with barcitinib, returned to baseline after week 24, and then remained stable through at least 104 weeks. For most patients, changes in lymphocyte count occurred within normal reference range.

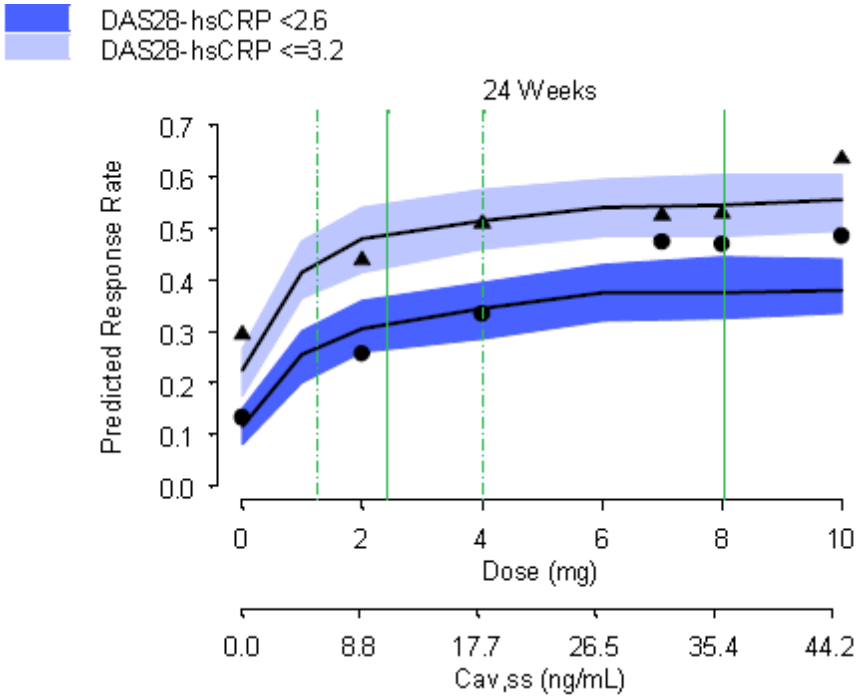
Pharmacodynamic interactions with other medicinal products or substances

Baricitinib should not be used with biologic DMARDs, for safety reasons, as the clinical consequences of blocking multiple pathways cannot be foreseen. However, the combination with conventional DMARDS was widely applied in the main clinical trials.

PK-PD relationship

Dose/exposure – response relationships were characterized for DAS28-hsCRP <=3.2 (Low Disease Activity) and <2.6 (remission) response rates by exposure quartile analysis and by PopPK/PD modeling. In the exposure response analysis, the majority of Cav,ss values in the lowest quartile were from the baricitinib 2-mg dose while values in the upper two quartiles were comprised almost entirely of values from the 4-mg dose. Higher rates of ACR and DAS28-hsCRP responses were observed in the 3 upper quartiles of exposure compared to the lowest quartile (see figure 12 below). No apparent concentration relationship for the 2- and 4-mg dose levels on anaemia or neutropenia was observed.

Figure 12. Model predicted dose/response relationships for percent of patients achieving DAS-hsCRP <=3.2 and <2.6 at Week 24 (pooled Phase 2/3 data)



$C_{av,ss}$ = average concentration during a dosing interval at steady state; Note: Solid black lines are model-predicted response. The bands are 90% prediction intervals that were constructed by simulation of 200 trials. Triangle and circle are for observed percentage of patients achieving DAS28-hsCRP <=3.2 and <2.6, respectively. Black and red colors are for QD and BID dosing, respectively. Vertical solid and dashed lines indicate the range (5th percentile to 95th percentile) of predicted concentrations for 4-mg and 2-mg, respectively

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Barcitinib's blood-to-plasma ratio indicates weak/moderate association with the blood cell compartment. The volume of distribution indicates that baricitinib distributes from plasma compartment into tissue.

In vitro data indicates that metabolism does not significantly contribute to the clearance of baricitinib. The enzymes involved in the limited metabolism of baricitinib were not identified, but this is also not warranted.

The total clearance is ~17 L/h and the renal clearance is ~13.4 L/h in healthy subjects. These results indicate that baricitinib is actively excreted into urine. Baricitinib is mainly excreted via urine and predominately as parent. The transporters P-glycoprotein, OAT3 and MATE2-K are most likely involved in the active excretion of barcitinib into urine.

BCRP may be involved in the excretion into faeces. However, excretion via faeces is limited (around 20%) and therefore the *in vivo* contribution of BCRP in to the excretion of baricitinib is most likely limited. This is most likely mainly unabsorbed baricitinib, since the bioavailability is ~79%.

Genetic polymorphisms in P-glycoprotein will most likely not have a clinically relevant effect on the PK of baricitinib. For MATE-2K, a conclusion whether SNPs in MATE-2K would lead to clinically significant changes in the PK of baricitinib cannot de drawn as current information is too limited. However, the current proposed dose is 4 mg, but good response to a 2 mg dose was observed in non-renal patients. Therefore, a higher clearance of baricitinib due to the rs12943590 variant in MATE-2K will most likely not lead to a clinically relevant effect. There are currently no known SNPs in OAT3 affecting the activity and therefore no discussion is warranted for OAT3.

A reduction in baricitinib renal clearance and an increase in the AUC were observed with increased severity of renal impairment. Dose reduction is therefore warranted for patients with renal impairment. A lower dose of 2 mg is recommended for patients with estimated glomerular filtration rate (GFR) between 30 and 60 mL/min/1.73m2. Olumiant is not recommended for use in patients with estimated GFR of <30 mL/min/1.73m2.

In patients with Rheumatoid Arthritis, a less pronounced effect of the renal function on the exposure of baricitinib was observed. This is consistent with a reduced fraction of excretion out of the total elimination pathways of baricitinib in patients with Rheumatoid Arthritis compared to healthy subjects.

Gender and race (American versus Japanese) were shown to have an effect on the PK of baricitinib. However this was considered, to be due to differences in body weight and, not clinically relevant.

Patients with severe hepatic impairment often have serious co-morbidities, which calls for caution when considering pharmacological treatment. Therefore, the use of baricitinib in patients with severe hepatic impairment is not recommended.

It is unlikely that baricitinib will lead to clinically relevant DDIs due to CYP inhibition or induction. Baricitinib is not an inhibitor of the transporters P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE-1 and MATE2-K at clinically relevant concentrations. Baricitinib may be an inhibitor of OCT1 at maximal

portal vein concentrations. Concomitant administration of baricitinib with drugs for which the rate limiting step is hepatic uptake by OCT1, may lead to an increase in Cmax. No *in vivo* studies were performed for inhibition of BCRP and MATE2-K.

In the clinical safety studies, an effect on the creatinine clearance was observed (decrease in creatinine clearance). Creatinine is cleared by the following transporters OCT2, OAT2, MATE1 and MATE2-K. Baricitinib was not an inhibitor of OCT2, MATE1 and MATE2-K at clinically relevant concentrations. The Applicant will investigate if inhibition of OAT2 by baricitinib may be the cause for the decrease in creatinine clearance (Post-Authorisation Measure included in the RMP).

Complete inhibition of BCRP may lead to a bioavailability of 100% which may result in an AUC increase of 1.25. This increase is not considered clinically relevant. Furthermore, the clinical significance of an interaction at MATE2-K would be minimised given the multiple exit routes of baricitinib from the proximal tubule cell. Maximal inhibition of MATE-2K will lead to a less than 2-fold increase in AUC of baricitinib, because other transporters can compensate for the lack of function. Therefore, inhibition of MATE-2K is likely not clinically relevant.

Increase in gastric pH does not affect the overall exposure to baricitinib. Therefore, baricitinib may be co-administered with drugs that are gastric pH modifying agents.

In vitro and *in vivo* data indicate that >10% of the baricitinib dose is metabolised. Baricitinib is actively excreted by the transporters P-glycoprotein, BCRP, OAT3 and MATE2-K. In clinical DDI studies, the potential of other drugs to affect the PK of baricitinib was investigated. A clinically significant interaction was observed when baricitinib was co-administered with probenecid (a strong OAT3 inhibitor). No other clinical DDI studies have been conducted with OAT3 inhibitors with less inhibition potential. The prodrug leflunomide, which rapidly converts to teriflunomide and teriflunomide, is an inhibitor of OAT3 (furosemide exposure was increased in patients concomitantly taking teriflunomide and furosemide). Therefore, concomitant administration of baricitinib with leflunomide or teriflunomide may lead to an increase in baricitinib exposure. A recommendation for dose reduction of 2mg once daily in patients taking Organic Anion Transporter 3 (OAT3) inhibitors with a strong inhibition potential, such as probenecid has been included in the SmPC.

Concomitant use of ibuprofen and diclofenac will most likely have no clinically meaningful effect on the PK of baricitinib, since they are weak inhibitors of OAT3. Co-administration of ketoconazole (strong CYP3A inhibition), fluconazole (strong CYP2C19 inhibition and moderate CYP2C9 and 3A inhibition), rifampicin (inducer via CAR/PXR of among others CYP3A and P-glycoprotein) and cyclosporine (P-glycoprotein inhibition) with baricitinib did not have a clinically relevant effect on the pharmacokinetics of baricitinib.

Pharmacodynamics

The *in-vitro* studies suggest that baricitinib provides only a temporary suppression above the IC50 level of the pSTAT pathways mediating IL-15, IL-21 IL-6 signalling during a dosing interval.

It could be questioned whether efficacy would be sufficient considering the short-term suppression of the target pathways by baricitinib during the dose interval. As will be discussed below, efficacy was established with 2 or 4 mg baricitinib once daily schedule. Twice daily dosing of 2 mg did not improve efficacy as compared to once-daily 4 mg, though it did lead to more adverse events like anaemia (see exploratory dose finding studies).

IL-6 plays a relevant role in fighting infection. According to the data provided, once-daily administration of baricitinib may allow for recovery of the IL-6 signalling pathway towards the end of the dosing interval which

might reduce the incidence of infections that have been reported for tocilizumab, a monoclonal antibody causing a prolonged suppression of IL-6.

However, as direct comparisons between baricitinib and longer acting drugs tocilizumab and tofacitinib are lacking, no final conclusions could be drawn from these *in-vitro* data, which were mainly based on simulations.

Data from healthy volunteers without inflammation were requested from the applicant to evaluate whether the lipid-increments in patients receiving baricitinib are rather secondary to a non-specific reduction of inflammation by baricitinib–since other DMARDs also increase lipids-, or whether this a specific drug-related effect. Though no changes in cholesterol levels were observed in healthy volunteers who received a once daily dose, the data may not fully exclude an drug-related effect, since an increasing trend was observed in healthy volunteers who received a 5 mg twice-daily dose –and thus has a more prolonged STAT suppression during the day.

It is not fully clear whether the increments of lipids that were observed in the clinical trials in RA patients, are directly related to the drug, or to the fact that RA patients in high active disease state may have relatively low cholesterol level, which recovers once inflammation is treated by DMARDs. In healthy volunteers, no changes in total cholesterol were noted as a single daily dosing, though a increment of cholesterol is not excluded at twice daily dosing.

Altogether, the exposure to baricitinib in healthy volunteers is too limited to draw final conclusions whether the lipid effects of baricitinib in patients, are drug-related or should be considered as a treatment response, secondary to the reduction of inflammation. At present, no further investigations are required regarding the underlying mechanism of hyperlipidaemia, also considering that lipid increments will be further followed in a PASS.

2.4.5. Conclusions on clinical pharmacology

The PK of baricitinib has been extensively investigated both *in vitro* and *in vivo*. Baricitinib is mainly renally cleared from the body, and dose adjustments are recommended in the SmPC for patients with moderate renal impairment which is acceptable. With regard to drug-drug interactions and the observed decrease in creatinine clearance, a PAM (outlined in the RMP) has been requested to investigate if baricitinib may be considered as an OAT2 inhibitor .

Baricitinib could interfere with production of erythrocytes, leukocytes, or platelets, besides the warranted immune-modulating effect on the cytokines. PK-PD modelling indicate that at doses of 4 mg QD, more patients are likely to achieve the plateau of the exposure-response curve than at the 2 mg dose, without further increments of leukopenia or anaemia.

Baricitinib has only a temporary inhibitory effect of the pSTAT pathways of IL 6, IL-15 and IL-21 above IC50 during the dose interval of 24 hrs. This is in contrast to tofacitinib and tocilizumab, which have a continuous suppressing effect above IC50. The clinical relevance of these findings regarding efficacy or the risks of infections has not been established in head-to-head comparative trials.

2.5. Clinical efficacy

2.5.1. Dose response studies

The Phase II study program consisted of 3 proof-of-concept and dose finding studies, where doses of 1-10 mg QD (once-daily) of baricitinib were explored. In Study JADA, also 2mg BID (twice daily) dosing was explored. Study JADN was performed in Japan, as a bridging study for non-Asian studies.

Results of the proof-of-concept Study JADC in patients, in which 3 dose levels were evaluated (4-, 7- and 10-mg once daily), indicated that baricitinib 4-mg once daily appeared to reside on the plateau of the efficacy dose-response curve. The percentage of subjects achieving ACR20 improvement at 12 weeks was 52%, 59%, and 53% for the 4 mg, 7 mg and 10 mg groups, respectively, and 32% for placebo. ACR50 responses were 35%, 31% and 30%, respectively, and 13% for placebo. As the active treatment deterred from placebo, the proof of concept has been shown in this study.

The primary reason for early discontinuation was adverse event, with a higher incidence of discontinuation in the BARI 10 mg group (15.6%) than in the lower dose group groups (6.3-9.4%) or placebo (6.5%). JAK1,2 interfere with erythropoietin. The Haemoglobin levels dropped in a dose dependent way: the mean from baseline to Week 12 were -2.4, -4.9, and -11.1 g/L in the 4 mg, 7 mg, and 10 mg groups, compared with 0 in the placebo group. In Study JADA and JADN, it was further confirmed that doses exceeding BARI 4 mg had no additional value, neither at the short as long-term (52 weeks, Study JADN).

In study JADA and JADN, also doses lower than baricitinib 4 mg were evaluated. In Study JADA, the ACR20 response rates at Week 12 were of 41% for placebo, 54% for the 2 mg dose, and 75% for the 4-mg dose. Twice-daily 2 mg dosing did not improve efficacy parameters after randomisation from 4 mg dose, but was associated with more laboratory abnormalities.

In a sub-study of 154 enrolled patients, MRI of the hand and wrist was performed. Compared to placebo, statistically significant improvements in measures including synovitis, osteitis, and total inflammation scores were observed for the baricitinib 4-mg and 8-mg groups at Week 12; no statistically significant improvements were 2-mg once daily group. In contrast, in Study JADN, both the 2 and 4 mg dose performed equally well for ACR50.

The 4 mg dose was chosen for the Phase 3 trials. A lower 2-mg once daily dose was included in two Phase 3 studies to confirm the minimum clinically effective dose.

2.5.2. Main studies

To confirm efficacy and safety in the three target populations (DMARD-naïve (first line), patients irresponsive/intolerant to convention DMARDs (second line), and patients irresponsive to biologic DMARDs ('third' line), in total 4 main double-blind randomised controlled trials were performed.

Two trials were long-term (52 weeks) active controlled trials: Study JADZ, which was performed in DMARD naïve patients, and study JADV, which was performed in patients irresponsive to methotrexate (MTX-IR). Active comparator was MTX in the first line study, and TNF-I adalimumab in the second line study.

Two trials were shorter-term (24 weeks) 3-arm randomised placebo-controlled trials with baricitinib 2 and 4 mg. One was performed in the second line setting (Study JADX), and one in bDMARDs irresponsive patients (Study JADW, 3rd line).

All patients who finished Study JADA, JADZ, JADV, JADX, JADW could enter the long-term extension study JADY. Patients could maintain their prior baricitinib 2 or 4 mg dose. Study JADY was single-blind. In a subgroup of patients in JADY who were stable DAS28-hsCRP LDA responders on a 4 mg dose, a randomised withdrawal study was performed. Subjects were re-randomised to either the 2 mg dose, or maintenance of the 4 mg dose.

Study JADA, JADZ, JADV, JADX JADW, and JADY were considered as being pivotal for this application.
The baseline characteristics of the study populations of the four main trials are summarized below:

Table 23. Baseline demographic features

	JADZ (N=584) DMARD-naive	**JADV (N=1305) MTX-IR**	**JADX (N=684) cDMARD-IR**	**JADW (N=527) TNF-IR**
Mean Age in Years (SD)	49.9 (13.4)	53.3 (12.1)	51.8 (12.3)	55.7 (11.0)
Age Group, n (%)				
<65	501 (85.8)	1064 (81.5)	587 (85.8)	411 (78.0)
≥65	83 (14.2)	241 (18.5)	97 (14.2)	116 (22.0)
≥75	9 (1.5)	33 (2.5)	14 (2.0)	15 (2.8)
Gender Female, n (%)	425 (72.8)	1008 (77.2)	560 (81.9)	431 (81.8)
Body weight (kg) (mean, SD)	71.0(19.1)	70.0 (17.6)	76.1 (21.8)	81.9 (21.8)
Race, Asian	165 (28.3)	392 (30.1)	180 (26.4)	32 (6.1)
Race, White	349 (59.8)	818 (62.7)	457 (66.9)	435 (83.0)
Geographic Region, n (%)				
USA/Canada	121 (20.7)	105 (8.0)	204 (29.8)	234 (44.4)
Central/South America or Mexico	169 (28.9)	380 (29.1)	86 (12.6)	52 (9.9)
Asia	111 (19.0)	378 (29.0)	120 (17.6)	30 (5.7)
European Union [b]	80 (13.7)	308 (23.6)	181 (26.5)	150 (28.5)

Table 24. Baseline disease activity main studies

DISEASE ACTIVITY				
	JADZ (N=584) MTX-naive	**JADV (N=1305) MTX-IR**	**JADX (N=684) cDMARD-IR**	**JADW (N=527) TNF-IR**
Tender joint count based on 28 joints, mean (SD)	15.3 (6.9)	13.9 (6.8)	13.8 (7.0)	15.9 (6.9)
Swollen joint count based on 28 joints, mean (SD)	11.5 (5.7)	11.1 (5.3)	9.8 (4.9)	11.9 (5.8)
Patient's assessment of pain (0-100 mm), mean (SD)	64.0 (22.9)	60.8 (22.3)	58.0 (22.1)	64.3 (21.5)
High-sensitivity C-reactive protein (mg/L), mean (SD)	23.44 (25.98)	21.14 (21.67)	16.7 (19.1)	20.09 (24.19)
DAS28-hsCRP, mean (SD)	5.89 (0.97)	5.73 (0.94)	5.55 (0.91)	5.93 (0.95)
RF positive/ACPA negative (SD)	44 (7.5)	89 (6.8)	51 (7.5)	44 (8.4)
RF positive/ACPA positive (SD)	517 (88.7)	1102 (84.4)	470 (68.7)	341 (64.8)
Time from RA diagnosis (years), median	0.2	6.3	3.5	10.7

RA therapies

	JADZ (N=584) MTX-naive	JADV (N=1305) MTX-IR	JADX (N=684) cDMARD-IR	JADW (N=527) TNF-IR
Current use of corticosteroid (yes), n (%)	206 (35.3)	766 (58.7)	346 (50.6)	304 (57.7)
Methotrexate average weekly dose (mg/week) (SD)	n/a d	14.8 (4.6)	16.2 (4.8)	16.3 (7.7)
Number of bDMARDs previously used, n (%)				
0	583 (99.8)	1303 (99.8)	684 (100.0)	4 (0.8)
1	1 (0.2)	2 (0.2)	0	221 (41.9)
2	0	0	0	160 (30.4)
≥3	0	0	0	142 (26.9)

bDMARDs= biologic DMARD

Endpoints

In all pivotal trials, ACR 20 is the primary endpoint, at Week 12 or 24 (Study JADZ). The ACR20 is defined as at least 20% improvement in the following ACR Core Set values:

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

Key secondary efficacy endpoints:

-Mean change from BL of the Health Assessment Questionnaire–Disability Index (**HAQ-DI**): a functional score.
-Mean change from BL of the van der Heijde Modified Total Sharp Score (**mTSS**); this score sums the extent of bone erosions and joint space narrowing for 44 and 42 joints, of the hands/wrists and feet, by Xray, with higher scores representing greater damage. Central readers assessed the X-rays.

-Mean change from BL of the **DAS28-hsCRP and DAS28-ESR:** measure of disease activity in 28 joints that consists of a composite numeric score of the following variables: tender joint count, swollen joint count, hsCRP or ESR, and Patient's Global Assessment of Disease Activity.

-Remission according to SDAI. The **SDAI** is a tool for measurement of disease activity in RA that integrates measures of physical examination, acute phase response, patient self-assessment, and evaluator assessment. The ACR/EULAR index-based definition of remission is an SDAI score of ≤3.3.

In Study JADV and JADX, patients' reported outcomes like Duration of Morning Joint Stiffness, Severity of Morning Joint Stiffness Numeric Rating Scale (NRS), Tiredness Severity Numeric Rating Scale (Worst Tiredness NRS), Pain Severity Numeric Rating Scale (Worst Joint Pain NRS) were key secondary.

Other Secondary endpoints:

DAS28-hsCRP and DAS28-ESR LDA and remission For the DAS28-ESR, remission is defined as DAS28-ESR<2.6 and LDA is defined as DAS28-ESR ≤3.2. Similar thresholds have also been used for DAS28-hsCRP

Clinical Disease Activity Index **(CDAI):** The CDAI is similar to the SDAI, but it does not use a laboratory result. Remission is defined as a CDAI score of ≤2.8. Low disease activity is defined as a CDAI score of ≤10.0.

ACR-EULAR **Boolean Remission**: All 4 criteria below must be met: Tender joint count 28 ≤1, Swollen joint count 28 ≤1, hsCRP ≤1 mg/dL (10 mg/L), Patient's Global Assessment of Disease Activity (on a 0 to 10.0 cm VAS) ≤1.

Statistical methods

Analyses were conducted using the modified intent-to-treat (mITT) analysis set, which is defined as all randomized patients who received at least 1 dose of study drug.

Categorical endpoints were analysed using logistic regression with NRI (non-responder imputation) for missing data. Key secondary continuous endpoints were analysed using analysis of covariance (ANCOVA) with modified baseline observation carried forward (mBOCF) imputation.

Mean change in mTSS was analysed using ANCOVA with linear extrapolation as the principal method of imputation. Sensitivity analyses were performed with LOCF.

In each of the Phase 3 studies, the primary and key secondary hypotheses were tested using multiple testing procedures that control familywise type I error rate - referred to as "major (gated) objectives".

Each procedure began with a test of the primary null hypothesis using 2-sided alpha =0.05 if superiority was aimed (or 1-sided alpha =0.025 when non-inferiority was the primary assessment). Following rejection of the primary null hypothesis, the testing procedures used across the studies, though different from each other, fit within the framework of sequentially rejective weighted Bonferroni tests. In such a testing procedure defined by a graphical scheme, each time a hypothesis was rejected, the graphical scheme was updated according to predefined rules to reallocate alpha from this hypothesis to the remaining ones. This iterative process of updating the graphical scheme and reallocating alpha was repeated until either all hypotheses were tested or no remaining hypotheses could be rejected at their corresponding alpha levels.

DMARD-naïve patients, Study JADZ (first-line)

Study JADZ was a 52-week, multi-centre, randomized, double-blind, active-controlled, parallel-group, study evaluating efficacy (signs and symptoms, physical function, PROs, and radiographic progression of structural joint damage) and safety in 588 patients with moderately to severely active early RA, who had limited or no prior treatment with MTX, and who were otherwise naive to cDMARD or biologic therapy.

The treatment groups were:

- 4-mg once-daily baricitinib as monotherapy
- MTX as monotherapy (escalated to a maximum dose of 20-mg once weekly)
- 4-mg once-daily baricitinib in combination with MTX (escalated to a maximum dose of 20-mg once weekly).

The primary objective was to demonstrate non-inferiority of baricitinib monotherapy to MTX monotherapy in the proportion of patients who achieved an ACR20 response rate at Week 24.

The pre-specified NI margin was +/-12% of the 95% CI of for the response rate difference between BARI monotherapy minus MTX monotherapy at Week 24.

Results Study JADZ (DMARD-naïve)

Though non-inferiority was aimed, superiority was shown for the primary analyses ACR20 for baricitinib alone or the combination BARI + MTX versus MTX alone. This was further supported by ACR 50 and ACR70 responder rates (see figure 13 below).

More importantly, superiority of remission responders according to the diverse disease activity scores (DAS28-hsCRP, DAS28-ESR, SLAI, CDAI) was achieved, even for the most critical one, i.e. Boolean remission (Week 24: MTX alone: 8.6%; BARI 4 mg: 16.3% (95% CI difference vs MTX: 1.5-13.9); BARI + MTX 18.9% (3.1-17.5). The effect was maintained till 52 weeks (figure 14). Remission was similar between baricitinib monotherapy and the combination.

The primary endpoint was supported by a significant improvement of function (HAQ-DI), and Patient Reported Outcomes (PRO's).

Structural prevention was superior for the combination towards MTX monotherapy. However, the decline of structural mTSS scores, which were overall small from baseline, was similar between baricitinib and MTX monotherapies.

Figure 13. ACR responders for Study JADZ: DMARD naïve patients (1st line)

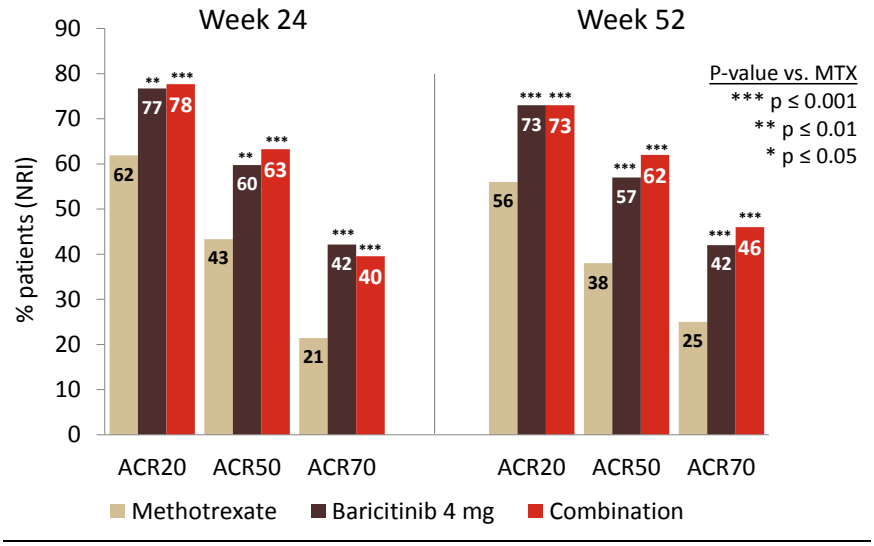
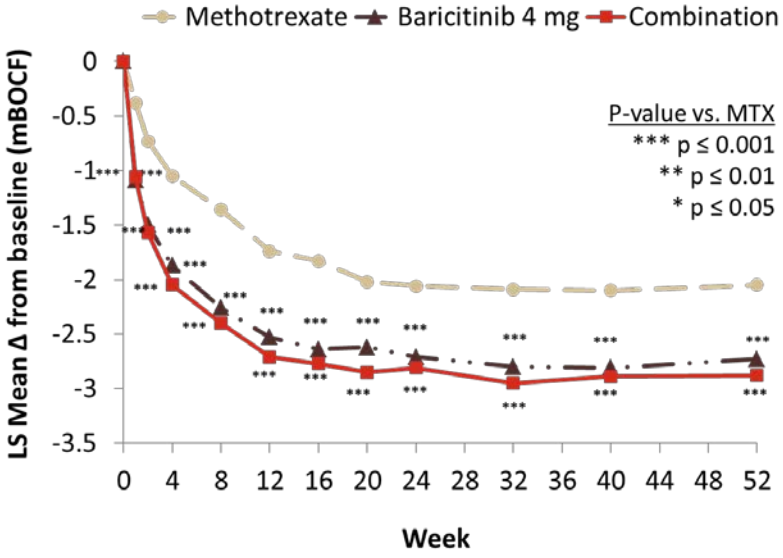


Figure 14. **Mean DAS28-hsCRP levels through Week 52 in Study JADZ. DMARD naïve patients (1st line)**



MTX-IR patients (Study JADV, second line)

Study JADV was a 52-week, Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group, outpatient study evaluating efficacy and safety in 1307 patients who had an inadequate response to MTX, and who had evidence of bone/joint erosion. Patients were required to continue stable doses of concomitant MTX during the study.

The treatment groups, as add-on therapy to stable MTX, were:

- 4-mg once-daily baricitinib (52 weeks)
- Placebo (24 weeks)
- 40-mg adalimumab administered subcutaneously every 2 weeks (ADA) (52 weeks)

Results Study JADV (second line, MTX-IR, active-controlled)

Superiority of BARI 4 mg was shown to both placebo and ADA in the primary analyses, whereas non-inferiority was aimed. ACR20 at Week 12 was 69.6% for BARI 4 mg, 61.2% for ADA, and 40.2% for placebo (difference vs. placebo 29.4 (95% CI 23.5, 35.4), vs. ADA (8.4 (1.7, 15.1). Superiority towards placebo and adalimumab was further confirmed for more stringent endpoints ACR50 and ACR70, and the effect was maintained till Week 52 (figure 15 and 16).

Low Disease Activity (LDA) responder rates and physical function scores of BARI 4 mg were superior to adalimumab at Week 52. . Though not formally tested, non-inferiority between BARI 4 mg and ADA was shown for the other endpoints regarding remission, the prevention of radiographic progression within ranges of -/+ 12% at Week 24 and 52. FACIT-F (fatigue), EQ-5D-5L (QOL), joint pain and morning joint stiffness scores were more favourable for baricitinib as compared to adalimumab (p< 0.01).

Figure 15. ACR responders for Study JADV: MTX-IR patients (2nd-line)

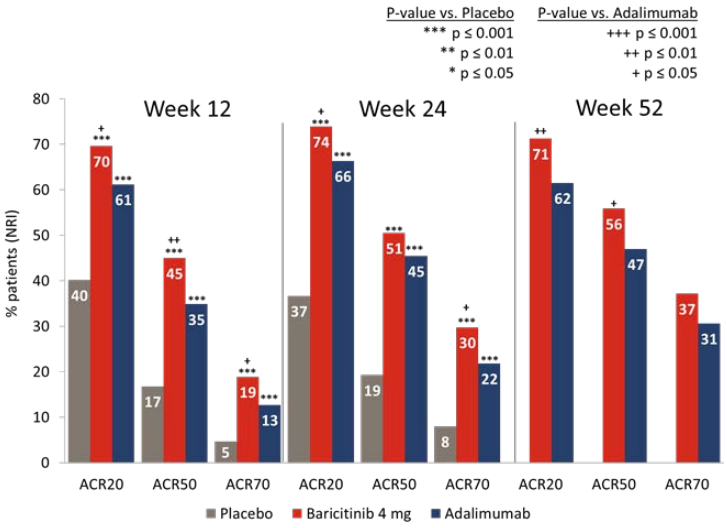
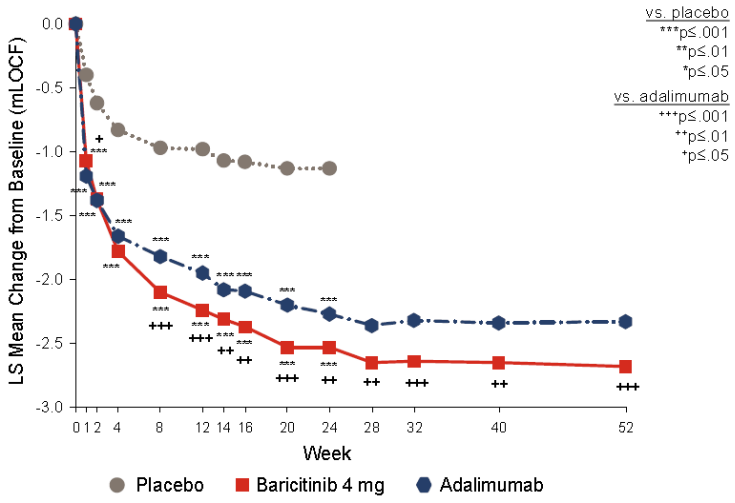


Figure 16. Mean DAS28-hsCRP scores through Week 52 in Study JADV: MTX-IR patients (2nd-line)



cDMARD-irresponsive / intolerant patients (Study JADX, dose finding, second line)

Study JADX was a 24-week, Phase 3, randomized, double-blind, placebo-controlled, study evaluating efficacy and safety in 684 patients with moderately to severely active RA despite previous or current treatment with cDMARDs. Patients in this study were allowed to continue cDMARD therapy during the study –if present.

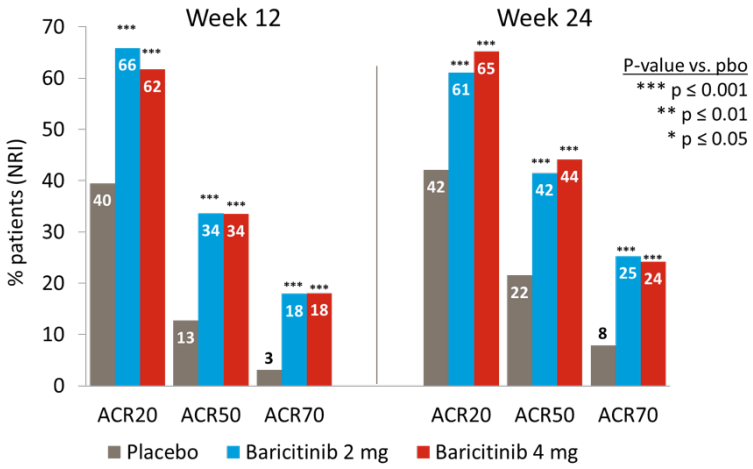
The treatment groups were:

- 4-mg once-daily baricitinib (24 weeks)
- 2-mg once-daily baricitinib (24 weeks)
- Placebo (24 weeks)

Results Study JADX (2nd line dose finding)

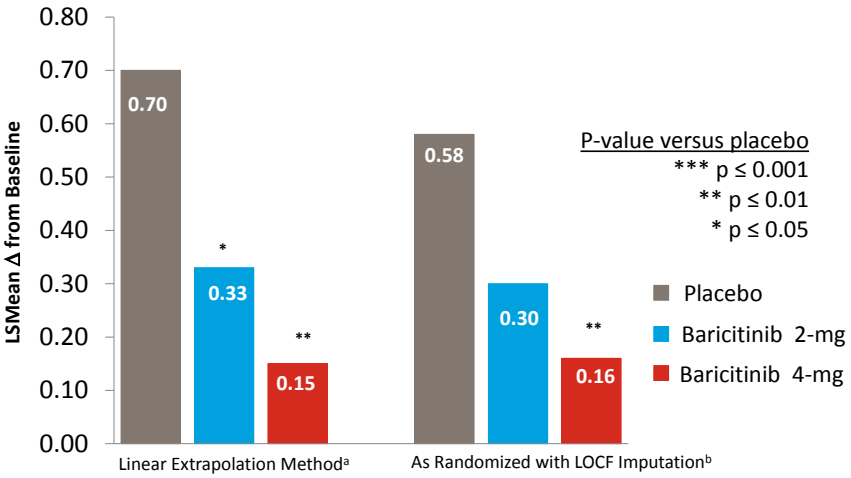
Both the 2-mg and 4-mg once daily doses of baricitinib demonstrated significant and clinically relevant improvements versus placebo with respect to signs and symptoms (ACR20/50/70), LDA and remission, physical function, and PROs (including morning joint stiffness, fatigue, pain, SF-36 PCS, and EQ-5D-5L). In contrast to what was observed in the Phase 2 studies, the outcomes for the 2 and 4 mg dose were highly similar for these endpoints. The primary endpoint of ACR20 response at Week 12 was 61.7% for BARI 4 mg, 65.9% for BARI 2 mg, and 39.5% for placebo (differences 22.2% (13.2, 31.2) and 26.5% (17.6, 35.3) for the 4 and 2 mg dose vs placebo, respectively.

Figure 17. ACR responders for Study JADX: cDMARD-IR patients (2nd-line); dose finding



Only an effect on the prevention of structural damage was more robustly shown for the 4 mg dose than the 2 mg dose. In the primary analyses of the mTSS scores, where linear imputation was used for missing data, both the 2 and 4 mg separated from placebo (see figure 18 below). However, in sensitivity analyses using more a conservative LOCF imputation, the placebo effect shrunk, and the 2 mg dose arm –and not the 4 mg- failed to distinguish from placebo.

Figure 18. **mTSS change from baseline at Week 24 in Study JADX:** Placebo, BARI 2 mg and BARI 4 mg, using two missing data imputation methods (linear extrapolation (left panel) and LOCF (right panel))



[a] Missing or post-rescue data imputed using linear extrapolation.
[b] Patients were allocated to the treatment group to which they were assigned at randomization regardless of rescue status. Data missing at Week 24 were imputed using last observation carried forward (LOCF).

A subgroup of cDMARD intolerant patients (N=48) received no background cDMARD, thus constituting a monotherapy experiment. Improvements in this subgroup were consistent with those seen in the overall study sample.

Biologic DMARD-IR patients (Study JADW, dose finding, third line)

Study JADW was a 24-week, Phase 3, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, study evaluating efficacy and safety in 527 patients with moderately to severely active RA despite past treatment with one or more biologics, including at least one TNF inhibitor. Patients in this study were required to continue stable doses of their current treatment with cDMARDs.

The treatment groups were as follows:

- 4-mg once-daily baricitinib (24 weeks)
- 2-mg once-daily baricitinib (24 weeks)
- Placebo (24 weeks)

Results Study JADW (dose finding, b-DMARD-IR patients)

In the analyses, Study JADW met its primary objective (ACR20) and the first two major secondary objectives **(**HAQ-DI and DAS28-hsCRP change from baseline) for baricitinib 4-mg versus placebo. According to the prior defined multiplicity testing rules, the analyses were stopped thereafter, as no statistical significance was observed for the next major (gated) endpoint, namely remission based on the SDAI (≤3.3) at Week 12. However, at other time-points, statistically significant improvements in this measure were demonstrated (see figure 20), as well as other measures of remission and low disease activity (CDAI ≤10; DAS28 ≤3.2; DAS28 <2.6).

Ignoring multiplicity rules, the response of the primary endpoint ACR20 at Week 12 was 55.4% for BARI 4 mg, 48.9% for BARI 2 mg and 27.3% for placebo (difference BARI 4 mg vs placebo: 28.1% (95% CI 18.2, 37.9), BARI 2 mg vs placebo 21.6 (11.7, 31.5). Overall, the outcomes were more robust for the 4 than the 2 mg dose regarding ACR50 and the diverse LDA scores (e.g. LDA according to DAS28-hsCRP: 31.6 for the 4 mg dose, 24.9 for the 2 mg does and 9.1 for placebo).

Boolean and CDAI remission response were not achieved for either dose (see Table 27 and 28 below)

Figure 19. ACR responders for Study JADW: biologic DMARD-IR patients ('3rd'-line); dose finding

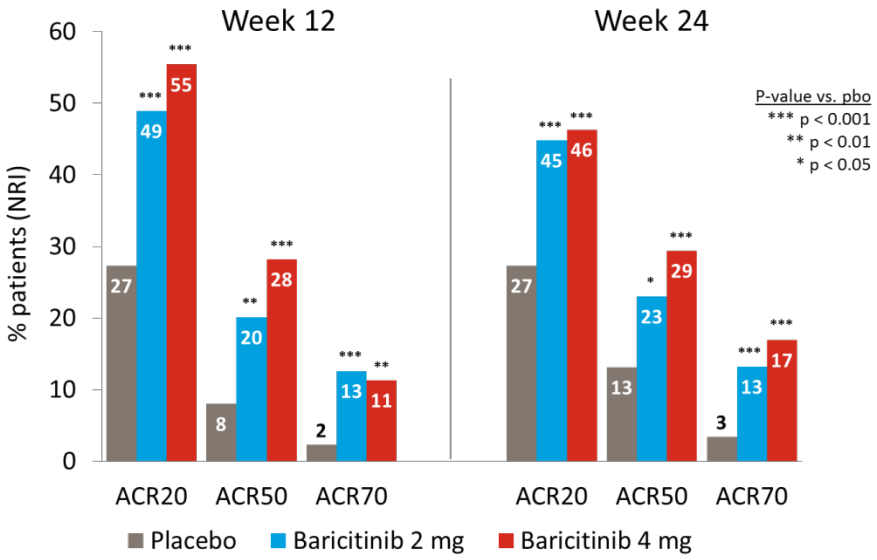


Figure 20. SDAI remission response rates Study JADW

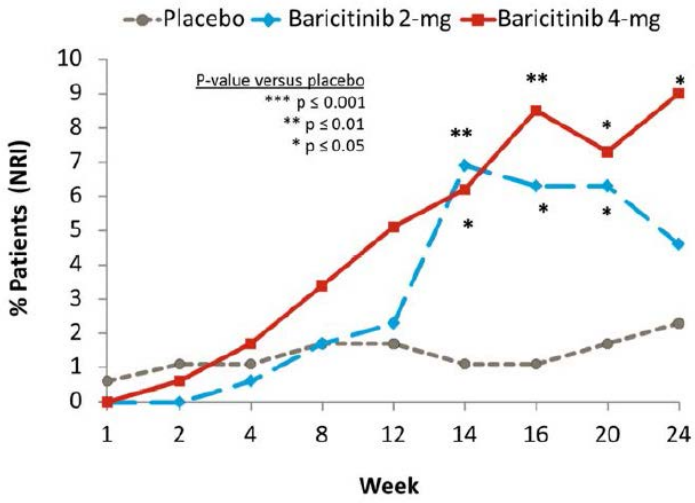


Table 25. DAS28-hsCRP < 3.2 (Low Disease Activity); main trials: primary time points

	JADZ (Week 24)			JADV (Week 12)			JADX (Week 12)			JADW (Week 12)		
	MTX (N=210)	BARI 4-mg +MTX (N=215)	BARI 4-mg (N=159)	PBO (N=488)	BARI 4-mg (N=487)	ADA (N=330)	PBO (N=228)	BARI 2-mg (N=229)	BARI 4-mg (N=227)	PBO (N=176)	BARI 2-mg (N=174)	BARI 4-mg (N=177)
DAS28-hsCRP <=3.2												
N-obs	210	215	159	488	487	330	228	229	227	176	174	177
Response, NRI, n(%)	80 (38.1)	129 (60.0)	91 (57.2)	67 (13.7)	214 (43.9)	116 (35.2)	39 (17.1)	82 (35.8)	89 (39.2)	16 (9.1)	42 (24.1)	56 (31.6)
Difference (%)		21.9	19.1		30.2	21.4		18.7	22.1		15.0	22.5
95% CI (a)		(12.6, 31.2)	(9.0, 29.3)		(24.9, 35.6)	(15.4, 27.4)		(10.8, 26.6)	(14.1, 30.1)		(7.4, 22.7)	(14.5, 30.6)
Odds ratio		2.5	2.2		5.2	3.5		2.8	3.3		3.3	4.8
95% CI (b)		(1.7, 3.7)	(1.4, 3.4)		(3.8, 7.2)	(2.5, 5.0)		(1.8, 4.3)	(2.1, 5.1)		(1.8, 6.2)	(2.6, 8.9)
P-value (b)		0.001	0.001		0.001	0.001		0.001	0.001		0.001	0.001

Table 26. DAS28-hsCRP < 2.6 (remission); main trials, main trials: primary time points

	JADZ (Week 24)			JADV (Week 12)			JADX (Week 12)			JADW (Week 12)		
	MTX (N=210)	BARI 4-mg +MTX (N=215)	BARI 4-mg (N=159)	PBO (N=488)	BARI 4-mg (N=487)	ADA (N=330)	PBO (N=228)	BARI 2-mg (N=229)	BARI 4-mg (N=227)	PBO (N=176)	BARI 2-mg (N=174)	BARI 4-mg (N=177)
DAS28-hsCRP <2.6												
N-obs	210	215	159	488	487	330	228	229	227	176	174	177
Response, NRI, n(%)	50 (23.8)	87 (40.5)	64 (40.3)	21 (4.3)	119 (24.4)	63 (19.1)	20 (8.8)	59 (25.8)	58 (25.6)	7 (4.0)	19 (10.9)	29 (16.4)
Difference (%)		16.7	16.4		20.1	14.8		17.0	16.8		6.9	12.4
95% CI (a)		(7.9, 25.4)	(6.9, 26.0)		(15.9, 24.4)	(10.2, 19.4)		(10.2, 23.7)	(10.0, 23.5)		(1.5, 12.4)	(6.2, 18.6)
Odds ratio		2.2	2.2		7.6	5.5		3.7	3.7		-	-
95% CI (b)		(1.5, 3.4)	(1.4, 3.5)		(4.7, 12.4)	(3.3, 9.3)		(2.1, 6.4)	(2.1, 6.5)		-	-
P-value (b)		0.001	0.001		0.001	0.001		0.001	0.001		0.015	0.001

Table 27. Boolean remission

	JADZ (Week 24)			JADV (Week 12)			JADX (Week 12)			JADW (Week 12)		
	MTX (N=210)	BARI 4-mg +MTX (N=215)	BARI 4-mg (N=159)	PBO (N=488)	BARI 4-mg (N=487)	ADA (N=330)	PBO (N=228)	BARI 2-mg (N=229)	BARI 4-mg (N=227)	PBO (N=176)	BARI 2-mg (N=174)	BARI 4-mg (N=177)
Boolean Remission												
N-obs	210	215	159	488	487	330	228	229	227	176	174	177
Response, NRI, n(%)	18 (8.6)	35 (16.3)	30 (18.9)	5 (1.0)	35 (7.2)	17 (5.2)	1 (0.4)	16 (7.0)	15 (6.6)	4 (2.3)	4 (2.3)	6 (3.4)
Difference (%)		7.7	10.3		6.2	4.1		6.5	6.2		0.0	1.1
95% CI (a)		(1.5, 13.9)	(3.1, 17.5)		(3.7, 8.6)	(1.6, 6.7)		(3.1, 10.0)	(2.8, 9.5)		(-3.1, 3.2)	(-2.3, 4.6)
Odds ratio		2.1	2.5		-	-		-	-		-	-
95% CI (b)		(1.1, 3.9)	(1.3, 4.8)		-	-		-	-		-	-
P-value (b)		0.017	0.005		0.001	0.001		0.001	0.001		1.000	0.751

Table 28. CDAI Low Disease Activity/Remission; main trials, primary time points

	JADZ (Week 24)			JADV (Week 12)			JADX (Week 12)			JADW (Week 12)		
	MTX (N=210)	BARI 4-mg +MTX (N=215)	BARI 4-mg (N=159)	PBO (N=488)	BARI 4-mg (N=487)	ADA (N=330)	PBO (N=228)	BARI 2-mg (N=229)	BARI 4-mg (N=227)	PBO (N=176)	BARI 2-mg (N=174)	BARI 4-mg (N=177)
CDAI <=10												
N-obs	210	215	159	488	487	330	228	229	227	176	174	177
Response, NRI, n(%)	81 (38.6)	127 (59.1)	95 (59.7)	83 (17.0)	196 (40.2)	108 (32.7)	47 (20.6)	79 (34.5)	79 (34.8)	19 (10.8)	41 (23.6)	49 (27.7)
Difference (%)		20.5	21.2		23.2	15.7		13.9	14.2		12.8	16.9
95% CI (a)		(11.2, 29.8)	(11.1, 31.2)		(17.8, 28.7)	(9.7, 21.8)		(5.8, 22.0)	(6.1, 22.3)		(5.0, 20.6)	(8.9, 24.9)
Odds ratio		2.37	2.45		3.42	2.47		2.05	2.13		2.7	3.3
95% CI (b)		(1.59, 3.52)	(1.59, 3.76)		(2.52, 4.63)	(1.76, 3.45)		(1.33, 3.14)	(1.39, 3.28)		(1.5, 4.9)	(1.8, 5.9)
P-value (b)		0.001	0.001		0.001	0.001		0.002	0.001		0.002	0.001
CDAI <=2.8												
N-obs	210	215	159	488	487	330	228	229	227	176	174	177
Response, NRI, n(%)	23 (11.0)	48 (22.3)	34 (21.4)	11 (2.3)	41 (8.4)	22 (6.7)	4 (1.8)	23 (10.0)	21 (9.3)	3 (1.7)	5 (2.9)	10 (5.6)
Difference (%)		11.4	10.4		6.2	4.4		8.3	7.5		1.2	3.9
95% CI (a)		(4.4, 18.4)	(2.8, 18.1)		(3.4, 9.0)	(1.4, 7.4)		(4.0, 12.5)	(3.4, 11.6)		(-2.0, 4.3)	(0.0, 7.8)
Odds ratio		2.41	2.28		-	-		-	-		-	-
95% CI (b)		(1.40, 4.16)	(1.27, 4.09)		-	-		-	-		-	-
P-value (b)		0.002	0.006		0.001	0.004		0.001	0.001		0.501	0.087

Table 29. HAQ-DI improvement >=0.3 from baseline responders (function): main trials, primary time points

	JADZ (Week 24)			JADV (Week 12)			JADX (Week 12)			JADW (Week 12)		
	MTX (N=210)	BARI 4-mg +MTX (N=215)	BARI 4-mg (N=159)	PBO (N=488)	BARI 4-mg (N=487)	ADA (N=330)	PBO (N=228)	BARI 2-mg (N=229)	BARI 4-mg (N=227)	PBO (N=176)	BARI 2-mg (N=174)	BARI 4-mg (N=177)
HAQ-DI MCID >=0.3												
N-obs	210	215	159	488	487	330	228	229	227	176	174	177
Response, NRI, n(%)	138 (65.7)	160 (74.4)	123 (77.4)	225 (46.1)	331 (68.0)	210 (63.6)	100 (43.9)	138 (60.3)	127 (55.9)	61 (34.7)	83 (47.7)	95 (53.7)
Difference (%)		8.7	11.6		21.9	17.5		16.4	12.1		13.0	19.0
95% CI (a)		(0.0, 17.4)	(2.5, 20.8)		(15.8, 27.9)	(10.7, 24.3)		(7.4, 25.4)	(3.0, 21.2)		(2.8, 23.3)	(8.8, 29.2)
Odds ratio		1.5	1.8		2.5	2.1		2.0	1.7		1.8	2.2
95% CI (b)		(1.0, 2.3)	(1.1, 2.8)		(1.9, 3.3)	(1.6, 2.8)		(1.4, 2.9)	(1.2, 2.4)		(1.1, 2.8)	(1.4, 3.4)
P-value (b)		0.060	0.018		0.001	0.001		0.001	0.007		0.011	0.001

Table 30. Radiographic outcomes of the pivotal studies

Study	**JADZ** MTX-naïve patients			**JADV** MTX-IR patients			**JADX** cDMARD-IR patients		
Treatment group	MTX	BARI 4 mg	BARI 4 mg + MTX	PBO[a]	BAri 4 mg	ADA 40 mg Q2W	PBO	BARI 2 mg	BARI 4 mg
N	210	159	215	488	487	330	228	229	227
Modified Total Sharp Score, mean change from baseline:									
Week 24	0.61	0.39	0.29*	0.90	0.41***	0.33***	0.70	0.33*	0.15**
Week 52	1.02	0.80	0.40**	1.80	0.71***	0.60***	NA	NA	NA
Erosion Score, Mean change from baseline:									
Week 24	0.47	0.33	0.26*	0.61	0.29***	0.24***	0.47	0.30	0.11**
Week 52	0.81	0.55	0.34**	1.23	0.51***	0.42***	NA	NA	NA
Joint Space Narrowing Score, mean change from baseline:									
Week 24	0.14	0.06	0.03	0.29	0.12**	0.10**	0.23	0.03	0.04
Week 52	0.21	0.25	0.06	0.58	0.21	0.19			
Proportion of patients with no radiographic progression[b]:									
Week 24	68 %	76 %	81 %**	70 %	81 %***	83 %***	74 %	72 %*	80 %**
Week 52	66 %	69 %	80 %**	70 %	79 %**	81 %**	NA	NA	NA

Abbreviations: ADA = adalimumab; MTX = methotrexate; NA= not available OLU = Olumiant; PBO = Placebo
[a] Placebo rates at week 52 derived using linear extrapolation, [b] No progression defined as mTSS change ≤ 0;

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for study JADZ); † p ≤ 0.05; †† p ≤ 0.01; ††† p ≤ 0.001 vs. adalimumab

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31. Summary of efficacy for trial JADZ; cDMARD-naïve RA patients (first line)

Title: A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had Limited or No Treatment with Disease-Modifying Anti-rheumatic Drugs				
Study identifier	**Study I4V-MC-JADZ**			
Design	52-week, multicentre, randomised, double-blind, active-controlled, parallel-group, study examining efficacy and safety in 588 patients with moderate-severe active early RA, naive to cDMARD or biologic therapy.			
	Duration of double-blind, active-controlled period:	Part A: 52 weeks		
Hypothesis	Non-inferiority, margin 12%			
Treatment groups	Baricitinib monotherapy	Baricitinib 4-mg once daily; 52 weeks; ITT 160		
	MTX monotherapy	MTX 20-mg once weekly; 52 weeks; ITT 213		
	Baricitinib plus MTX	Baricitinib 4-mg once daily plus MTX 20-mg once weekly; 52 weeks; ITT 215 patients		
Endpoints and definitions	Primary endpoint	ACR20 response rate at Week 24		
	Major secondary endpoints	ACR20, HAQ-DI change from baseline, DAS28-hsCRP change from baseline, SDAI ≤3.3, and mTSS change from baseline at Week 24.		
Database lock	Final database lock: 29 September 2015			
Results and Analysis: ACR20				
Analysis description	**Primary Analysis**: ACR20 (NRI), non-inferiority **Major Secondary Analyses**: ACR20 (NRI), superiority			
Analysis population and time point description	Week 24 using the mITT analysis set.			
Descriptive statistics and estimated variability	Treatment group	MTX monotherapy	BARI monotherapy	BARI plus MTX
	N	210	159	215
	ACR20 – n (%)	130 (61.9)	122 (76.7)	168 (78.1)
Effect estimate per comparison	Primary endpoint	Comparison groups		BARI monotherapy vs MTX monotherapy
		Difference in response rate (95% CI)		14.8 (5.5, 24.1)
		OR (95% CI)		2.0 (1.3, 3.2)

		P-value (non-inferiority)		0.001
	Major secondary endpoint	Comparison groups		BARI monotherapy vs MTX monotherapy
		Difference in response rate (95% CI)		14.8 (5.5, 24.1)
		OR (95% CI)		2.0 (1.3, 3.2)
		P-value (superiority)		0.003
	Major secondary endpoint	Comparison groups		BARI + MTX vs MTX monotherapy
		Difference in response rate (95% CI)		16.2 (7.7, 24.8)
		OR (95% CI)		2.2 (1.4, 3.4)
		P-value		0.001
Analysis description	**Major Secondary Analysis**: **HAQ-DI change from baseline (mBOCF)**			
Analysis population and time point description	Week 24 using the mITT analysis set.			
Descriptive statistics and estimated variability	Treatment group	MTX monotherapy	BARI monotherapy	BARI + MTX
	N	210	159	215
	Δ HAQ-DI –LSM (95% CI)	-0.72 (-0.80, -0.63)	-1.00 (-1.10, -0.91)	-0.95 (-1.03, -0.87)
	SE	0.043	0.049	0.043
Effect estimate per comparison	Major secondary endpoint	Comparison groups		BARI monotherapy vs MTX monotherapy
		LSMD in Δ from baseline (95% CI)		-0.29 (-0.41, -0.16)
		P-value		0.001
	Major secondary endpoint	Comparison groups		BARI + MTX vs MTX monotherapy
		LSMD in Δ from baseline (95% CI)		-0.23 (-0.35, -0.12)
		P-value		0.001
Analysis description	**Major Secondary Analysis**: **DAS28-hsCRP change from baseline (mBOCF)**			
Analysis population and time point description	Week 24 using the mITT analysis set.			
Descriptive statistics and estimated variability	Treatment group	MTX monotherapy	baricitinib monotherapy	baricitinib plus MTX
	N	210	159	215
	ΔDAS28-hsCRP LSM (95% CI)	-2.06 (-2.26, -1.86)	-2.75 (-2.97, -2.52)	-2.84 (-3.03, -2.64)
	SE	0.100	0.114	0.099
Effect estimate per comparison	Major secondary endpoint	Comparison groups		baricitinib monotherapy vs MTX monotherapy
		LSMD in Δ from baseline (95% CI)		-0.69 (-0.98, -0.40)
		P-value		0.001
	Major secondary endpoint	Comparison groups		baricitinib plus MTX vs MTX monotherapy

		LSMD in Δ from baseline (95% CI)		-0.78 (-1.05, -0.51)
		p-value		0.001
Analysis description	**Major Secondary Analysis**: Remission according SDAI ≤3.3 (NRI),			
Analysis population and time point description	Week 24 using the mITT analysis set.			
Descriptive statistics and estimated variability	Treatment group	MTX monotherapy	baricitinib monotherapy	baricitinib plus MTX
	N	210	159	215
	SDAI ≤3.3 response rate - n (%)	22 (10.5)	35 (22.0)	49 (22.8)
Effect estimate per comparison	Major secondary endpoint	Comparison groups		baricitinib monotherapy vs MTX monotherapy
		Difference in response rate (95% CI)		11.5 (3.9, 19.2)
		OR (95% CI)		2.5 (1.4, 4.4)
		P-value		0.003
	Major secondary endpoint	Comparison groups		baricitinib plus MTX vs MTX monotherapy
		Difference in response rate (95% CI)		12.3 (5.3, 19.3)
		OR (95% CI)		2.6 (1.5, 4.5)
		p-value		0.001
Analysis description	**Major Secondary Analysis**: **mTSS change from baseline (linear extrapolation)**			
Analysis population and time point description	Week 24 using the mITT analysis set.			
Descriptive statistics and estimated variability	Treatment group	MTX monotherapy	BARI monotherapy	BARI + MTX
	N	210	159	215
	ΔmTSS - LSM (95% CI)	0.61 (0.40, 0.82)	0.39 (0.16, 0.63)	0.29 (0.09, 0.49)
	SE	0.11	0.12	0.10
Effect estimate per comparison	Major secondary endpoint	Comparison groups		BARI monotherapy vs MTX monotherapy
		LSMD in Δ from baseline (95% CI)		-0.22 (-0.52, 0.08)
		p-value		0.158
	Major secondary endpoint - ΔmTSS	Comparison groups		baricitinib plus MTX vs MTX monotherapy
		LSMD in Δ from baseline (95% CI)		-0.32 (-0.60, -0.04)
		p-value		0.026

Table 32. Summary of efficacy for trial JADV; MTX-IR patients (2nd line)

Title: A Randomized, Double-Blind, Placebo- and Active-Controlled, Phase 3 Study Evaluating the Efficacy and Safety of Baricitinib in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate Therapy

Study identifier	**Study I4V-MC-JADV**			
Design	52-week, Phase 3, multicentre, randomised, double-blind, double-dummy, placebo- and active-controlled, parallel-group, study examining efficacy and safety in 1307 patients with moderately to severely active RA despite treatment with MTX (i.e., who had an inadequate response to MTX and who had never been treated with a bDMARD) and evidence of bone/joint erosion.			
	Duration of double-blind, placebo- and active-controlled period: Duration of double-blind, active-controlled period: Duration of post-treatment follow-up period:	Part A: 24 weeks Part B: 28 weeks Part C: 28 days		
Hypothesis	Superiority			
Treatment groups	BARI 4-mg once-daily	4-mg baricitinib QD, 52 weeks, 488 patients randomised		
	placebo	placebo, 24 weeks, 489 patients randomised (switched to baricitinib 4-mg after 24 weeks)		
	40-mg adalimumab (ADA) administered subcutaneously every 2 weeks	40-mg adalimumab Q2W, 52 weeks, 330 patients randomised.		
Endpoints and definitions	Primary endpoint	Baricitinib versus placebo based on ACR20 response at Week 12		
	Major secondary endpoints	ACR20 baricitinib versus adalimumab Noninferiority comparison at Week 12 (NI margin 12%); mTSS change from baseline at Week 24; HAQ-DI change from baseline at Week 12; DAS28-hsCRP change from baseline at Week 12 (vs placebo and vs ADA); SDAI ≤3.3 at Week 12; Duration of Morning Joint Stiffness (ePRO Diary) at Week 12; Severity of Morning Joint Stiffness NRS (ePRO Diary) at Week 12; Worst Tiredness NRS (ePRO Diary) at Week 12; Worst Joint Pain NRS (ePRO Diary) at Week 12.		
Database lock	Final database lock: 02 October 2015			
Results and Analysis: ACR20				
Analysis description	**Primary Analysis**: ACR20 (NRI) BARI 4-mg vs placebo **Major Secondary Analyses**: ACR20 (NRI) BARI 4-mg vs ADA			
Analysis population and time point description	Week 12 (using NRI) for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	BARI 4 mg	ADA
	N	488	487	330
	ACR20 – n (%)	196 (40.2)	339 (69.6)	202 (61.2)
Effect estimate per comparison	Primary endpoint	Comparison groups		BARI 4-mg vs placebo
		Difference in response rate (95% CI)		29.4 (23.5, 35.4)
		OR (95% CI)		3.6 (2.7, 4.7)
		p-value		0.001
	Major secondary	Comparison groups		BARI 4-mg vs ADA

	endpoint	Difference in response rate (95% CI)	8.4 (1.7, 15.1)	
		OR (95% CI)	1.5 (1.1, 2.0)	
		p-value	0.014	
Analysis description	**Major Secondary Analyses**: **mTSS change from baseline (linear extrapolation)**			
Analysis population and time point description	Week 24 using the mITT analysis set.			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 4-mg	adalimumab
	N	488	487	330
	ΔmTSS - LSM (95% CI)	0.90 (0.70, 1.09)	0.41 (0.22, 0.60)	0.33 (0.11, 0.56)
	SE	0.10	0.10	0.11
Effect estimate per comparison	Major secondary endpoint	Comparison groups	baricitinib 4-mg vs placebo	
		LSMD in Δ from baseline (95% CI)	-0.49 (-0.73, -0.25)	
		P-value	0.001	
Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 4-mg	adalimumab
	N	488	487	330
	Δ HAQ-DI - LSM (95% CI)	-0.34 (-0.39, -0.29)	-0.65 (-0.70, -0.60)	-0.55 (-0.61, -0.49)
	SE	0.026	0.026	0.030
Effect estimate per comparison	Major secondary endpoint	Comparison groups	baricitinib 4-mg vs placebo	
		LSMD in Δ from baseline (95% CI)	-0.31 (-0.38, -0.25)	
		P-value	0.001	
Analysis description	**Major Secondary Analyses**: **DAS28-hsCRP change from baseline (mBOCF)**			
Analysis population and time point description	Week 12 for the mITT population			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 4-mg	adalimumab
	N	488	487	330
	Δ DAS28-hsCRP - LSM (95% CI)	-0.96 (-1.08, -0.85)	-2.19 (-2.30, -2.08)	-1.91 (-2.04, -1.78)
	SE	0.058	0.057	0.067
Effect estimate per comparison	Major secondary endpoint	Comparison groups	baricitinib 4-mg vs placebo	
		LSMD in Δ from baseline (95% CI)	-1.23 (-1.37, -1.09)	
		P-value	0.001	
	Major secondary	Comparison groups	baricitinib 4-mg vs adalimumab	

	endpoint	LSMD in Δ from baseline (95% CI)	-0.28 (-0.44, -0.12)	
		P-value	0.001	
Analysis description	**Major Secondary Analyses**: **Remission by SDAI ≤3.3 (NRI)**			
Analysis population and time point description	Comparison between the baricitinib and placebo treatment groups in the SDAI ≤3.3 response rate at Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 4-mg	adalimumab
	N	488	487	330
	SDAI ≤3.3 – n (%)	9 (1.8)	41 (8.4)	24 (7.3)
Effect estimate per comparison	Major Secondary endpoint	Comparison groups	baricitinib 4-mg vs placebo	
		Difference in response rate [95% CI]	6.6 (3.8, 9.3)	
		OR [95% CI]	-	
		P-value	0.001	

Table 33. Summary of efficacy for trial JADX; cDMARD irresponsive/intolerant patients (2nd line)

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Inadequate Response to Conventional Disease-Modifying Antirheumatic Drugs with Moderately to Severely Active Rheumatoid Arthritis		
Study identifier	**Study I4V-MC-JADX**	
Design	24-week, Phase 3, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group, study examining efficacy and safety in patients with moderately to severely active RA despite previous or current treatment with cDMARDs (cDMARD-IR [inadequate response] patients) and who had never been treated with a biologic DMARD	
	Duration of double-blind, placebo-controlled period: Duration of posttreatment follow-up period:	Part A: 24 weeks Part B: 28 days
Hypothesis	Superiority	
Treatment groups	BARI 4 mg	4 mg baricitinib QD for 24 weeks (n= 227)
	BARI 4 mg	2 mg baricitinib QD for 24 weeks (n= 229)
	placebo	Placebo for 24 weeks (n=228)
Endpoints and definitions	Primary endpoint (BARI 4 mg vs placebo)	Proportion of patients who achieved ACR20 at Week 12
	Major secondary endpoints (BARI 2 and 4 mg vs placebo)	ACR20 (baricitinib 2-mg vs placebo); HAQ-DI change from baseline; DAS28-hsCRP change from baseline; SDAI ≤3.3; Duration of Morning Joint Stiffness; Severity of Morning Joint Stiffness NRS; Worst Tiredness NRS; Worst Joint Pain NRS at Week 12
Database lock	27 January 2015	
Analysis description	Primary Analysis: ACR20 (NRI) Major secondary endpoint analysis: ACR20 (NRI)	

Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 2-mg	baricitinib 4-mg
	N	228	229	227
	ACR20 – n (%)	90 (39.5)	151 (65.9)	140 (61.7)
Effect estimate per comparison	Primary endpoint	Comparison groups		baricitinib 4-mg vs placebo
		Difference in response rate (95% CI)		22.2 (13.2, 31.2)
		OR (95% CI)		2.5 (1.7, 3.7)
		P-value		0.001
	Major secondary endpoint	Comparison groups		baricitinib 2-mg vs placebo
		Difference in response rate (95% CI)		26.5 (17.6, 35.3)
		OR (95% CI)		3.0 (2.0, 4.4)
		P-value		0.001
Analysis description	**Major Secondary Analyses**: **HAQ-DI change from baseline (mBOCF)**			
Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 2-mg	baricitinib 4-mg
	N	228	229	227
	ΔHAQ-DI - LSM (95% CI)	-0.34 (-0.41, -0.26)	-0.54 (-0.62, -0.47)	-0.53 (-0.61, -0.46)
	SE	0.037	0.036	0.037
Effect estimate per comparison	Major secondary endpoint	Comparison groups		baricitinib 4-mg vs placebo
		LSMD in Δ from baseline (95% CI)		-0.20 (-0.30, -0.10)
		P-value		0.001
	Major secondary endpoint	Comparison groups		baricitinib 2-mg vs placebo
		LSMD in Δ from baseline (95% CI)		-0.21 (-0.30, -0.11)
		P-value		0.001
Analysis description	**Major Secondary Analyses**: **DAS28-hsCRP change from baseline (mBOCF)**			
Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 2-mg	baricitinib 4-mg
	N	228	229	227
	ΔDAS28-hsCRP - LSM (95% CI)	-1.08 (-1.25, -0.91)	-1.83 (-1.99, -1.66)	-1.92 (-2.09, -1.75)
	SE	0.086	0.084	0.086
Effect estimate per comparison	Major secondary	Comparison groups		baricitinib 4-mg vs placebo

	endpoint	LSM Difference (95% CI)		-0.84 (-1.07, -0.62)
		P-value		0.001
	Major secondary endpoint	Comparison groups		baricitinib 2-mg vs placebo
		LSM Difference (95% CI)		-0.75 (-0.97, -0.53)
		P-value		0.001
Analysis description	**Major Secondary Analyses**: **Remission by SDAI ≤3.3 response rate (NRI)**			
Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	baricitinib 2-mg	baricitinib 4-mg
	N	228	229	227
	SDAI ≤3.3: n (%)	2 (0.9)	21 (9.2)	20 (8.8)

ePRO = electronic patient-reported outcome, LSM = least squares mean; LSMD = least squares mean difference; mBOCF = modified baseline observation carried forward ; mITT = modified intent to treat (defined as randomised and received at least one study drug tablet); NRI = non-responder imputation; NRS = numeric rating scale

Table 34. Summary of efficacy for trial JADW; bDMARD-IR patients (3rd line)

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Evaluating the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Tumor Necrosis Factor Inhibitors		
Study identifier	**Study I4V-MC-JADW**	
Design	24-week, Phase 3, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group, study examining efficacy and safety in patients with moderately to severely active RA despite past treatment with one or more biologic TNF inhibitors (TNF-IR [inadequate response] patients).	
	Duration of double-blind, placebo-controlled period Duration of post-treatment follow-up period	Part A: 24 weeks Part B: 28 days
Hypothesis	Superiority	
Treatment groups	4-mg BARI	BARI 4 mg QD for 24 weeks (n=177)
	2-mg BARI	2 mg BARI QD for 24 weeks (n= 174)
	Placebo	Placebo for 24 weeks (n=176)
Endpoints and definitions	Primary endpoint (BARI 4-mg vs placebo)	Proportion of patients who achieved ACR20 at Week 12
	Major secondary endpoints (BARI 2 mg and BARI 4 mg vs placebo)	ACR20 (BARI 2 mg vs placebo); HAQ-DI change from baseline; DAS28-hsCRP change from baseline; SDAI ≤3.3 response rate at Week 12
Database lock	12 November 2014	
Analysis description	**Primary Analysis: ACR20 (NRI), BARI 4 mg superiority versus placebo** **Major Secondary Analysis ACR20 (NRI): BARI 2 mg versus placebo**	

Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	BARI 2-mg	BARI 4-mg
	N	176	174	177
	ACR20 – n (%)	48 (27.3)	85 (48.9)	98 (55.4)
Effect estimate per comparison	Primary endpoint	Comparison groups		BARI 4-mg vs placebo
		Difference in response rate (95% CI)		28.1 (18.2, 37.9)
		OR (95% CI)		3.4 (2.2, 5.4)
		P-value		0.001
	Major secondary endpoint	Comparison groups		BARI 2-mg vs placebo
		Difference in response rate (95% CI)		21.6 (11.7, 31.5)
		OR (95% CI)		2.7 (1.7, 4.2)
		P-value		0.001
Analysis description	**Major Secondary Analyses**: **HAQ-DI change from baseline (mBOCF)**			
Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	BARI 2-mg	BARI 4-mg
	N	176	174	177
	ΔHAQ-DI - LSM (95% CI)	-0.17 (-0.26, -0.09)	-0.37 (-0.46, -0.29)	-0.40 (-0.48, -0.31)
	SE	0.04	0.04	0.04
Effect estimate per comparison	Major secondary endpoint	Comparison groups		BARI 4-mg vs placebo
		LSMD in Δ from baseline (95% CI)		-0.23 (-0.33, -0.13)
		P-value		0.001
	Major secondary endpoint	Comparison groups		BARI 2-mg vs placebo
		LSMD in Δ from baseline (95% CI)		-0.20 (-0.30, -0.10)
		P-value		0.001
Analysis description	**Major Secondary Analyses**: **DAS28-hsCRP change from baseline (mBOCF)**			
Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	BARI 2-mg	BARI 4-mg
	N	176	174	177
	ΔDAS28-hsCRP - LSM (95% CI)	-0.83 (-1.05, -0.61)	-1.49 (-1.71, -1.27)	-1.79 (-2.01, -1.56)
	SE	0.11	0.11	0.11
Effect estimate per comparison	Major secondary endpoint	Comparison groups		BARI 4-mg vs placebo
		LSM Difference (95% CI)		-0.95 (-1.22, -0.69)
		P-value		0.001
	Major secondary endpoint	Comparison groups		BARI 2-mg vs placebo

		LSM Difference (95% CI)		-0.66 (-0.93, -0.39)
		P-value		0.001
Analysis description	**Major Secondary Analyses**: **SDAI ≤3.3 (remission)**			
Analysis population and time point description	Week 12 for the mITT population.			
Descriptive statistics and estimated variability	Treatment group	placebo	BARI 2-mg	BARI 4-mg
	N	176	174	177
	SDAI ≤3.3 response rate – n (%)	3 (1.7)	4 (2.3)	9 (5.1)
Effect estimate per comparison	Major secondary endpoint	Comparison groups		BARI 4-mg vs placebo
		Difference in response rate (95% CI)		3.4 (-0.4, 7.1)
		OR (95% CI)		-
		P-value		0.140
	Major secondary endpoint	Comparison groups		BARI 2-mg vs placebo
		Difference in response rate (95% CI)		0.6 (-2.3, 3.5)
		OR (95% CI)		-
		P-value		0.723

Analysis performed across trials (pooled analyses and meta-analysis)

Subgroup analyses were performed for pooled analyses for the four main trials. No relevant trends were observed for gender, age groups, race, disease duration, and baseline disease activity (cut-off DAS28-hsCRP 5.1).

In a subgroup of elderly > 65 years of age, who were irresponsive to bDMARDs, showed an increased incidence of h. zoster in a dose dependent way (see Safety section below). In this special group, the possibility of dose reduction was explored. However, the response of to the 2 mg dose for endpoints of LDA and remission was reduced by 50% as compared to the 4 mg dose.

A lower response for patients with bodyweight > 100 kg (8.8% of the study population) and/or high BMI was observed, including LDA and HAQ-DI endpoints. E.g. the OR to obtain a Low Disease Activity (DAS28-CRP <3.2) response versus placebo was 6.56 for patients with low body weight (< 60 kg), 3.75 for patients with intermediate BW (≥60 and <100), and 2.32 for patients with high bodyweight (≥100 kg).

This can only partly be explained by a reduced plasma levels at higher bodyweight, since the reduction in plasma exposure were marginal in the heavy-weights. Also patients with a high bodyweight achieving the target PK levels still responded less than the general population. It was also noted that patients with a high body weight had higher disease activity at baseline. Considering the risks of higher baricitinib doses, and as lower plasma levels only explained to small extent the attenuated response in this subgroup, it was concluded that no dose adjustment are required for this population.

Furthermore, a lower treatment response was observed in patients who were sero-negative for both RF and ACPA –about 8% of the total population. This is in line with RA studies for other products.

Clinical studies in special populations

There were no dedicated dose response or phase III clinical trials in special populations

Supportive studies

All subjects finishing the main clinical trials could continue baricitinib treatment in the long-term extension Study JADY. In this study the possibility of a low 2 mg maintenance dose was explored in a subset of 293 patients, who achieved sustained Low Disease Activity after at least 15 months of treatment (randomised withdrawal).

After 12 weeks, 93% of patients continuing with 4 mg versus 84% of the patients stepping down to 2 mg, maintained Low Disease Activity level (p = 0.03). Maintenance of efficacy of the 4 mg dose was further established by the study.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In general, the study populations are considered representative for the target population of moderate-severe RA patients.

Two of the main studies were active-controlled: Study JADZ in naïve-patients (active control MTX), and Study JADY in patients irresponsive to MTX (active control adalimumab). Study JADX and JADW were placebo-controlled studies with baricitinib 2 and 4 mg as parallel arms.

General comments on the main studies (JADZ, JADY, JADX, JADW)

The primary endpoint, ACR20, representing a change from baseline of signs of symptoms of 20% or more, is considered a low target, taking in consideration that efficacious DMARDs are available. The placebo response was high for this endpoint, indicating it is less sensitive to distinct a treatment effect. A change of 20% may in fact be a small absolute effect in patients with moderate active disease state at baseline. The current draft EMA guideline proposed target disease activity endpoints such as remission and LDA, as primary endpoint, since the clinical relevance of these outcomes is clearer than relative changes from BL. Remission and LDA scores will therefore be taken into account in the B/R assessment. Since LDA and remission scores met their endpoints throughout the studies, no questions are raised regarding the choice of the primary endpoint.

It has been reported that for DMARDs targeting acute phase reactants, such as baricitinib, DAS28-CRP may overestimate clinical response, and that there may be silent residual inflammation in the joints even though CRP is low. In the analyses, also responder analyses by SDAI and CDAI scores were included, which are less influenced by CRP. In general, the conclusions for the DAS28-CRP outcomes of LDA (Low Disease Activity), were congruent with LDA estimates using SDAI/CDAI. However, DAS28 remission rates were indeed higher for DAS28-CRP, the SDAI (and Boolean remission by ACR-EULAR) was more conservative.

It is noted that a large number of outcomes were evaluated, which were either closely related or overlapping. E.g. remission was calculated by SDAI, CDAI, DAS28-ESR, DAS28-hsCRP, and according to ACR-EULAR Boolean score. It is therefore supported that multiplicity was addressed in the statistical analyses by following a pre-defined order of key-secondary (gated) endpoints and correction of the alpha.

Non Responder Imputation (NRI) was applied for missing data of responder outcomes, which is supported. BOCF was applied for key secondary continuous endpoints, which is in general considered sufficiently conservative.

The outcomes of the radiographic mTSS scores, however, were largely influenced by the used method of imputation. Linear extrapolation increased the mTSS (modified Total Sharp Score) in the placebo arm significantly more than the active treatments, thereby inflating the treatment effect. The secondary imputation by LOCF does not accurately reflect the natural course of decline, and may have been too conservative for estimating placebo-response. Post-hoc sensitivity analyses with multiple, imputation methods by the placebo-response supported the conclusions of the LOCF analyses, i.e. that the response to the 4 mg dose was more robust that the 2 mg dose.

Study JADZ

MTX monotherapy may not be considered as an optimal comparator for naïve patients. As MTX has to be gradually up titrated, it is recommended to commence MTX therapy together with other synthetic DMARDS or low dose corticosteroids, to achieve a more rapid onset of effect, according to EULAR treatment recommendations of 2013. This may favoured the baricitinib treatment effect.

No placebo was included in active-controlled Study JADZ, which hampers assessment of assay sensitivity. Assay sensitivity, however, could be considered as established since baricitinib was superior to the active control MTX monotherapy, which is considered as standard first-choice treatment option in RA.

Study JADV

The choice of the active comparator adalimumab in MTX-irresponsive patients, is considered adequate. The 52 weeks duration of the controlled phase provides sufficient insight in maintenance of efficacy.

Study JADW (patients with an inadequate response to biologic DMARDs)

As a general rule in RA studies, add-on studies are performed in patients failing on prior DMARDS, thereby continuing the prior treatments. In the study in bDMARD-IR patients (JADW), prior biologic DMARDs were discontinued. This is understood from a safety perspective, since the consequences of inhibiting multiple immune-modulatory pathways by a combination of baricitinib + bDMARDs may be serious. From a methodological perspective, it would have been preferred if prior bDMARDs were still continued in the placebo arm, as patients may remain partially responsive. Thus, the active treatment arms (baricitinib 2 and 4 mg) may have been favoured as compared to placebo by withdrawal of prior biological DMARDS. However, since the response to baricitinib was overall robust and clearly distinguished from placebo in a dose-dependent way, the treatment effect is considered relevant and not much inflated.

However, remission according to SDAI is a high hurdle target, with responder rate of less than 10% at active treatment across studies. Retrospectively, it may not have been a realistic goal for this population of patients irresponsive to one or multiple biologics, which is, in general, only prescribed after the patient failed on multiple synthetic DMARDs

Efficacy data and additional analyses

Efficacy has been robustly demonstrated to a clinically relevant extent, showing superiority of relevant outcomes, remission and LDA towards standard care of MTX or adalimumab. The primary endpoints were supported by remission or LDA responder outcomes, an improvement of physical functioning (HAQ-DI), fatigue, morning stiffness and diverse PRO and QOL scales, highlighting the consistency of the results.

Prevention of structural damage has been established as well. Maintenance of efficacy has been demonstrated in the 52-weeks active-controlled trials, and in the randomised withdrawal study JADY.

For Study JADZ, in DMARD-naïve patients, the primary response of ACR20 was 76.7% for baricitinib monotherapy, 78.1% for the combination, and 61.9% for MTX alone (BARI monotherapy vs MTX: difference 14.8% (95% CI 5.5, 24.1), BARI + MTX combination vs MTX alone: difference 16.2% (7.7, 24.8)). Remission (defined as DAS28-hsCRP<2.6) was achieved in 40.3% of the subjects treated with baricitinib monotherapy, 40.5% for the combination, and 23.8% for MTX alone (BARI monotherapy vs MTX: 16.4% (6.9, 26.0), BARI + MTX combination vs MTX: 16.7% (7.9, 25.4) , at Week 24). Also strict remission criteria according to ACR-EULAR (Boolean) were met for baricitinib+ MTX combination versus monotherapy (17% vs 11.4% MTX monotherapy, difference 9.5% (2.6, 16.4) at Week 52, though this was not formally met for baricitinib monotherapy. Physical function (HAQ-DI improvement of ≥0.3 points) was improved for baricitinib monotherapy (77.4%) and the combination with MTX (74.4%), versus MTX alone (65.7%) (difference BARI monotherapy vs. MTX: 11.6 (2.5, 20.8), BARI + MTX combination vs. MTX: 8.7 (0.0, 17.4)). Only for the combination therapy of baricitinib 4 mg + MTX, a statistically significant improvement was shown for the percentage of subjects without any radiographic progression from baseline after 52 weeks, in comparison to MTX monotherapy (80% vs. 66%, difference 14.1% (6.1, 22.0)). For baricitinib monotherapy, this was 69%.

In Study JADV, in patients irresponsive to MTX, ACR20 responder rates were 73.9% for baricitinib 4 mg, 66.4% for active comparator adalimumab, and 36.7% for placebo (week 24) (BARI vs Placebo difference: 37.2% (31.5, 43.0), BARI vs ADA: 7.6% (1.1, 14.0)). Whereas non-inferiority was aimed, superiority was obtained in favour of baricitinib. Also the Low Disease Activity responder rate (DAS28-hsCRP ≤ 3.2) of baricitinib of 55.6% was superior to the response obtained for adalimumab (48.2%), though to marginal extent (difference: 7.5% (0.55-14.4)). Physical function, i.e. the percentages of patients with a considerable HAQ-DI improvement of ≥0.3 points from baseline, was 66.7% for baricitinib, 59.7% for adalimumab, and 37.1% for placebo (BARI vs ADA: difference 7% (0.3, 13.8)). Non-inferiority was established between baricitinib and adalimumab regarding the percentage of responders without radiographic progression (week 52 difference -2.1% (-6.5, 2.3). Both baricitinib and adalimumab separated from placebo at Week 24 (81%, 83% and 70%, respectively), indicating assay sensitivity for this endpoint.

In the 24-weeks dose-finding study JADX in patients irresponsive or intolerant to cDMARDs, the 2 mg dose performed as well as the 4 mg dose regarding ACR outcomes and LDA or remission (e.g. LDA /remission rates according to DAS28-hsCRP were 46.3/30.6% for the 2 mg dose, 51.5/33.0% for the 4 mg dose, and 23.7/10.5% for placebo, all p-values < 0.001). In this short-term study, the 4 mg dose separated from placebo regarding the percentage of patients without structural bone damage over the observational period of 24 weeks (80% vs 74% for placebo, difference 6.0% (95% CI 0.1-13.9)) , whereas this was not achieved for the 2 mg dose.

A notable response was observed for baricitinib in patients who were irresponsive to one or multiple bDMARDs, even though it is an oral treatment. Primary ACR20 scores were similar between the two dosages tested. A higher response was obtained for the 4 mg dose than the 2 mg dose regarding more critical outcomes, like DAS28-hsCRP ≤ 3.2. Also outcomes that are not dependent on acute phase reactant CRP, such as CDAI, showed a robust effect in a dose dependent way. Furthermore, these endpoints of disease activity were supported by secondary outcomes like functional endpoints (HAQ-DI >=0.3). Subgroup analyses showed a relevant effect in patients irresponsive to multiple bDMARDs including a non-TNF-inhibitor drug.

Long-term efficacy data (Study JADY)

Dose finding

A 4 mg dose has been proposed as the standard dose, as at this dose level, a more robust response was shown regarding the prevention of structural bone damage in Study JADX, and higher remission rates were achieved for the 4 mg dose versus the 2 mg dose in the multi therapy resistant bDMARD-IR population (Study JADW).

The choice of 4 mg dose as standard is supported from a clinical efficacy perspective. From a safety perspective the low dose is recommended for vulnerable patients, such as very elderly, and patients with recurrent infections. This is discussed further in the Benefit-Risk section.

In sensitivity analyses, a diminished treatment effect of baricitinib was observed in heavy weight patients > 100 kg. However, dose adjustments are not foreseen. It is agreed not to titrate the dose over 4 mg in heavy weight, for safety reasons (e.g. anaemia was more common at dosages > 4 mg in the Phase II study). Moreover, it is generally known that patients with high bodyweight are less responsive to DMARDs, possibly because of role of adipose tissue on inflammatory reactants.

2.5.4. Conclusions on the clinical efficacy

Overall, efficacy has been established for baricitinib, at a clinically relevant effect size. Barcitinib was superior in comparison to active comparator MTX in the first-line treatment setting in naïve patients with moderate-severe RA, and in several aspects it was superior to adalimumab in patients irresponsive to MTX. Maintenance of efficacy has been shown. Baricitinib showed efficacy in patients who were irresponsive to multiple bDMARDs. The response to the 4 mg dose was overall more robust than to the 2 mg dose.

2.6. Clinical safety

Patient exposure

A total of 3464 patients were exposed to baricitinib in RA studies, representing 4214.1 patient-years of exposure (PYE); 2166 patients (62.5%) were exposed for ≥52 weeks, and 467 patients (13.5%) were exposed for ≥104 weeks.

An update of the safety data after the cut-off date of 15 August 2015 of the original dossier till 01 January 2016 was provided in response to Day 120 LoQ, extending the total data to 5134.4 PY of 3492 subjects.

Patients' characteristics

Demographics and disease stage are summarised in section 2.5.2 of this report.

Regarding co-morbidities, a DMARD-naïve early RA study population had less CV risk factors at baseline – such as diabetes, hyperlipidaemia and hypertension- than the more treatment experience study populations (see Table 35 below). Only patients with stable prior CV disorders were included.

Table 35. Co-morbidities at baseline of the main study populations

	Co-morbidities at Baseline			
	JADZ (N=584) MTX-naive	JADV (N=1305) MTX-IR	JADX (N=684) cDMARD-IR	JADW (N=527) TNF-IR

	1st line	2nd line	2nd line	3rd line
Diabetes mellitus	8.0	8.1	9.4	13.3
Cardiovascular disorders (Cardiac failure, Cardiomyopathy, Cerebro-vascular disease, Ischaemic heart disease)	3.4	4.1	6.3	5.3
hypertension	22.3	33.2	37.0	45.2
Hyperlipidemia	12.5	13.3	17.1	25.8
Statin use	7.2	8.5	9.9	18.2
Renal impairment	0	0	0.6	1.1

Adverse events

The treatment-emergent adverse events by MedDRA preferred term within system organ class of baricitinib and placebo up to week 24 are presented in table 36 below.

Table 36. Treatment-Emergent Adverse Events by MedDRA Preferred Term within System Organ Class of BARI 4-mg and Placebo up to Week 24 (most frequent preferred terms selected by CHMP)

System Organ Class Preferred Term	PBO (N=1070) (PYE=393.8) n (%) [PY]	BARI 4-mg (N=997) (PYE=409.4) n (%) [PY]
Patients with >= 1 TEAE	659 (61.6) [167.3]	695 (69.7) [169.8]
Blood and lymphatic system disorders	48 (4.5) [12.2]	54 (5.4) [13.2]
Cardiac Disorders	8 (0.7) [2.0]	13 (1.3) [3.2]
Vascular disorders	35 (3.3) [8.9]	39 (3.9) [9.5]
Congenital, familial and genetic disorders	0	1* (0.1) [0.2]
Ear and labyrinth disorders	15 (1.4) [3.8]	21 (2.1) [5.1]
Endocrine disorders	4 (0.4) [1.0]	2 (0.2) [0.5]
Eye disorders	31 (2.9) [7.9]	33 (3.3) [8.1]
Gastrointestinal disorders	146 (13.6) [37.1]	165 (16.5) [40.3]
General disorders and administration site conditions	71 (6.6) [18.0]	51 (5.1) [12.5]
Hepatobiliary disorders	12 (1.1) [3.0]	18 (1.8) [4.4]
Immune system disorders	8 (0.7) [2.0]	9 (0.9) [2.2]
Infections and infestations	299 (27.9) [75.9]	362 (36.3) [88.4]
Injury, poisoning and procedural complications	50 (4.7) [12.7]	63 (6.3) [15.4]
Investigations	81 (7.6) [20.6]	126 (12.6) [30.8]
Metabolism and nutrition disorders	65 (6.1) [16.5]	91 (9.1) [22.2]
Musculoskeletal and connective tissue disorders	147 (13.7) [37.3]	122 (12.2) [29.8]
Neoplasms benign, malignant and unspecified (incl cysts and polyps	7 (0.7) [1.8]	10 (1.0) [2.4]
Nervous system	77 (7.2) [19.6]	92 (9.2) [22.5]
Psychiatric disorders	31 (2.9) [7.9]	27 (2.7) [6.6]
Renal and urinary disorders	20 (1.9) [5.1]	26 (2.6) [6.4]
Reproductive system and breast disorders	10 (0.9) [2.5]	15 (1.5) [3.7]
Amenorrhoea	1 (0.1) [0.3]	5 (0.6) [1.5]
Respiratory, thoracic and mediastinal disorders	60 (5.6) [15.2]	79 (7.9) [19.3]
Skin and subcutaneous tissue disorders	68 (6.4) [17.3]	66 (6.6) [16.1]

*meningocele

Adverse events from the primary analyses (16 weeks) were screened for possible ADRs (adverse drug reactions) by the Applicant, using the following criteria:

1) Baricitinib 4-mg incidence ≥10%

2) A statistically significant positive dose relationship across the baricitinib treatment groups

3) Baricitinib 4-mg statistically significantly higher than placebo

4) The Mantel-Haenszel odds ratio is ≥2 for baricitinib 4-mg compared to placebo, and the baricitinib incidence is ≥1%

Using these criteria, and clinical medical judgment, the following events were classified as ADR and reported in section 4.8 of the SmPC: nausea, upper respiratory tract infections, herpes simplex, herpes zoster, acne, increased creatine phosphokinase, increased LDL cholesterol and triglycerides, increased liver function tests (AST, ALT), neutropenia and thrombocytosis (see table 37 below).

Table 37. Identified risks

	Trials Evaluating BARI 4 mg (6 Trials)		**Trials Evaluating BARI 2 mg and BARI 4 mg (4 Trials)**		
Preferred term	**Placebo+ cDMARDs n=1070 (%)**	**Baricitinib 4 mg+ cDMARDs n=997 (%)**	**Placebo+ cDMARDs n=551 (%)**	**Baricitinib 2 mg+ cDMARDs n=479 (%)**	**Baricitinib 4 mg+ cDMARDs n=479 (%)**
Adverse events					
Nausea	1.6	2.8	2.0	2.7	2.9
Upper respiratory tract infections[a]	11.7	14.7	11.4	16.3	17.3
Herpes simplex[b]	0.7	1.8	0.5	0.8	0.8
Herpes zoster	0.4	1.4	0.4	1.0	1.9
Acne	0	0.8	0	0.2	1.0
Laboratory Parametres[c]					
Creatine Phosphokinase >5 x ULN	0.3	0.8	0.6	0.8	1.5
LDL cholesterol ≥3.36 mmol/L	10.3	33.6	11.6	20.2	28.5
Triglycerides ≥5.65 mmol/L	0.5	0.4	0.8	0.9	0.2
ALT ≥3 x ULN	1.0	1.4	0.4	1.7	1.3
AST ≥3 x ULN	0.8	0.8	0.4	1.3	1.1
Neutropenia <1x109 cells/L	0	0.3	0	0.6	0.2
Thrombocytosis >600 x 10^9 cell/L	1.1	2.0	1.3	1.1	2.3

a Includes acute sinusitis, acute tonsillitis, chronic tonsillitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinobronchitis, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection.

b Includes eczema herpeticum, genital herpes, herpes simplex, ophthalmic herpes simplex, oral herpes.

c As assessed by measured values within the clinical trial database. Frequencies are based on shifts from pre-treatment to post-treatment (with number at risk as the denominator), except for ALT and AST for which frequencies are based on observed elevation during treatment.

The following adverse events of interest were pre-defined, based on previously reported events across RA studies for other DMARDs including JAK-inhibitors:

- infections (serious infections and opportunistic infections, including tuberculosis and herpes zoster)

- malignancies

- change in lipid levels

- major adverse cardiovascular events (MACE) and other cardiovascular events

- impairment in renal function

- potential for myelosuppression (including haematological abnormalities)

- elevation of liver enzymes

- gastrointestinal (GI) perforations

Infections

Through 24 weeks of treatment with data up to rescue, there was a statistically significant larger proportion of patients treated with BARI 4 mg compared to placebo with infections (36.3% vs. 27.9%, respectively, Odds Ratio 1.4 (95% CI 1.2-1.7), $p < 0.001$). There were no differences between BARI 4 mg and placebo in the proportion of patients with serious infections according to ICH criteria (1.5% vs 1.6%, respectively). The rate of infections moderately increased with the baricitinib dose (32.6% vs. 38.2% till Week 24, and 48.5% vs. 53.4% in the long-term extension phase of 52 weeks, for the 2 and 4 mg dose, respectively).

The overall incidence of infections of baricitinib exceeded the active comparators, i.e. MTX in Study JADZ in DMARD-naïve patients and adalimumab in MTX-IR patients in study JADV, to modest extent by a difference of 3-5%. The rate of infections was modestly increased for patients who were more heavily pre-treated with DMARDs and other immune-modulating drugs than naïve patients (see Table 38). This was observed both for baricitinib, as the comparators and placebo. The difference versus placebo was similar (about 8%) over the different study populations (DMARD-naïve, conventional DMARD-IR (second line), and biological DMARD-IR patients 'third' line).

At longer term follow-up, the incidence rate of (serious) infections stabilised and eventually decreased (see figure 15 below).

Figure 15. Incidence rate of serious infections by time periods for All BARI RA patients.

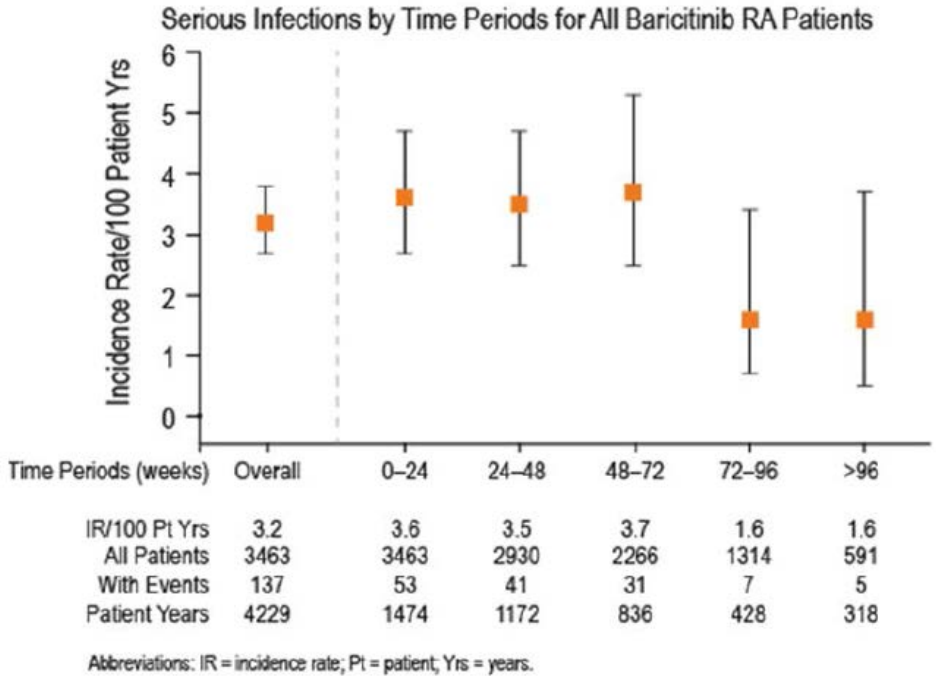


Table 38. Rate of infections (SIR) and herpes zoster (HZos) till Week 24 , for the three target populations

Population (study code)	Baricitinib 4 mg mono-therapy	Baricitinib 4 mg + MTX (or csDMARD)	Baricitinib 2 mg	Active comparator	Placebo + csDMARD
DMARD-naïve (JADZ), first-line	28.3 (2.5) HZ: 1.9%	34.4 (3.3) HZos:1.4	NA	27.6 (1.9) HZ:0.5 (Methotrexate)	NA
MTX-IR (JADV) Second line	NA	36.1 (1.4) HZos: 1.4	NA	33.3 (1.0) HZos:1.2 (Adalimumab)	27.5 (0.6) HZos : 0.4
cDMARD-IR (JADX) Second line	NA	42.3 (1.8) HZ:1.3	30.6 (0.9) HZ:1.7	NA	34.6 (1.8) HZos:0
bDMARD-IR (JADW) 'third'-line	NA	39.5 (3.4) HZos:4.0	43.7 (2.3) HZ:1.1	NA	31.3 (2.8) HZos: 1.1

csDMARD= conventional synthetic DMARD (including MTX), SIR=Serious Infection Rate according to ICH

Type of infections

The most commonly reported infections were upper respiratory tract infections, herpes zoster and herpes simplex.

Herpes zoster

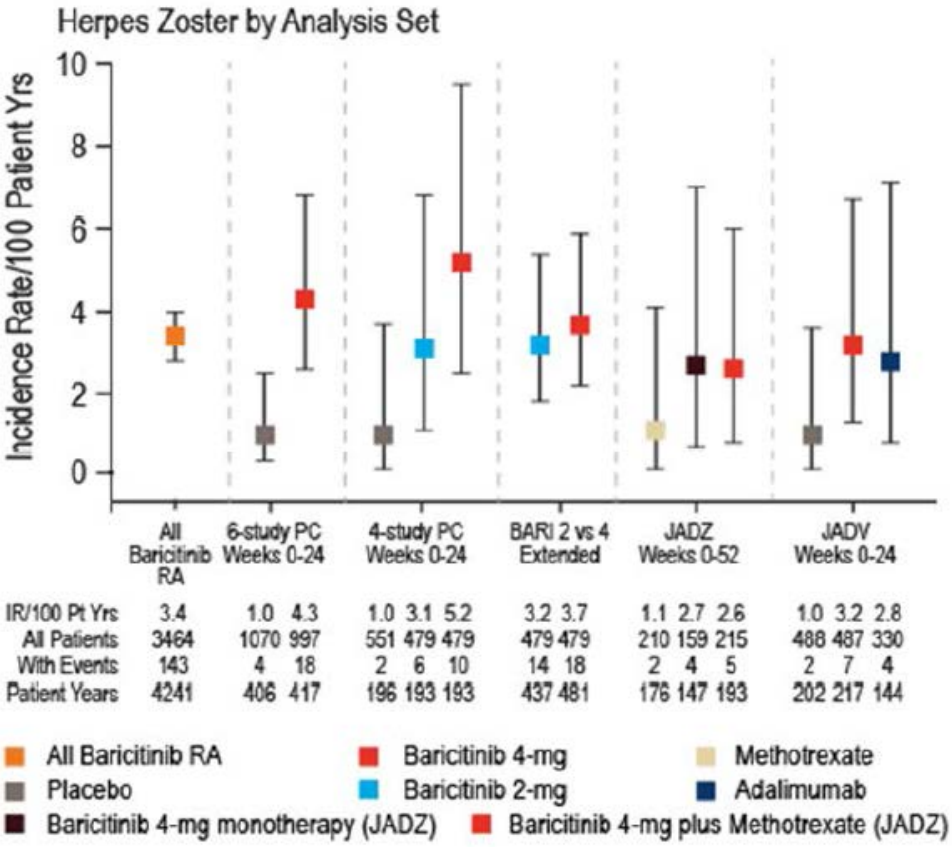
In the pooled analyses of placebo-controlled studies, the incidence of herpes zoster for baricitinib 4 mg versus placebo was 1.8% vs 0.4% till Week 24 (Odds ratio 4.59 (95% CI 1.5, 13.6). The incidence of herpes zoster increased with the dose (see figure 16). The rate of HZ infections remained stable for 72 weeks and decreased thereafter. As compared to historic controls of other DMARDs, the point estimate for the incidence rate of herpes zoster of 3.4 per 100 PY as observed for baricitinib, appeared lower as described previously for tofacitinib (4.4-5.4 per 100 py), though higher than e.g tocilizumab (2.4 per 100 py).

In DMARD-naïve subjects (Study JADZ), the risk of herpes zoster was overall low, but about twice as high for baricitinib as comparator MTX at Week 52 (MTX 1.0% [1.17 per 100 PY], BARI 4 mg: 2.5% [2.78], and BARI + MTX: 2.3% [2.65]). However, the incidence rate of herpes zoster of baricitinib 4 mg was more aligned to active-control adalimumab in the second line treatment setting; 2.3% [2.5 per 100 PY] and 1.5% [1.8] at Week 52, for BARI 4 mg and ADA, respectively.

More heavily pre-treated patients were more vulnerable. The highest incidence and background risk was observed in patients irresponsive to biologic DMARDS (Study JADW), especially at the 4 mg dose (4.0 % [9.55 per 100 py] at the BARI 4 mg dose, and 1.1% for 2 mg dose [2.86], which was the same as placebo (1.1% [3.04]).

Of 141 reported cases, complicated or disseminated events were reported in 5 cases: 2 associated with facial palsy and 3 considered disseminated based on the pattern of dermatome involvement. About 14% was reported as SAE.

Figure 16. Herpes zoster incidence rates in main baricitinib trials



Abbreviations: IR = incidence rate; PC = placebo controlled; Pt = patient; RA = rheumatoid arthritis; Yrs = years.

Subject were allowed and encouraged to receive zoster vaccination 4-6 weeks before randomisation, in accordance to international treatment guidelines (ACR and EULAR) on zoster vaccination in RA patients. The Incidence Rates (IR) for the patients immunised within 6 weeks of randomisation, the patients immunised longer than 6 weeks before randomisation, and non-immunised groups were 1.1, 2.8, and 3.2 per 100 patient-years, respectively. See Table 39 below.

Table 39. Treatment-emergent Herpes Zoster by Zoster immunisation status before study entry

All Treatment Periods
All BARI RA Analysis Set (Studies with Applicable Data: JADV/JADY, JADW/JADY, JADX/JADY, and JADZ/JADY)

	Patients with Zoster Immunization within 6 weeks before randomization	Patients with Zoster Immunization > 6 weeks before randomization	Patients with Zoster Immunization anytime before randomization	Patients without Zoster Immunization before randomization	All Patients
	(N=63)	(N=62)	(N=125)	(N=2765)	(N=2890)
	n (%)	n (%)	n (%)	n (%)	n (%)
	PYE IR	PYE IR	PYE IR	PYE IR	PYE IR
	[95% CI](a)	[95% CI](a)	[95% CI](a)	[95% CI](a)	[95% CI](a)
Total patients with >=1 Treatment Emergent Herpes Zoster	1 (1.6)	3 (4.8)	4 (3.2)	134 (4.8)	138 (4.8)
	88.8 [1.1]	106.0 [2.8]	194.8 [2.1]	4133.5 [3.2]	4328.4 [3.2]
	[0.0,6.3]	[0.6,8.3]	[0.6,5.3]	[2.7,3.8]	[2.7,3.8]

Other opportunistic infections

Beyond herpes zoster and tuberculosis, ten potential opportunistic infections were reported including wound infection with coccidioides species (1 event), oesophageal candidiasis (5 events), pneumocystis pneumonia (3 events) and blood beta-D-glucan increased (1 event). None of these cases could either be confirmed or were considered treatment related on review. The reported wound infection with coccidioides was considered a reporting error by the investigator. The case reports regarding –suspected- pneumocystis pneumonia came from Japanese sites, where beta-D-glucan values were routinely screened as a marker of invasive fungal infections.

In the RA Phase 3 studies, approximately 8% of randomized patients at baseline were diagnosed with latent TB. One TB case was reported in the placebo/active comparator controlled phase in Study JADX, for baricitinib 4 mg at Day 137. According to the Applicant, a protocol violation had occurred for the TB case under baricitinib treatment, as sscreening IGRA of this subject was indeterminate, but no repeat or latent TB X-ray was performed. Seven other cases were reported for baricitinib 4 mg in the uncontrolled extension phase, within the range of background risk.

All patients were receiving other concomitant DMARDs, and 4 were receiving concomitant corticosteroids. All cases occurred in area's where TB is endemic (Asia, South-Africa, Russia. Argentina,). The overall EAIR of tuberculosis in RA patients treated with baricitinib 4-mg once daily was 0.20 events/100PY, which was lower than compared to adalumimab active comparator in Study JADV (0.36 events/100 PY), and the expected background risk in background risks 0.64 events/100 PY in the total population

Patients with hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were also allowed to participate. When these cases were tested for HBV DNA, a similar incidence of cases with detectable DNA were reported for baricitinib and adalimumab (0.6% in 52 weeks for both active treatments), and no cases were reported for placebo (24 weeks). These cases were not considered as active hepatitis B infection as expression of HBV DNA was low.

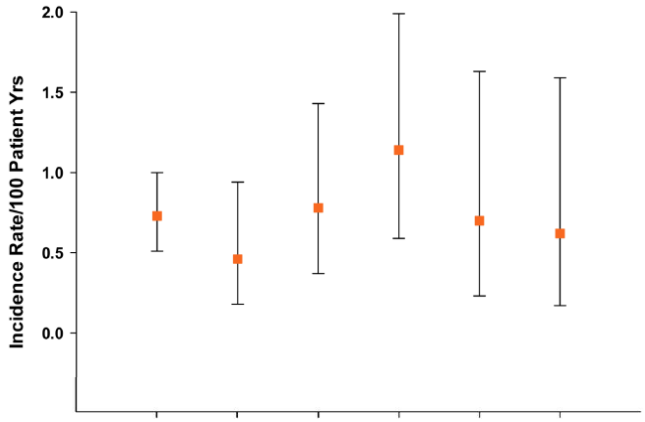
In addition, one case of CMV (Cytomegalovirus) infection and a single case of Epstein-Barr (EB) virus infection was reported. Infections were of mild-moderate severity.

Malignancies

For baricitinib (all doses, pooled dataset), the incidence rate of malignancies (*without* NMSC) was 38 cases and 0.73 per 100 py (95% CI 0.5, 1.0) (update 01-01-2016). There was no clear dose effect for baricitinib. For pooled data of the comparators placebo, MTX and adalimumab, the incidence rates for malignancies *without* NMSC were 0.18, 0.48, and 0 per 100 py, respectively (see Table 40). As the comparator groups were small and placebo was short, the incidence of malignancies in the comparator arms could not be reliably estimated.

At longer term follow-up, the incidence rates of malignancies w.o. NMSC gradually increased from 0.47 within the first 24 weeks, till 1.17 per 100 PY in the observational period of 48-72 weeks (figure 17). Thereafter, the incidence rates appear to stabilize, though this was difficult to establish since the confidence intervals were wide.

Figure 17. Incidence rate malignancy without NMSC (updated data till 1-1-2016)

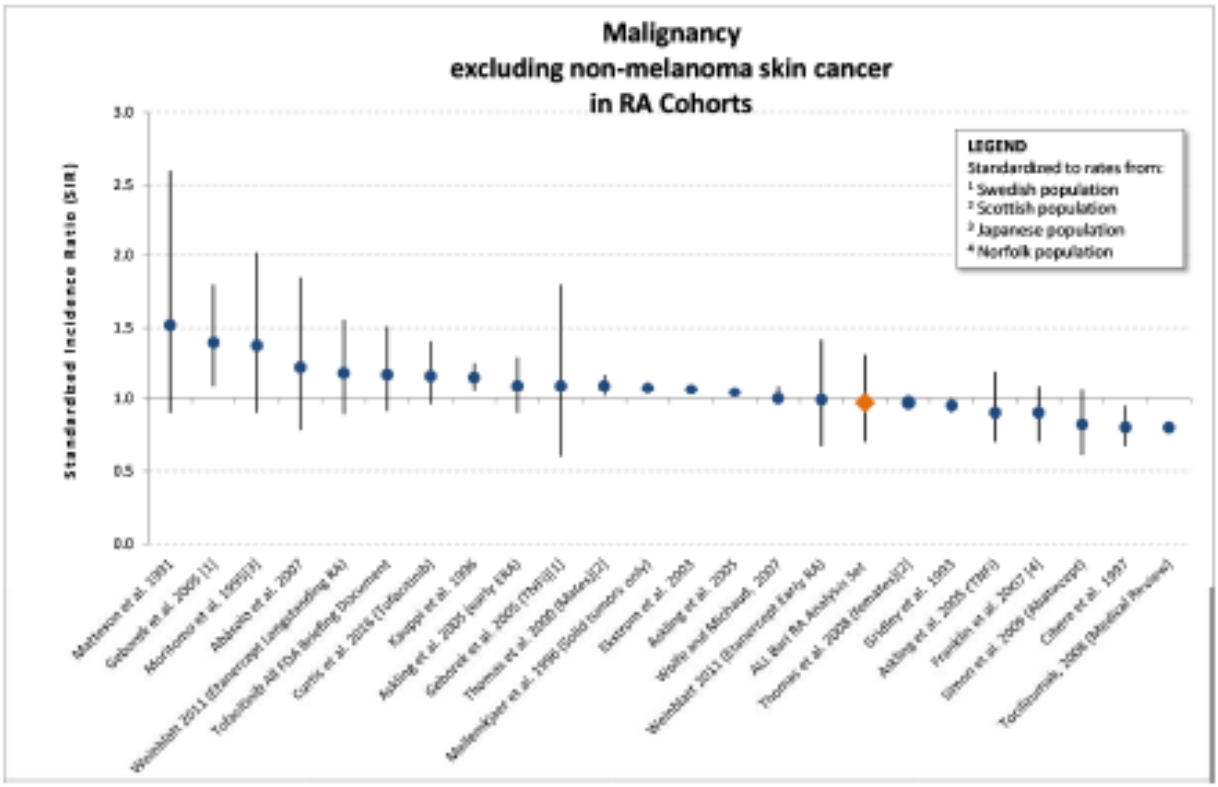


Time Periods (weeks)	Overall	0-24	24-48	48-72	72-96	>96
IR/100 Pt Yrs	0.7	0.5	0.8	1.1	0.7	0.6
Lower CI	0.5	0.2	0.4	0.6	0.2	0.2
Upper CI	1.0	0.9	1.4	2.0	1.6	1.6
Patient Years	5233	1531	1289	1052	716	645
No. of Patients	3492	3492	3114	2583	1940	1167
Patients with Events	38	7	10	12	5	4

Abbreviations: CI = confidence interval; IR = incidence rate; Pt = patient; Yrs = years.

Figure 4.1. **Incidence rate of malignancies excluding nonmelanoma skin cancer by time period of report in all baricitinib patients with rheumatoid arthritis.**

Figure 18. Standardized incidence ratios for malignancies excluding non-melanoma skin cancer in rheumatoid arthritis cohorts



Abbreviations: FDA = US Food and Drug Administration; RA = rheumatoid arthritis; TNFi = tumour necrosis factor inhibitor.

Table 40. Summary of Malignancies Excluding NMSC by Dose Group (pooled data set, cut off 15-08-2015)

	Patient Population						
Site	**Screening**	**PBO N = 1,070 (PYE = 393.8)**	**MTX mono N = 210 (PYE = 171.5)**	**ADA N = 330 (PYE = 275.9)**	**BARI 2-mg N = 479 (PYE = 730.0)**	**BARI ≥4-mg N = 1508 (PYE = 2050.3)**	**BARI ≥4-mg after S/R N = 1424 (PYE = 1429.8)[d]**
Adrenal						1	
Breast		1			1	4	
Bone/cartilage							1
ENT							1
Gallbladder						1	
GI			1			2	2
GYN		1			1	1	1
Kidney					1	2	
Lymphoma							3
Lung					1	2	1
Pancreas							1
Prostate							1
Skin/Soft Tissue						1	1
Thyroid	1				1		
Total n (%) [per 100 PY]	1	2 (0.18%) [0,51]	1 (0.48%) [0.58]	0	5 (1.04%) [0.68]	14 (0.93%) [0.68]	12 (1.08%) [0.84]

Abbreviations: N = number of patients; PYE = patient years of exposure; ENT = ears, nose, and throat; GI = gastrointestinal; GYN = gynecological; S/R = switch or rescue

Mama and digestive tract carcinoma were most frequently reported.

Whereas in the original dossier three cases of lymphoma were reported, two additional cases emerged in the updated dataset. This results in an IR of 0.095 per 100 patient-years of exposure (PYE) (95% CI, 0.031, and 0.223). These values do not exceed the published background rates from clinical trials (0.02 to 0.21) in patients with RA with concomitant methotrexate or other cDMARD) therapy (which each of the 5 patients with lymphoma were taking) (0.04-0.16), or patients with RA with concomitant anti-tumour necrosis factor therapy (0.04-0.34) . EBV (Epstein-Barr virus) was confirmed in one of the 5 lymphoma cases (a B-cell lymphoma in Asia, patients was pre-treated with MTX and prednisone). EBV status was confirmed negative in one T-cell lymphoma, or not reported in the other cases. One case was related to H.pylori infection (MALT).

There was one case of lymphoproliferative disorders in elderly.

The incidence rate of NMSC was 0.4 per 100 PY. The incidence rates remained stable over time (96 weeks). For other DMARDs, incidence rates of 0.17-0.69 per 100 PY had been reported.

Lipids

Abnormal LDL-C (Low Density Lipoprotein-Cholesterol) values, including categories of high or very high, were very common in both PBO (11.8%) and BARI 4-mg (10.5%) at baseline.

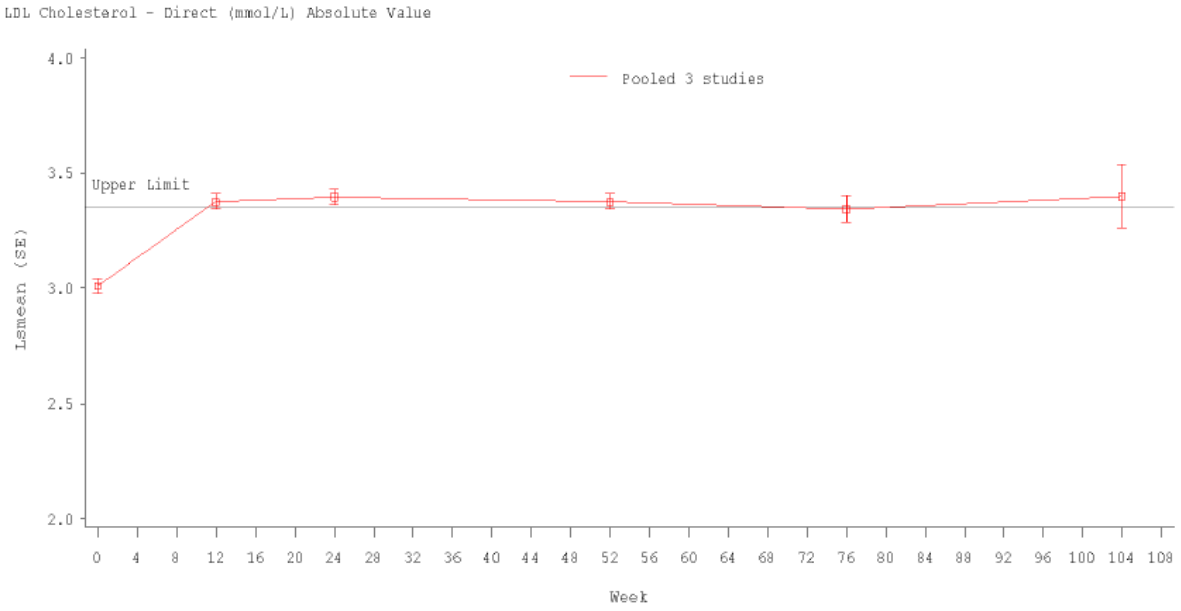
Baricitinib induced a significant increment of LDL-C and HDL-C from baseline within the first 12 weeks of treatment, in a dose-dependent way, which remained stable thereafter. Overall, the LDL/HDL ratio remained unchanged after baricitinib treatment.

Table 41. Effects of baricitinib 4 mg on lipids (16 weeks)

Lipid Analytes	**All BARI RA Analysis Set** N=3464 PYE=4214 n/Total (%)
Total Cholesterol	
Δ from 'Desirable' (<5.17 mmol/L) to 'High' (≥6.21 mmol/L)	365/1842 (19.8)
LDL-C	
Δ from 'Optimal or Near Optimal' (<3.36 mmol\L) to 'High or Very high'a (≥4.14 mmol/L) <<denominator is total patients with baseline optimal or near optimal (add together the totals from each category) numerator is the sum of patients with a postbaseline category of high + very high>>	242/1768 (13.7) (very high: 0%)
HDL-C	
Δ from 'Low' (<1.03 mmol/L) to 'Normal or High' (≥1.03 mmol/L)	96/222 (43.2)
Δ from 'Normal or High' (≥1.03 mmol/L) to 'Low' (<1.03 mmol/L)	17/2327 (0.7)
Triglycerides	
Δ from 'Normal' (<1.69 mmol/L) to 'High or Very high' (≥2.26 mmol/L)	298/2309 (12.9)

n = number of patients increased to category. Total = total number of observations minus number missing at baseline. N = number of patients in the safety analysis set. PYE = patient years of exposure.

Figure 19. Central tendency of LDL cholesterol



Data censored at any dose change (including step-down) or rescue in JADY. Data included up to week 104. LSMean (SE) from MMRM model: [Response Variable = Visit (Type III sums of squares)].
Quintiles reference ranges were used for LDL.

The change in lipid was lower for comparator MTX in Study JADZ. Baricitinib 4 mg monotherapy cause a shift of LDL-C from normal to high in 17.4% of the subjects treated with baricitinib monotherapy, versus 5.3% in subjects treated with MTX alone. In general, lipid levels increased significantly for active comparator adalimumab in Study JADV as compared to placebo, but to lesser extent than for baricitinib. E.g. LDL-C shifts (4.14 mmol/L) were reported for 10.0% for adalimumab, 24.4% for baricitinib 4 mg, versus 5.5% for placebo in 24 weeks. Similar rates of LDL-C increments as observed for baricitinib were reported for II-6 inhibitor tocilizumab.

Statins were initiated only in a small percentage of the subjects assigned to baricitinib 4 mg (2,5-3.5 % within 24 weeks), to similar extent as placebo. The effect of statin therapy was comparable between baricitinib and placebo arms. In only a few isolated cases of patients that were already treated with statins at baseline, the statin dose was increased.

To characterize changes in lipids, lipid NMR (Nuclear Magnetic Resonance) scans and apolipoproteins were examined. Significant increases in the number of large LDL-C particles and statistically significant decreases in the number of small, medium-small and very small LDL-C particles were observed in BARI 4-mg and adalimumab as compared to PBO. Large LDL-C particles are considered less atherogenic than small ones.

Baricitinib was also associated with weight gain. In pooled analyses, 9.8% of the subjects treated with baricitinib 4 mg, had more than 7% weight gain from baseline at Week 24, versus 2.8% for placebo (Odds Ration 3.6, 95% CI 2.4,5.6). The proportion of patients reporting weight gain was the largest in subgroups with low BMI at baseline. Also the waist circumference increased from baseline with 1-1.5 cm after 52 weeks of baricitinib treatment, versus 0.6 cm for MTX and 1.2 cm for adalimumab.

Cardiovascular risks

Baricitinib did not cause a change in blood pressure. No signal of QTc prolongation was observed for baricitinib in a positive controlled study.

For the baricitinib Phase 3 studies, an independent external committee was established to adjudicate potential cardiovascular adverse events. MACE was defined as cardiovascular death, MI, or stroke. Cardiovascular event were hospitalization for unstable angina or heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, or coronary revascularizations.

The incidence rates of MACE and CV events were overall lower than comparators placebo and MTX, though the point estimate was slightly lower for adalimumab. To be noted, the comparators' arms were too small to draw definitive conclusions.

Table 42. MACE and CV risks (pooled dataset pivotal trials)

N (PYE)	PBO N=892 [a] (354.2)	MTX mono N=210 (171.5)	ADA N=330 (275.9)	BARI 2-mg N=403 (603.6)	BARI 4-mg N=1265 (1755.7)	BARI after S/R N=1194 (1102.2)
Total patients with at least 1 MACE	2 [0.57]	2 [1.16]	1 [0.36]	3 [0.50]	8 [0.46]	5 [0.46]
Total patients with at least 1 positively adjudicated other CV event	3 [0.85]	-	1 [0.36]	7 [1.16]	14 [0.72]	4 [0.36]

Renal safety

Baricitinib causes a steady increment of creatinine serum levels (mean change from baseline: 6.2 µmol/L versus 1.1 for placebo, 95% CI of he difference 4.3, 6.0). This was reversible after treatment discontinuation. As serum creatinine increased, the GFR estimated based on creatinine, decreased accordingly.

Baricitinib 4 mg was also explored in patients with diabetic nephropathy in Study JAGQ. Baricitinib in doses up to 4 mg, had no influence on eGFR if calculated by Cystatin C. Moreover, baricitinib improved urine albumin loss in these nephropathy patients.

The number of cases of renal SAEs was higher for placebo than baricitinib 4 mg in the pooled analyses.

Table 43. Renal function laboratory parameters (pooled Phase 3 trials)

	Central Tendency BARI 4-mg				TE Abnormalities		
	BL Mean (SD)[a]	Change from BL LSM (SE)[a]	Change from BL (95% CI)[a]	DIFF mean change from BL BARI-PCO	High (H) / Low (L)[c]	% with any worsening [d]	% worsened to select criteri[e]
Creatinine (µmol/L)	64.5 (15.1)	6.2 (0.41)	(5.4, 7.0)	5.1*	NS	2.4 vs 2.1 placebo	0.2
Estimated GFR (mL/min/bsa)	92.8 (24.1)	-9.0 (0.50)	(-10.0, -8.0)	-8.0*	↑L*, ↓H*	-	-
Creatinine Clearance (mL/sec)	1.869 (0.641)	-0.125 (0.0096)	(-0.144, -0.107)	-0.108*	↑L*, ↓H*	-	-

Hepatic safety

In general, baricitinib induced a steady increment of transferases ALT and AST that continued during treatment. Peak in ALT and AST exceeding ULN > 5 times were less than 1%, and were generally transient. In contrast, alkaline phosphatase steadily declined from baseline. Bilirubin remained stable after baricitinib treatment, and there were no hepatoxicity cases meeting Hy's law for baricitinib.

Table 44. Central tendencies of liver function tests (pooled Phase 3 studies)

	Central Tendency BARI 4-mg				TE Abnormalities		
	BL Mean (SD)[a]	Change from BL LSM (SE)[a]	Change from BL (95% CI)[a]	Difference BARI 4-mg vs PBO for[a,b]	High (H) / Low (L)[c]	% any worsening in criteria or grade[d]	Percentage worsened to select criteria or grade[e]
ALT (U/L)	20.2 (10.6)	5.6 (1.03)	(3.6, 7.6)	5.5*	↓L*, ↑H*	20.7	0.6
AST (U/L)	20.4 (7.9)	5.4 (0.64)	(4.1, 6.6)	4.9*	↓L*, ↑H*	17.7	0.4
Alkaline Phosphatase (U/L)	84.6 (26.1)	-7.3 (0.77)	(-8.8, -5.8)	-6.3*	↑L*	4.6	0
Total Bilirubin (µmol/L)	6.2 (3.3)	0.9 (0.12)	(0.7, 1.2)	0.9*	NS	1.3	0
Direct Bilirubin (µmol/L)	1.8 (0.8)	0.1 (0.04)	(0.0, 0.2)	0.1*	NS	-	-
Albumin (g/L)	42.2 (3.1)	1.6 (0.10)	(1.4, 1.8)	2.2*	↑H*	-	-

*p≤0.05. Abbreviations: H = high; L = low; NS = not statistically significant;

a Those presented are from the last baseline to last post baseline analyses.

b Difference is always baricitinib 4-mg minus placebo.

c ↑ = compared to PBO, the proportion of patients experiencing high/low abnormalities for the given analyte was larger in BARI 4-mg. ↓= compared to PBO, the proportion of patients experiencing high/low abnormalities for the given analyte was smaller in BARI 4-mg.

d Provided for the analytes for which these analyses were performed; - indicates analysis not done. Worsened in NCEP category indicates an increase in analytes except HDL where proportion of patients with a decrease in NCEP category are displayed.

e For ALT, criteria grade 3 was equivalent to >5 x ULN; for AST, criteria grade 3 was equivalent to >5 x ULN, for alkaline phosphatase, criteria grade 3 was equivalent to >5 x ULN, and for total bilirubin, criteria grade 3 was equivalent to >3 x ULN.

Overall, the incidence of ALT or AST peak increments was similar as reported for MTX alone or adalimumab (table 45).

Table 45. AST increments baricitinib 4 mg versus comparators MTX and adalimumab

	From <3 x ULN to >=3 x ULN n/N-obs (%)	From <5 x ULN to >=5 x ULN n/N-obs (%)	From <10 x ULN to >=10 x ULN n/N-obs (%)
BARI 4-mg RA PC Analysis Set up to Week 24			
Placebo (N=1070)	14/1058 (1.3)	4/1059 (0.4)	0
Bari 4-mg (N=997)	15/987 (1.5)	7/988 (0.7)	2/988 (0.2)
Study JADZ through Week 52			
MTX (N=210)	6/206 (2.9)	2/206 (1.0)	0
Bari 4-mg (N=159)	2/158 (1.3)	1/158 (0.6)	0
Bari 4-mg + MTX (N=215)	15/211 (7.1)	3/211 (1.4)	2/212 (0.9)
Study JADV through Week 52			
Bari 4-mg + MTX (N=487)	15/483 (3.1)	4/484 (0.8)	1/484 (0.2)
Adalimumab + MTX (N=330)	11/330 (3.3)	3/330 (0.9)	1/330 (0.3)

Three case reports suspected of DILI (drug-induced liver injury) were reported. Formally, these cases did not meet Hy's law criteria of DILI. None of them were reported to be treatment related. One case was thought to be due to cholecystitis, and one to alcohol use.

One case of jaundice starting two days after baricitinib, with moderate increments of bilirunine (< 2 times ULN), ALT >3 and < times ULN, GGT >10 times ULN, without further cause like hepatitis or alcohol use, recovered spontaneously at discontinuation of baricitinib (positive de-challenge).

GI perforations

Two cases occurred during the extended treatment phase of the trials (one case of diverticular perforation after baricitinib for 242 days, and one case of ruptured appendicitis after baricitinib for 416 days). Both patients used corticosteroids. Overall, the frequency in the trial population [0.05 per 100 py] ls was below what is generally reported for RA patients [0.17], or tocilizumab and tofacitinib [0.13].

Serious adverse event/deaths/other significant events

Serious adverse events of barcitinib compared to placebo are shown in table 46 below.

Table 46. Serious Adverse Events of BARI 4 mg compared to placebo (up to Week 24)

	PBO (N=1070) (PYE=393.8) n (%) [PY]	**BARI 4-mg (N=997) (PYE=409.4) n (%) [PY]**
Patients with >= 1 SAE	**50 (4.7) [12.7]**	**53 (5.3) [12.9]**
Blood and lymphatic disorders	2 (0.2) [0.5]	4 (0.4) [1.0] (Anaemia (3), Lymphocytosis (1))
Cardiac disorders	5 (0.5) [1.3]	6 (0.6) [1.5] Coronary artery disease(2), Myocardial Infarction (2), Angina pectoris (1), Cardiac failure (1), sinus bradycardia (1)
Ear and labyrinth disorders	0	2 (0.2) [0.5] Motion sickness (1), positional vertigo(1)
Eye disorders	0	1 (0.1) [0.2] Cataract (1)
Gastrointestinal disorders	4 (0.4) [1.0]	2 (0.2) [0.5] Gastric ulcer (1), Inguinal hernia (1)
Hepatobiliary disorders	2 (0.2) [0.5]	1 (0.1) [0.2] DILI(1)
Infections and infestations	16 (1.5) [4.1]	14 (1.4) [3.4] Herpes zoster (3), Cellulitis (2), urinary tract infection (2), Bacterial infection nos (1), disseminated tuberculosis (1), epiglottitis (1), gastroenteritis (1), gastroenteritis viral (1), Helicobacter (1), LRTI (1), pneumonia(1), URTI (1), vulval abscess(1)
Injury, poisoning and procedural complications	3 (0.3) [0.8]	7 (0.7) [1.7]
Investigations	1 (0.1) [0.3]	4 (0.4) [1.0] ALAT increased (1), ASAT increased (1), Alkaline Phosphatase increased (1), GFR decreased (1)
Metabolism and nutrition disorders	5 (0.5) [1.3]	1 (0.1) [0.2] Diabetes mellitus (1)
Musculoskeletal and connective tissue disorders	10 (0.9) [2.5]	4 (0.4) [1.0]
Neoplasms	1 (0.1) [0.3]	1 (0.1) [0.2] breast cancer(1)
Nervous system disorders	3 (0.3) [0.8]	3 (0.3) [0.7] Basilar artery thrombosis(1) , Headache (1), Transient amnesia (1), Vertebral artery thrombosis (1)
Psychiatric	4 (0.4) [1.0]	0
Renal and urinary system	6 (0.6) [1.5]	0
Reproductive	0	1 (0.1) [0.2] Metrorrhagia (1)
Respiratory system	2 (0.2) [0.5]	5 (0.5) [1.2] Allergic bronchitis (1), COPD (1), Pleural effusion (1), Pleuritic pain (1), pulmonary embolism (1)
Skin	1 (0.1) [0.3]	2 (0.2) [0.5] Allergic dermatitis(1), Rash pruritic (1)
Surgical and medical procedures	1 (0.1) [0.3]	0
Vascular disorders	3 (0.3) [0.8]	1 (0.1) [0.2] Thrombophlebitis (1)

LRTI=lower respiratory tract infection, URTI: upper respiratory tract infection

The SAE rates were similar for baricitinib and placebo, and with heterogeneous causes. More often than placebo, lab abnormalities were reported as SAE. More injuries (mainly fractures) were reported for baricitinib. These were not reported to be related to higher incidence of falls.

Table 47. Summary of Cause of Death (as Assessed by the Sponsor) by Dose Group in RA Patients (Studies JADC, JADA, JADN, JADZ, JADV, JADX, JADW, JADY)

	Patient Population						
N (PYE)	**In Screening**	**PBO N=1070 (393.8)**	**MTX mono N=210 (171.5)**	**ADA N=330 (275.9)**	**BARI 2-mg N=479 (730.0)**	**BARI ≥4-mg N=1508 (2050.2)**	**BARI ≥4-mg after S/R N=1424 (1429.8)**
Infection		2		1		2	
Pulmonary Embolus			1			1	
Stroke/CNS hemorrhage		1				1	1
Pulmonary Fibrosis			1				
MI/CAD	2					1[e]	1
Unwitnessed death			1				1
Malignancy						1	1
Natural causes					1		
Non-infectious ARF					1		
Non-CNS hemorrhage						1	

Abbreviations: N = number of patients; PYE = patient years of exposure; S/R = switch or rescue; CNS = central nervous system; CAD = coronary artery disease; ARF = acute respiratory failure

[e] Event occurred on baricitinib 8-mg QD. All other events in this patient population occurred on baricitinib 4-mg QD.

According to the Investigators, the causes of death were not considered treatment related. Overall, the causes were heterogeneous. Deaths due to infections and MACE were rare, and showed similar incidences amongst treatment arms.

Laboratory findings

Chemistry

There were no notable changes in glucose, sodium, potassium, or Total Protein.

Treatment with baricitinib was commonly associated with a rapid increase in Creatine Phosphokinase (CPK) of 80% from baseline values, which plateaued after approximately 12 weeks of treatment. Less than 15 cases (0.8%) were severe increments (> 5 x ULN), compared to 0.2 for placebo. The risk of high CPK value increased in patients with renal impairment at baseline.

CPK increment was not clearly associated with severe muscle pain. Treatment-Emergent Muscle Symptoms were slightly more commonly reported for baricitinib 4 mg than Placebo (1.6 [5.5 per 100 PY] versus 1.1% [4.0], respectively).

One case of possible rhabdomyolysis was reported (rated as non-serious). Causality is unclear since the patient had elevated CPK at baseline (778 U/L), and continued baricitinib treatment despite high CPK levels. The increment was considered to be attributed to heavy exercise by the Investigator.

Table 48. CPK central tendency (pooled data main studies)

	Central Tendency BARI 4-mg					TE Abnormalities		
	Baseline Mean (SD)[a]	Change from baseline LSM (SE)[a]	Change from baseline median[a]	Change from baseline (95% CI)[a]	Difference in LSM between BARI 4-mg and PBO for Change from baseline[a,b]	Treatment-Emergent High (H)/ Low (L)[c]	Percentage with any worsening in criteria or grade[d]	Percentage worsened to select criteria or grade[e]
General Chemistry Analytes								
CPK (U/L)	78 (110)	59 (3.5)	40	(52, 66)	54*	↓L*, ↑H*	33.6	0.8

Haematology

Because of its mode of action of baricitinib as a JAK inhibitor on the interruption of signalling of cytokines and growth factors (EPO) involved in regulation of haematopoiesis, haematological parameters and myelosuppression were monitored throughout the studies.

Anaemia: Haemoglobin, haematocrit

Baricitinib 4 mg induced an overall small decline of haemoglobin (Hb), haematocrit (Ht) and erythrocytes counts from baseline. Mean difference of change of Hb from baseline for the 4 mg dose was 0.05 mmol/mL (95% CI -0.01-0.1, equivalent to 0.016-0.16 g/dL), as compared to placebo treatment. The effects of baricitinib 2 and 4 mg were similar. Compared to placebo, the rate of low haemoglobin (defined as < 12 g/dL for females and 13.5 g/dL for males) was 27.5% for baricitinib 4mg versus 24.5% for placebo (pooled data primary safety analysis, 16 weeks). A drop of Hb <8 g/dL (≥3 CTCAE Hb values) was rare (<0.5%), and occurred at similar rates as compared to placebo or MTX-monotherapy.

The initial decrease of Hb and erythrocytes was associated with increased reticulocytes counts, indicating compensatory mechanism, and Hb returned to baseline levels after 24 weeks. In total 4 subjects interrupted baricitinib treatment because of anaemia (out of 3822 treated with baricitinib). In the patients who interrupt treatment because of anaemia, Hb was reversible towards baseline within 28 days (i.e. the scheduled interim visit period).

Platelets

Baricitinib caused a short lasting increment of platelets. These were not related to venous thrombosis events.

Leukocytes

Mean leukocyte counts, and specifically neutrophil counts, dropped from baseline shortly after the start of baricitinib treatment, in a dose dependent way. Grade 3 neutropenia (< 1.0 billion cells /L) was rarely reported (0.3% in baricitinib 4 mg dose).

Table 49. Neutrophil counts

	BARI 4-mg RA PC analysis set			BARI 2-mg vs 4-mg RA analysis set		
	Placebo	BARI 4-mg	BARI 4-mg vs. PBO	BARI 2-mg	BARI 4-mg	BARI 2-mg vs BARI 4-mg
	N-obs = 1026 within group LSM	N-obs = 957 within group LSM	LSMD (95% CI)	N-obs = 475 within group LSM	N-obs = 474 within group LSM	LSMD (95% CI)
Change from baseline (last to last, billion cells/L)	-0.02	-1.08*	-1.06* (-1.22, -0.90)	-0.76*	-0.94*	-0.18 (-0.39, 0.04)

NK cells

NK cells increased in the first two weeks, but then dropped by 20% from baseline and slowly recovered near baseline levels at Week 52. Similar effects were reported for MTX.

Lymphocytes

Overall, administration of baricitinib was associated with an increase in mean lymphocyte counts within 1 week of starting treatment; values declined to baseline by 12 to 24 weeks and remained stable. Grade 3 lymphopenia (<0.5 billion cells /L) was reported in 1.9% of all RA patients exposed to baricitinib 4 mg, which is within the ranges as reported for placebo or MTX. There was a weak relationship between lymphopenia and infections.

Lymphocyte subsets were analysed throughout the confirmatory trials. B-cells (CD19+/CD20+ and mature naïve cells) increased by about 70-100%. To be noted, gamma globulins slightly decreased with baricitinib, which might be considered as a treatment response of inflammation. Align with the increments of the total lymphocyte counts, CD3+, CD4+, and to lesser extent CD8+, increased from baseline till Week 24. After that, CD3/4/8 levels gradually retuned to baseline. There was a marginal decrease in T-helper cells.

Safety in special populations

Females

Amenorrhoea was reported more frequently for baricitinib than placebo up to 24 weeks (1.5 per 100 py versus 0.3 per 100 py), in studies where baricitnib was given add-on to MTX.

Elderly

The baricitinib RA programme included 605 patients who were 65 years of age and older, 77 patients who were 75 years and older, and 1 patient above 85 years of age.

Infections were reported more often for elderly as compared to younger subjects, but a similar tendency was noted for the placebo-arm. In elderly > 65 years who were heavily pre-treated with prior biologics, there was a dose dependent risk of h. zoster. However, a dose-dependent tendency was not confirmed in elderly treated with synthetic DMARDs only (see table 50 below).

Table 50. Occurrence of Treatment Emergent Herpes Zoster in cDMARD-IR and bDMARD IR Subpopulations of Patients Aged ≥ 65 Years

	EXT BARI 2-mg vs 4-mg RA (Updated through 01 January 2016)			
	cDMARD-IR		bDMARD-IR	
	BARI 2-mg	BARI 4-mg	BARI 2-mg	BARI 4-mg
n/N [incidence rate]	3/47 [6.2]	2/46 [3.3]	1/35 [2.5]	6/41 [13.4]
IRR[a] 4-mg vs 2-mg	0.51		5.42	

Abbreviations: n = number of patients in specified category; N = number of patients in the safety analysis set; IRR = incidence rate ratio; TE = treatment emergent.

[a] IRR was estimated from an exact Poisson regression model with explanatory terms for study and treatment using an offset term = time to event.

Anaemia was more frequently reported for elderly >75 years (40% for baricitinib versus 11% placebo).

Event Category	<65 Years BARI N=2859 n (%)	65 to 74 Years BARI N=528 n (%)	75 to 84 Years BARI N=76 n (%)	>=85 Years BARI N=1 n (%)
Total TEAEs	2161 (75.6)	423 (80.1)	63 (82.9)	1 (100)
SAEs by ICH	263 (9.2)	99 (18.8)	22 (28.9)	0
Fatal	2 (0.1)	1 (0.2)	3 (3.9)	0
Hospitalization	226 (7.9)	86 (16.3)	20 (26.3)	0
Life-threatening	3 (0.1)	1 (0.2)	1 (1.3)	0
Disability	2 (0.1)	0	0	0
Other	53 (1.9)	23 (4.4)	3 (3.9)	0
AE leading to study medication discontinuation	182 (6.4)	61 (11.6)	12 (15.8)	0
Cardiac disorders (SOC)	68 (2.4)	27 (5.1)	2 (2.6)	0
Infections and infestations (SOC)	1354 (47.4)	264 (50.0)	37 (48.7)	1 (100)
Nervous system disorders (SOC)	337 (11.8)	77 (14.6)	10 (13.2)	0
Psychiatric disorders (SOC)	131 (4.6)	23 (4.4)	1 (1.3)	0
Renal and urinary disorders (SOC)	77 (2.7)	33 (6.3)	5 (6.6)	0
Vascular disorders (SOC)	182 (6.4)	32 (6.1)	12 (15.8)	0
Accidents and injuries (SMQ)	280 (9.8)	83 (15.7)	20 (26.3)	0
Anaphylaxis Events (SMQ)	1 (0.0)	0	0	0
Central nervous system haemorrhages and cerebrovascular conditions (SMQ)	3 (0.1)	6 (1.1)	2 (2.6)	0
Gastrointestinal Perforations (SMQ)	5 (0.2)	1 (0.2)	0	0
Hepatic Disorders (SMQ)	212 (7.4)	27 (5.1)	2 (2.6)	0
Hyperlipidemia Events (LSC)	326 (11.4)	42 (8.0)	2 (2.6)	0
Malignancies (SMQ)	21 (0.7)	13 (2.5)	3 (3.9)	0
Myelosuppresive Events (SMQ)	167 (5.8)	48 (9.1)	14 (18.4)	0
QT Prolongation Events (SMQ)	18 (0.6)	4 (0.8)	0	0
Hypotension, falls, fractures (LSC)	114 (4.0)	43 (8.1)	15 (19.7)	0
Muscle Symptoms (LSC)	87 (3.0)	22 (4.2)	1 (1.3)	0
Photosensitivity Reactions (LSC)	5 (0.2)	0	0	0
Anticholinergic syndrome (PT)	0	0	0	0
QOL decreased (PT)	0	0	0	0

Renal impairment

As baricitinib is predominantly cleared by the kidney, a lower dose of 2 mg is recommended for patients with renal impairment. It is noted that patients with mild-moderate renal impairment at baseline, had a higher risk of anaemia (29.6 % for BARI 4 mg and 21.8% for placebo).

Immunological events

There was no clear signal of hypersensitivity reactions or photosensitivity reactions for baricitinib.

Safety related to drug-drug interactions and other interactions

As reported in detail in the PK section of this report, concomitant administration of probenecid doubled the plasma exposure to baricitinib. Other OAT3 inhibitors, such as ibuprofen and diclofenac, have less inhibition potential than probenecid.

Discontinuation due to adverse events

The 4 mg dose leads to an increased incidence of SAE, and temporary interruption of treatment as compared to the 2 mg dose in head-to-head comparison trial JADX and JADW.

When compared to active comparators, baricitinib monotherapy was overall similarly tolerated as MTX monotherapy in DMARD-naïve patients, with the exception of a higher incidence of infections (43.3 vs. 38.1) and herpes zoster (2.5 vs 1.0%), not in favour of baricitinib. However, the combination of baricitinib + MTX was poorly tolerated in DMARD-naïve patients, with high rates of SAE (16.3%), treatment discontinuations (10.7%) or interruptions (20%) due to AEs, which was about twice as a high as compared to the subsequent monotherapies (see table 51 below)

Baricitinib 4 mg was also less tolerated than adalimumab in the second line setting (Study JADV), where Background treatment with MTX was maintained in this study. The drop-out rate was 7.4 vs. 3.9% for baricitinib and adalimumab, respective, after 52 weeks. The rates of serious infections and herpes zoster, however, were more align in this treatment setting.

Table 51. Adverse Events from Study JADZ in DMARD-naïve patients. Patients were assigned to methotrexate (MTX), baricitinib (BARI) 4 mg or a combination of MTX+ BARI. Study JADZ

	Week 0-24			**Week 0-52**		
	MTX Monotherapy (N=210) n (%)	**BARI 4-mg Monotherapy (N=159) n (%)**	**BARI 4-mg + MTX (N=215) n (%)**	**MTX Monotherapy (N=210) n (%)**	**BARI 4-mg Monotherapy (N=159) n (%)**	**BARI 4-mg + MTX (N=215) n (%)**
SAE ICH-defined	9 (4.3)	5 (3.1)	8 (3.7)	23 (11.0)	17 (10.7)	35 (16.3)
≥1 TEAE	136 (64.8)	103 (64.8)	146 (67.9)	151 (71.9)	113 (71.1)	167 (77.7)
TEAEs severe	10 (4.8)	4 (2.5)	12 (5.6)	17 (8.1)	9 (5.7)	22 (10.2)
Discontinuations due to AE or death	5 (2.4)	6 (3.8)	15 (7.0)	11 (5.2)	11 (6.9)	23 (10.7)
AEs leading to interruption	20 (9.5)	7 (4.4)	24 (11.2)	28 (13.3)	13 (8.2)	43 (20.0)
infections	58 (27.6)	45 (28.3)	74 (34.4)	80 (38.1)	69 (43.4)	108 (50.2)
Serious infections				8 (3.8)	6 (3.8)	5 (2.3)
Herpes zoster	1 (0.5)	3 (1.9)	3 (1.4)	2 (1.0)	4 (2.5)	5 (2.3)
Tuberculosis	0	0	0	0	0	0
Malignancies				1 (0.5)	1 (0.6)	4 (1.9)
MACE	0	1 (0.6)	0	2 (1.0)	1 (0.6)	0

Table 52. Adverse Events from Study JADV active-compared, placebo-controlled study in RA patients irresponsive to MTX. Adverse Event Overview, Weeks 0 to 24 and Weeks 0-52

	Week 0-24			Week 0-52	
	Placebo (N=488) n (%)	**BARI 4-mg (N=487) n (%)**	**Adalimumab (N=330) n (%)**	**BARI 4-mg (N=487) n (%)**	**Adalimumab (N=330) n (%)**
SAE ICH-defined	**22 (4.5)**	**23 (4.7)**	**6 (1.8)**	**38 (7.8)**	**13 (3.9)**
SAE Protocol-only	**13 (2.7)**	**12 (2.5)**	**7 (2.1)**	**18 (3.7)**	**12 (3.6)**
Treatment-Emergent Adverse Events					
≥1 TEAE	**295 (60.5)**	**347 (71.3)**	**224 (67.9)**	**384 (78.9)**	**253 (76.7)**
TEAEs severe	**19 (3.9)**	**21 (4.3)**	**6 (1.8)**	**34 (7.0)**	**12 (3.6)**
Discontinuations due to AE or death	**17 (3.5)**	**24 (4.9)**	**7 (2.1)**	**36 (7.4)**	**13 (3.9)**
AEs leading to interruption	**45 (9.2)**	**48 (9.9)**	**29 (8.8)**	**72 (14.8)**	**38 (11.5)**
infections	**134 (27.5)**	**176 (36.1)**	**110 (33.3)**	**233 (47.8)**	**145 (43.9)**
Serious infections	**7 (1.4)**	**5 (1.0)**	**2 (0.6)**	**10 (2.1)**	**5 (1.5)**
Herpes zoster	**2 (0.4)**	**7 (1.4)**	**4 (1.2)**	**11 (2.3)**	**5 (1.5)**
Tuberculosis	**0**	**0**	**2 (0.6)**	**0**	**2 (0.6)**
Malignancies	**3 (0.6)**	**2 (0.4)**	**0**	**3 (0.6)**	**0**
MACE	**0**	**1 (0.2)**	**0**	**2 (0.4)**	**1 (0.3)**

Table 53. Averse Event Overview: Patients irresponsive to cDMARDs. Study JAWX, Week 0-24

	PBO (N=228) n (%)	**BARI 2-mg (N=229) n (%)**	**BARI 4-mg (N=227) n (%)**
SAEs			
ICH-defined	11 (4.8)	6 (2.6)	12 (5.3)
Protocol-defined	5 (2.2)	9 (3.9)	8 (3.5)
TEAEs			
TEAEs rated as severe	10 (4.4)	12 (5.2)	17 (7.5)
AEs leading to interruption	23 (10.1)	15 (6.6)	24 (10.6)
Infections			
Serious (by ICH) infections	4 (1.8)	2 (0.9)	4 (1.8)
Herpes zoster	0	4 (1.7)	3 (1.3)
TB	0	0	1 (0.4)
Malignancies	0	0	1 (0.4)
MACE	2 (0.9)	0	0

Table 54. Adverse Event Overview: Patients irresponsive to bDMARDs. Study JAWD, Week 0-24

	PBO (N=176) n (%)	BARI 2-mg (N=174) n (%)	BARI 4-mg (N=177) n (%)
SAEs			
ICH-defined	13 (7.4)	7 (4.0)	18 (10.2)
Protocol-defined	2 (1.1)	5 (2.9)	5 (2.8)
TEAEs	112 (63.6)	123 (70.7)	137 (77.4)
TEAEs rated as severe	16 (9.1)	14 (8.0)	21 (11.9)
TEAEs leading to interruption	12 (6.8)	26 (14.9)	27 (15.3)
Infections	55 (31.3)	76 (43.7)	70 (39.5)
Serious infections	5 (2.8)	4 (2.3)	6 (3.4)
Severe infections	2 (1.1)	6 (3.4)	6 (3.4)
Herpes zoster	2 (1.1)	2 (1.1)	7 (4.0)
Malignancies	0	0	2 (1.1)
NMSC	0	0	2 (1.1)
MACE	0	0	2 (1.1)

Post marketing experience

At the time of submission the product was not marketed in any country.

2.6.1. Discussion on clinical safety

Baricitinib has a complex safety profile. Therefore, it is recommended in the SmPC that baricitinib should only be used under supervision of an experienced specialist.

The following Adverse Drugs Reactions have been included in the SmPC: infections (URTI, h. simplex and h. zoster, gastroenteritis and urinary tract infections), neutropenia and thrombocytosis, increment of CPK, LDL-cholesterol and triglycerides, liver function tests (AST, ALT), nausea and acne.

As expected for an immune-modulating drug, baricitinib causes infections. These were mainly upper-respiratory tract infections. The rate of infections was higher for baricitinib than for placebo. Serious infections rates according to ICH criteria were overall low. The rate of infections moderately increased with the baricitinib dose.

In contrast to JAK1,3 inhibitor tofacitinib, JAK1,2 inhibitor baricitinib did not reduce lymphocyte counts. Whether this would lead to a different risk regarding infections of baricitinib versus tofacitinib has not been established.

Although there was no treatment related effect, as precautionary measures, routine monitoring of neutropenia and lymphopenia is included in the SmPC (see section 4.4). This is supported, as these are known to be related to infections, and baricitinib reduced neutrophil leukocytes by on average 10% from baseline. Even though baricitinib on itself did not reduce lymphocytes, lymphopenia is commonly reported for RA patients -possibly related to concurrent corticosteroid use-, and baricitinib may further increase the risk of infection in this group of patients.

Due to its mode of action, baricitinib causes viral reactivation. Herpes zoster and herpes simplex were more frequently reported for baricitinib than for placebo and MTX monotherapy. According to the literature, post-herpetic neuralgia (PHN) is a frequent complication, especially in elderly where RA is common. In European elderly, the risk of developing PHN was estimated as 12-15% (Family Practice (2002) 19 (5): 471-5, J Infect. 2015; 70(2):178-86). PHN was not routinely monitored in the studies. As Investigators may have used global terms of h.zoster in their reports, the occurrence of PHN remains uncertain.

Due to the risks of complicated h. zoster infection, several risk minimization measures have been put in place, such as lowering the dose to 2 mg for patients at risk (e.g. in elderly, patients with a history of recurrent infections), the instructions in the SmPC (section 4.4) to interrupt treatment at first sign of h. zoster and a patient' alert card to help patients identify the signs of infection by h. zoster. Outcomes in a subgroup of patients, who were vaccinated prior to treatment, were supportive of zoster vaccination. A recommendation for vaccination –in accordance to EULAR guideline on live vaccines- has been included in the SmPC (see SmPC section 4.4).

Thus far, there was no signal of opportunistic infections above the background risk. Because of the mode of action of baricitinib, opportunistic infections are certainly not excluded, and it is therefore supported that these are included in the RMP as potential risk. Since 1 case of PML has been reported with Jakavi, another JAK1,2 inhibitor, this is addressed in the RMP for baricitinib as well.

The point estimates of malignancies in the pooled analyses were within the range as reported for other RA populations. However, the confidence intervals were wide, indicating uncertainty of the estimates, particularly at longer term follow-up.

Mama and digestive tract carcinoma were most frequently reported, as may be expected considering the target population of middle-aged women and elderly.

For lymphoma, an increasing trend is not excluded considering that two new cases emerged in a relative short time-frame, though the number are too low to draw firm conclusions at present stage. Malignancy will be further followed in a PASS.

A general warning of enhanced risk of malignancies including lymphoma in the general RA patient population has been added to the SmPC (see section 4.4).

Baricitinib is known to interfere with haematopoiesis above the therapeutic dose. Overall, the rate of anaemia was marginally increased at the proposed dose level of 4 mg. A warning has been included in the SmPC (section 4.4) to monitor Hb routinely, also considering that anaemia is common in the general target population of RA patients.

Baricitinib had a clear and consistent inducing effect on cholesterol –both LDL and HDL. Moreover, weight and waist circumference also increased. Thus far, these changes are not been associated with a higher incidence of CV events for baricitinib, what normally would be expected if cholesterol increases.

There was no obvious relationship between the levels of LDL-C and the occurrence of MACE in the studies (MACE was overall uncommon). In contrast, there appeared to be more MACE in patients who had a decrease in LDL-C with baricitinib treatment in pooled analyses in RA studies.

A NMR study indicated that the mechanism by baricitinib induced hypercholesterolaemia mainly consisted of large LDL- and HDL-C particles, which have more favourable atherogenic properties than small particles. Furthermore, baricitinib related LDL-C increments were responsive to statin treatment.

According to the literature, the DMARD-induced increments of cholesterol appear not to be harmful for RA patients, in contrast to what is expected of cholesterol increments for the general population. Systematic reviews showed an 50% reduction of the risk of CV events for TNF-I (Arthritis Care Res 2011;63:522-9).

It is known that RA patients with high active disease activity have reduced lipid levels. Despite relatively low lipids levels in patients with high active disease state, uncontrolled RA is associated with an increased risk of CV events, probably because of inflammation of the vascular system. It is thought that the related benefits of suppression of inflammation seems to outweigh the risk of lipid changes. This is called the lipid paradox in the literature (for overview, see Ann Rheum Dis 2014; 73: 1281-1283, Rheumatology 2014; 53: 2143-54).

Whether this is also the case for baricitinib, which had an unprecedented high effect on lipids , 2-3 times exceeding alternative treatments, needs to be further confirmed post-marketing in the general target population, which may be at higher risk than the selected trial population. Lipid increments will be further followed in a PASS.

MACE and CV were included in the RMP. There might be a point where the benefits of disease activity control do not outweigh the risks of increased LDL-C levels at long-term. Limited data from healthy volunteers without inflammation did not fully exclude that baricitinib on itself might induce cholesterol. Routine monitoring of lipids is recommended in the SmPC (section 4.4).

ALT and AST elevations were very common, although severe ALT or AST elevations were overall rare and reported to similar extent as the active comparators. There was no obvious tendency of bilirubine increment –which would indicate more severe liver toxicity. Routine monitoring of Liver Function Tests is recommended in the SmPC (section 4.4).

In treatment naïve patients, starting with a combination of baricitinib + MTX was poorly tolerated as compared to monotherapies, with high rates of drop-out and interruptions because of hepatic events and infections.

There was one positive de-challenge case of jaundice –with moderately increased total bilirubin-, which occurred two days after the introduction of baricitinib. Although this case formally did not meet Hy's law criteria of DILI, causality is not excluded. DILI has been adequately addressed in the RMP.

Baricitinib 4 mg caused a steady increment of serum creatinine levels of about 5 µg/ml in the total study population (i.e non-renal patients).

The Applicant postulated that the increased creatinine was due to an interaction effect of baricitinib on tubular transporters of creatinine, by inhibition of the OCT-2, MATE-1, and MATE-2K transporters.

Consecutively, GFR estimates based on creatinine levels decreased with on average 8.0 mL/min/BSA from baseline, which remained stable for 104 weeks.

In a study in diabetic nephropathy where other markers than creatinine were used to estimate GFR (such as cystatin C), no impact of baricitinib on renal function was observed. Possibly, this effect is an interaction at the tubular level of creatinine excretion, and this is no signal of loss of renal capacity. This has been adequately addressed in the SmPC section 5.1.

Overall, there are no signals of nephrotoxicity.

Also CPK increments were commonly reported. However, these were not clearly accompanied with clinical symptoms of muscle damage, and therefore do not contribute negatively to the overall B/R balance. Myopathy has been included in the RMP as potential risk.

The risk of infections was increased in elderly which could be expected due to higher comorbidity in these patients. Particularly in elderly patients > 65 years who were heavily pre-treated including bDMARDs, the incidence of h. zoster was 5-times higher for the 4 mg dose as compared to the low 2 mg dose. However, a reduction to 2 mg dose in elderly >65 years would lead to a relevant loss of efficacy, as shown in subgroup analyses.

The dose recommendation of the low 2 mg dose for very elderly >75 years is supported (see SmPC section 4.2), since there is limited experience in this vulnerable group, and infection risks may be even worse.

For moderate renal impaired patients, the dose is restricted to 2 mg (SmPC section 4.2), to prevent accumulation of the drug, which is renally cleared. Modelling and simulation data, together with clinical data, justified this dose recommendation. Renal patients may have low expression of erythropoietin, which is also targeted by baricitinib. There was a limited increased incidence of anaemia in renal patients when treated by baricitinib. The SmPC recommends routine monitoring for all patients, independent of renal function, which is considered adequate.

A higher rate of amenorrhoea was reported for baricitinib (9 cases), add-on to MTX, as compared to placebo (one). However, in most cases, there were confounding factors, such as age above 50 years, concurrent oral contraceptive use, hypothyroidism and –possibly- major depression. One patient in whom there are no obvious confounding factors was diagnosed with bone TB approximately 2 months after the amenorrhoea was reported. In conclusion, the majority of amenorrhoea cases were confounded, and as such no warnings were included in the SmPC.

During the baricitinib clinical program, 15 women had become pregnant during study participation; 12 of these women were exposed to baricitinib. Pregnancy outcomes are available for 9 of the 12 baricitinib-treated patients: 2 resulted in a birth without evidence of fatal adverse effect, 2 resulted in premature births without evidence of fatal adverse effect, 4 resulted in spontaneous abortions, and 1 was an elective termination. According to the Applicant, spontaneous abortion data in the clinical programme are similar to background rates observed; 17% of pregnancies in the US general population, 33% of pregnancies in RA patients treated with anti-TNF treatments and MTX or leflunomide, and 24% of RA patients treated with anti-TNF treatments without MTX end in foetal loss (Verstappen et al. 2011; Ventura et al. 2012).

As the data are very limited, no firm conclusion could be drawn regarding the use of baricitinib during pregnancy. Based on pre-clinical studies in two models, the risk of bone malformation in the foetus is not excluded. Because of this uncertainty, a contra-indication has been formulated for pregnancy (SmPC section 4.3). For discussion regarding fertility, pregnancy and lactation, see also preclinical part of this report.

2.6.2. Conclusions on the clinical safety

Infections including herpes zoster, increased lipids, and LFT increments are associated risks of baricitinib. Case reports of lymphoma emerging after long-term exposure are a matter of concern, even though the overall incidence was comparable to general target population of RA patients. Overall, the risks were sufficiently addressed with monitoring advices in the SmPC and RMP, and by a dose reduction for patients at risk of infections. Also a recommendation to consider zoster vaccination has been included in the SmPC.

Uncertainties are noted regarding long-term safety regarding CV risks due to hyperlipidaemia and malignancies. This could only reasonably be addressed in a large population in a post-marketing setting. A PASS in a US insurance database and the US registry Corrona is proposed by the Applicant, and a DUS to evaluate the adherence to risk minimisation measures. Also European registries will be involved, which is

supported, as there may be differences in the background risks of malignancy, opportunistic infections and CV events (e.g. smoking, diet), treatment modalities and access to healthcare/biologics between the two continents (see RMP section below).

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Herpes zoster • Hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia)
Important Potential Risks	• Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • Myelosupression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for drug-induced liver injury • Gastrointestinal perforation • Major adverse cardiovascular events (MACE) • Foetal malformation following exposure in utero
Missing Information	• Long-term safety • Use in very elderly (≥75 years) • Use in patients with evidence of hepatitis B or hepatitis C infection • Use in patients with severe hepatic impairment • Use in patients with a history of or current lymphoproliferative disease • Use in patients with active or recent primary or recurrent malignant disease • Use in paediatric patients • Effect on fertility, on pregnancy and the foetus, and use in breastfeeding • The effect on vaccination efficacy, the use of live/attenuated vaccines • Use in combination with bDMARDs or with other JAK inhibitors • Inhibitory effect of baricitinib on OAT2

Pharmacovigilance plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Observational US Postmarketing safety registry (Category 3)	To monitor the incidence rate and profile of serious infections (including opportunistic infections such as tuberculosis and *Candida* infections and PML), major adverse cardiovascular events (MACE), and malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) among patients with long-term exposure to baricitinib compared to patients with long-term exposure to other medications indicated for moderate-to-severe RA. We will also aim to describe the occurrence of lymphoma, herpes zoster, opportunistic infections such as tuberculosis, *Candida* infections, and PML, rhabdomyolysis, agranulocytosis, gastrointestinal perforations, and evidence of drug-induced liver injury	Important identified Risks: Herpes Zoster, Hyperlipidaemia Important potential risks: malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers), serious and opportunistic infections (including tuberculosis, *Candida* infections, PML), myelosuppression (agranulocytosis), myopathy including rhabdomyolysis, potential for drug-induced liver injury, gastrointestinal perforation, and MACE	Planned	No interim reports are planned. Final report: Anticipated Q1 2031; Final report will be submitted with next appropriate PSUR, unless there are safety findings which change the benefit/risk
Observational safety study using an existing database (Category 3)	(1) To monitor the incidence rate and profile of serious infections (including opportunistic infections such as tuberculosis and Candida infections, major adverse cardiovascular events (MACE), and malignancies (including lymphoma and malignancies that are typically virus-induced, such as cervical and many oropharyngeal cancers) among patients with long-term exposure to baricitinib compared to patients with long-term exposure to other medications indicated for moderate-to-severe RA. We will also aim to describe the occurrence of lymphoma, herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, gastrointestinal perforations, and evidence of drug-	Important identified Risks: Herpes Zoster, Hyperlipidaemia Important potential risks: malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancer), serious and opportunistic infections (such as Tuberculosis, Candida infections, PML), myelosuppression (agranulocytosis), myopathy including rhabdomyolysis, potential	Planned	No interim reports are planned. Final report: Anticipated Q1 2031 Final report will be submitted with next appropriate PSUR, unless there are safety findings which change the benefit/risk

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	induced liver injury. (2) To validate the results of the post-marketing safety registry.	for drug-induced liver injury, gastrointestinal perforation, and MACE.		
Assessment of the Effectiveness of the Patient Alert Card and Healthcare Professional Educational Material (Category 3)	(1)To assess the understanding of and adherence to the key risk minimisation messages and required mitigating actions regarding: • Use in Pregnancy • Infections • Lipids in the HCP Educational Material and Patient Alert Card (PAC) among a sample of HCPs. (2) To assess patient outcomes, i.e., occurrence of pregnancy, among RA patients who would have received the PAC (3) To understand the pattern of use of baricitinib, including among women of childbearing age and during pregnancy	Important Identified Risks • Herpes Zoster • Hyperlipidaemia Important Potential Risks: • Serious infections (including opportunistic infections) • MACE • Foetal malformation following exposure in utero • Use in pregnancy and breast feeding	Planned	Final report: Anticipated within 4 months of end of data collection Final report will be submitted with next appropriate PSUR, unless there are safety findings which change the benefit/risk
Vaccine addendum to Protocol I4V-MC-JADY (Category 3)	To monitor the use of baricitinib with live, attenuated vaccines in everyday clinical practice To evaluate the proportion of RA patients with satisfactory humoral responses to pneumococcal conjugate vaccine and tetanus toxoid containing vaccines 5 weeks post-vaccination in patients receiving baricitinib without background MTX (baricitinib without MTX) and in those receiving baricitinib including background MTX (baricitinib + MTX).	Missing information: The effect on vaccination efficacy, the use of live/attenuated vaccines	Started	Abstract: Q3 2017 To be submitted with next appropriate PSUR, unless there are safety findings which change the benefit/risk
Observational post marketing disease registry in EU patients (Category 3)	As possible given data available in the EU registries: (1) To monitor the incidence rate and profile of serious and opportunistic infections (such as tuberculosis and Candida infections), major adverse cardiovascular events (MACE), and malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers) among patients with long-term exposure to baricitinib compared to	Important identified Risks: Herpes Zoster, Hyperlipidaemia Important potential risks: malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers),	Planned The availability of data to address the safety objectives is currently under investigation, including the	Final report: TBD Final report will be submitted with next appropriate PSUR, unless there are safety findings which change the benefit/risk

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	patients with long-term exposure to other medications indicated for moderate-to-severe RA. (2) We will also aim to describe the occurrence of lymphoma, herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, gastrointestinal perforations, and evidence of drug-induced liver injury.	serious and opportunistic infections (such as Tuberculosis, Candida infections, PML), myelosuppression (agranulocytosis), myopathy including rhabdomyolysis, potential for drug-induced liver injury, gastrointestinal perforation, and MACE.	possibility of linking data from an RA registry to additional data sources, e.g., Nordic healthcare data, for improved assessment of adverse events with long latency.	
In vitro study to investigate the effect of inhibition of OAT2 by baricitinib (Category 3)	Investigate if inhibition of OAT2 by baricitinib may help explain the increase in serum creatinine	Missing information: Inhibitory effect of baricitinib on OAT2	Planned	Q2 2017 Final report will be submitted with the next appropriate PSUR

Risk minimisation measures

Important Identified Risk	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Herpes zoster	The proposed text in the SmPC (4.4, the Special Warnings and Special Precautions for Use section) will: o inform that viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies with baricitinib, and advise that if a patient develops herpes zoster, baricitinib treatment should be interrupted until the episode resolves.	Healthcare Professional Educational Material Patient Alert Card
Hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia)	Increases in LDL and triglycerides are included in the SmPC as adverse drug reactions. The proposed text in the SmPC (4.4, the Special Warnings and Special Precautions for Use section) will inform that increases in lipid parameters were reported in patients treated with baricitinib, and advise that patients should be managed according to international clinical guidelines for hyperlipidaemia.	Healthcare Professional Educational Material Patient Alert Card
Important Potential Risk		
Malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers)	The proposed text in the SmPC (Section 4.4, Special warnings and precautions for use) will inform that the risk of malignancy including lymphoma is increased in patients with RA and that immunomodulatory medicinal products may increase the risk of malignancies and lymphoma.	None.
Serious and opportunistic infections (including Tuberculosis, Candida infections, PML)	Specific infections are included in Section 4.8 of the SmPC as adverse drug reactions. The proposed text in the SmPC (4.4, the Special Warnings and Special Precautions for Use section) will: • inform that baricitinib treatment is associated with an increased rate of infections such as upper respiratory tract infections. • advise that the risks and benefits of treatment with Olumiant should be carefully considered prior to initiating therapy in patients with active, chronic, or recurrent infection. • advise that if such an infection develops, the patient should be monitored carefully and Olumiant should be temporarily interrupted if the patient is not responding to standard therapy. It will also advise not to resume baricitinib until the infection resolves. • inform that patients should be screened for TB before commencing baricitinib, and that baricitinib should not be given to patients with active TB, and advise to consider anti-TB therapy prior to initiation of baricitinib in patients with previously untreated latent TB. • inform that viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster, herpes simplex), were reported in clinical studies with baricitinib, and advise that if a patient develops herpes zoster, baricitinib treatment should be temporarily interrupted until the episode resolves. • advise that patients with hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, should be monitored for expression of hepatitis B virus (HBV) DNA; and if HBV DNA is detected, a liver specialist should be consulted.	Healthcare Professional Educational Material Patient Alert Card
	• inform that neutropenia (<1 x 109 cells/L) was seen in <1% of patients in clinical trials. It will advise to avoid initiation or temporarily interrupt baricitinib treatment in patients with an absolute neutrophil count (ANC) <1 x 109 cells/L.	
Myelosupression (agranulocytosis)	Neutropenia is included in Section 4.8 of the SmPC as an adverse drug reaction. Section 4.4 of the SmPC (Special warnings and precautions for use) will	None

	inform that Absolute Neutrophil Count (ANC) < 1 x 109 cells/L was reported in less than 1 % of patients in clinical trials and advise that treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 109 cells during routine patient management.	
Myopathy including rhabdomyolysis	Section 4.8 of the SmPC will inform prescribers that increases in CPK values were common adverse drug reactions in clinical trials but that there were no confirmed cases of rhabdomyolysis. Further characterisation of the ADR is also provided in section 4.8 of the SmPC	None
Potential for drug-induced liver injury	Increases in aminotransferases are included in table and text in Section 4.8 of the SmPC as adverse drug reactions. The proposed text in the SmPC (4.4, the Special Warnings and Special Precautions for Use section) will: • inform that baricitinib treatment is associated with increases in aminotransferases and that increases to ≥5 and ≥10 x ULN were uncommonly observed for both ALT and AST, in patients treated with baricitinib in clinical trials. • advise that if increases in ALT or AST are observed, and drug-induced liver injury is suspected, baricitinib should be interrupted until this diagnosis is excluded. SmPC Section 4.2 will advise that the use of baricitinib in patients with severe hepatic impairment is not recommended.	None
MACE	Increases in LDL and triglycerides are included in the SmPC as adverse drug reactions. The proposed text in the SmPC (4.4, the Special Warnings and Special Precautions for Use section) will inform that increases in lipid parameters, including total cholesterol, LDL, HDL, and triglycerides, were reported in patients treated with baricitinib, and advise that patients should be managed according to international clinical guidelines for hyperlipidaemia.	Healthcare Professional Educational Material (lipid monitoring) Patient Alert Card.
Foetal malformation following exposure in utero	Section 4.3 of the SmPC includes a contraindication for use in pregnancy The proposed text in the SmPC (4.6 Fertility, Pregnancy and Lactation) will inform that there are limited data from the use of baricitinib in pregnant women, and that studies in animals have shown reproductive toxicity, so state that baricitinib should not be used during pregnancy. In addition, advice is provided that women of childbearing potential have to use effective contraception while taking baricitinib and for at least 1 week after final treatment. If a patient becomes pregnant while taking Olumiant the parents should be informed of the potential risk to the foetus Reference to the specific abnormalities observed in non-clinical species is also included in Section 5.3 of the SmPC.	Healthcare Professional Educational Material Patient Alert Card.
GI Perforations	None	None
Missing Information		
Long-term safety	Section 4.4 of the SmPC states that the effect of lipid elevations on cardiovascular morbidity and mortality has not been determined and that the clinical data are insufficient to assess the potential incidence of malignancies following exposure to baricitinib. Section 4.8 of the SmPC states that the rate of serious infections, the pattern and incidence of elevation in ALT/AST, lipids, CPK and platelets as well as decreases in neutrophils, remained stable with long term treatment.	None
Use in very elderly (≥75 years)	Section 4.2 of the SmPC will advise that therapeutic experience in patients ≥75 years is very limited, and in these patients a starting dose of 2-mg is appropriate.	None
Use in patients with evidence of hepatitis B or hepatitis C infection	Section 4.4 of the SmPC will advise that screening for viral hepatitis should be performed before starting treatment and that if HBV DNA is detected, a liver specialist should be consulted to determine if treatment interruption is warranted.	None
Use in patients with severe hepatic impairment	Section 4.2 of the SmPC will advise that Olumiant is not recommended for use in patients with severe hepatic impairment; Section 5.2 will provide further pharmacokinetic data on use in patients with hepatic impairment.	None
Use in patients with a	Section 4.4 of the SmPC will advise that rare cases of lymphoproliferative	None

history of or current lymphoproliferative disease	disorders have been reported.	
Use in patients with active or recent primary or recurrent malignant disease	None.	None
Use in paediatric patients	Inclusion of wording in Section 4.2 of the SmPC to the effect that the safety and efficacy of Olumiant in children and adolescents aged 0 to 18 years have not yet been established, and that no data are available.	None
Effect on fertility, on pregnancy and the foetus, and use in breastfeeding	Section 4.3 of the SmPC includes a contraindication for use in pregnancy Section 4.6 of the SmPC will state that women of childbearing potential have to use effective contraception during and for at least 1 week after treatment. If a patient becomes pregnant while taking Olumiant the parents should be informed of the potential risk to the foetus. It will further state that a risk to newborns/infants cannot be excluded and Olumiant should not be used during breast feeding. The impact on fertility in female rats in non-clinical studies is included in section 5.3 of the SmPC	None
The effect on vaccination efficacy, the use of live/attenuated vaccines	Section 4.4 of the SmPC will advise that use with live, attenuated vaccines during, or immediately prior to, Olumiant therapy is not recommended	None
Use in combination with bDMARDs or with other JAK inhibitors	Section 4.4 of the SmPC recommends against use with bDMARDs or other JAK inhibitors as a risk of additive immunosuppression cannot be excluded.	None
Inhibitory effect of baricitinib on OAT2	Section 5.1 of the SmPC advises that, due to inhibition of creatinine secretion by baricitinib in the renal tubules, estimates of the glomerular filtration rate based on serum creatinine may be slightly reduced, without actual loss of renal function or the occurrence of renal adverse events.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant compared the structure of baricitinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers baricitinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet, for the purpose of providing online access to information extracted from the package leaflet and additional information on the disease for which the medicinal product is indicated, has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

-the package leaflet

-additional information on the disease (found acceptable as compliant with Article 62 of Directive 2001/83).

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Olumiant (baricitinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

RA is a common chronic auto-immune disorder with synovitis of the joints. If the inflammation is insufficiently treated, it may lead to permanent structural joint deformations and loss of function. The aim of the treatment of baricitinib (and other DMARDS) is to suppress inflammation and disease progression.

3.1.2. Available therapies and unmet medical need

RA patients are treated with disease-modifying anti-rheumatic drugs (DMARDs), often in combination of multiple DMARDS and/or steroids. As an early intervention with DMARDs has shown to preserve function, the classification criteria of RA were modified by the ACR-EULAR in 2010 to allow DMARDs in an earlier disease phase. Treatment-to-target is recommended, i.e. that disease activity is continuously monitored and treatment is adjusted to obtain remission or at least LDA (low Disease Activity).

First choice of treatment is, in general, methotrexate (MTX), often accompanied with other synthetic DMARDs or corticosteroids at the start of treatment and at flares. About 50% of the patients do not respond sufficiently to MTX, and require additional treatments with biologic DMARDs like TNF-inhibitors (TNF-I), tocilizumab (IL-6 inhibitor) and abatacept (inhibits T-cell activation). These biologic DMARDs, in combination with MTX, are also indicated for DMARD-naïve patients with *severe* RA, but in clinical practice bDMARDs are mainly used as second line therapy. Rituximab, a B-cell antagonist, is registered as a treatment option in patients irresponsive to TNF-I.

There is an unmet medical need for alternative treatment options with a new mode of action for patients irresponsive to multiple DMARDs including biologics. Furthermore, there is a need for alternative oral options when biological DMARDs are of limited availability or for patients unable to administer parenteral products.

3.1.3. Main clinical studies

Four randomised confirmatory trials were performed to confirm efficacy and safety in RA (DMARD naïve, patients with inadequate response to cDMARDs and bDMARDs).

Two of the trials were active-controlled non-inferiority trials, where the active control was maintained for 52 weeks. In the second line setting, baricitinib 4 mg was compared to TNF-I adalimumab (52 weeks) and placebo (24 weeks) in MTX-IR patients (Study JADV, N = 1307). The patients maintained prior treatment of MTX in this study. This large-scaled, long-term active-controlled trial is considered a pivotal study.

In the first line setting in DMARD-naïve patients, baricitinib 4 mg, with or without MTX, was compared to MTX alone (Study JADZ, N=584). Since the application for the first-line indication has been withdrawn, this study is considered as supportive evidence for efficacy (see discussion below).

The other trials were dose-finding studies with baricitinib 2 and 4 mg, and placebo in second line. All treatments were add-on to MTX or other cDMARDs like leflunomide. One dose-confirmation trial was performed in patients with an inadequate response to conventional synthetic DMARDS, but not treated with biologic DMARDs (Study JADX, N=684). The other dose confirmation trial was performed in more treatment-experienced patients irresponsive to one or more biologic DMARDs (N= 527, Study JADW).

All subjects from the Phase III trials could enter open-label extension study JADY. In this study, the possibility of dose tapering was investigated in a subset of patients (N = 293), who achieved sustained Low Disease Activity after at least 15 months of treatment on a 4 mg dose. Subjects were randomised to either continuation of the 4 mg dose or a low 2 mg dose (double-blinded).

3.2. Favourable effects

Although non-inferiority was aimed, baricitinib 4 mg showed superior efficacy for primary endpoint ACR20, as compared to active-control adalimumab in MTX-IR patients (Study JADV). In the primary analyses, ACR20 at Week 12 was 69.6% for baricitinib 4 mg, 61.2% for adalimumab, and 40.2% for placebo (difference vs. placebo 29.4% (95% CI 23.5, 35.4), vs. adalimumab (8.4 (1.7, 15.1)). Low Disease Activity (LDA) responder rates of baricitinib 4 mg were -marginally- superior to adalimumab at Week 52 (see effects table below). Non-inferiority between baricitinib 4 mg and adalimumab was shown for the other endpoints regarding remission, prevention of radiographic progression and physical function, within acceptability ranges of -/+ 12% for the responder rates (see effects table below).

Furthermore, in Study JADZ in DMARD-naïve patients, baricitinib 4 mg was superior to MTX monotherapy regarding ACR20 and remission outcomes, including the most critical one, the ACR-EULAR Boolean definition. The prevention of structural joint damage was superior for the baricitinib + MTX combination versus MTX monotherapy -though not for baricitinib monotherapy. See effects table below.

In Study JADX, in patients with an inadequate response to conventional DMARDs (second line), both the baricitinib 2 and 4 mg dose were superior to placebo after 12 and 24 weeks, without relevant differences between 2 and 4 mg dose for the primary endpoint ACR20. The prevention of structural damage by X-ray, however, was more robustly shown for the 4 mg dose than the 2 mg dose as confirmed by conservative sensitivity analyses such as LOCF. About 30% of the subjects in this study received other synthetic DMARDs than MTX as background therapy. This had no relevant impact on efficacy outcomes.

In more treatment-experienced patients irresponsive to biologic DMARDS in Study JADW, there was a more clear distinction between the 2 and 4 mg dose. The response of the primary endpoint ACR20 at Week 12 was 55.4% for baricitinib 4 mg, 48.9% for baricitinib 2 mg and 27.3% for placebo (difference baricitinib 4 mg vs placebo: 28.1% (95% CI 18.2, 37.9), 2 mg vs placebo 21.6 (11.7, 31.5). More clinical meaningful treatment effects were shown for the 4 mg dose regarding LDA and remission. E.g. the percentage of subject with DAS28-hsCRP≤ 3.2 at Week 24, was 33.3% for baricitinib 4 mg, 20.1% for baricitinib 2 mg, and 11.4% for placebo (baricitinib 4 mg vs PBO: difference 22.0% (95% CI 13.6, 30.3); baricitinib 2 mg vs PBO: 8.8% (1.2, 16.3)). Similar results were observed for LDA by CDAI, an outcome which is unbiased for the specific effect of acute phase reactants by baricitinib (see effects table below)

Maintenance of efficacy has been further established in the two long-term 52 weeks active controlled studies (JADZ and JADV) (see effects table below).

The possibility of dose-tapering was further evaluated in a subset of patients from the long-term extension Study JADY. After 12 weeks, 93% of patients continuing with 4 mg versus 84% of the patients stepping down to 2 mg, maintained Low Disease Activity level (p = 0.03).

3.3. Uncertainties and limitations about favourable effects

In study JADZ in naïve patients, the active comparator consisted of MTX monotherapy. This may be considered suboptimal. The recent EULAR RA treatment guideline recommends a combination of low dose steroids or other synthetic DMARDs with MTX in naïve patients, to overcome the fact that MTX has to be slowly titrated and, therefore, has a slow onset of effect.

3.4. Unfavourable effects

Haematology /immunology

Baricitinib reduced the levels of neutrophil granulocytes and NK-cells. Severe neutropenia (< 1.0 billion cells /L), however, was rarely reported (0.2 and 0.6 % after the 2 and 4 mg dose, respectively, versus 0 placebo). The risk of infections was higher at neutropenia. About 20% of the subjects had NK-levels below normal level. Monitoring guidance on absolute neutrophil count has been included in the SmPC (see section 4.4).

Infections

A statistically significant larger proportion of patients treated with baricitinib 4 mg had infections comparing to placebo (36.3% vs. 27.9%, respectively, Odds Ratio 1.4 (95% CI 1.2-1.7), p < 0.001). Most infections were upper-respiratory tract infections or gastro-enteritis. The rates of serious infections were overall modest (1.5% vs 1.6%, for baricitinib 4 mg vs placebo, leading to permanent discontinuations: 1.5% vs. 0.7%). The rate of infections increased with the baricitinib dose (e.g. 30.6% vs. 42.5% for the 2 and 4 mg dose, respectively Study JADX). A warning regarding initiation of baricitinib therapy has been included in the SmPC (see section 4.4).

Baricitinib induced viral reactivation. In the pooled analyses at Week 24, the incidence of herpes zoster was 1.8% versus 0.4% placebo (Odds ratio 4.59 (95% CI 1.5, 13.6), and maintained stable at longer-term follow up. The incidence was also higher as compared to active comparator MTX and –to lesser extent- adalimumab (see effects table below). The majority of the cases were uncomplicated: 5 out of the 138 cases involved of multiple dermatomes and/or facial nerve palsy). The highest incidence and background risk of h. zoster was observed in heavily re-treated patients irresponsive to biologic DMARDS (see effects table). It is recommended in the SmPC (section 4.4) that in case a patient develops herpes zoster, Olumiant should be temporarily interrupted.

There was no obvious signal of opportunistic infections.

Malignancies

The mean incidence rate of malignancies excluding NMSC (non-melanoma skin cancer) in the pooled dataset was 0.73 per 100 py (95% CI 0.5, 1.0), which was within the range of historical data from trials with other DMARDs (0.56-1,43 per 100 py). The point estimate of the IR of all malignancies excluding NMSC was higher for the 4 mg dose (1.1/100 PY), than for the 2 mg dose arm (0.4/100 PY), although the 95% CI of the incidences overlapped (0.4, 2.4 for 4 mg dose, and 0.1, 1.6 for the 2 mg dose). Most commonly reported

solid malignancies were mamma carcinoma (6 of the in total 36 cases), lung cancer (5 cases) , GI tract cancer (5 cases) and melanoma (2 cases). The mean incidence of NMSC was 0.4/100 PY (95% CI 0.2, 0.6), which is compatible to other RA study populations.

In the data original submitted, with a cut-off date of 15 Augustus 2015, three cases of lymphoma were reported. In the follow-up period of 4 months till 1 January 2016, two new cases were reported. The IR increased from 0.06 to 0.095 per 100 PY (95% CI, 0.031, 0.223). The latter IR is still within the range as reported for the general RA patients' population, which is a population at risk of lymphoma. Of the in total 5 cases, Epstein Barr virus involvement was confirmed for one B-cell lymphoma, one was related to H.pylori (MALT), and the one case of T-cell lymphoma was confirmed EBV negative, and two cases were not evaluated on EBV involvement.

Lipids

It is known that RA patients with high active disease activity have reduced lipid levels. Despite relatively low lipids levels in patients with high active disease state, uncontrolled RA is associated with an increased risk of CV events, probably because of inflammation of the vascular system. It is thought that the related benefits of suppression of inflammation seems to outweigh the risk of lipid changes.

Whether this is also the case for baricitinib, which had an unprecedented high effect on lipids , 2-3 times exceeding alternative treatments, needs to be further confirmed post-marketing in the general target population, which may be at higher risk than the selected trial population. Lipid increments will be further followed in a PASS.

Hepatotoxicity

ALT and AST increments from baseline < 3 x ULN were commonly reported (about 20%). Significant ALT or AST increments (>5 x ULN) were in general rare and transient. If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, Olumiant should be temporarily interrupted until this diagnosis is excluded.

Gastrointestinal

In naïve patients, nausea and vomiting were reported at similar rates for baricitinib and MTX monotherapy, though the combination was less well tolerated (see effects table)

GI perforations are an established risk of other DMARDS targeting IL6 pathway. The incidence of GI perforation for baricitinib is low (two cases, 0.05 per 100 PY).

Creatine Phosphokinase (CPK)

Baricitinib induces an increment of CPK levels. The incidence rates of significant increments (> 5 x ULN) were 1.3% for the 4 mg dose, 0.8% for the 2 mg dose, and 0.3% for placebo. There was no clinical sequela.

Pregnancy

Because of the pre-clinical findings of skeletal deformations in foetus, a contra-indication in pregnancy has been included in the SmPC. The need for a pregnancy prevention plan was evaluated, since several pregnancies (15) occurred in the trial setting, despite restrictive measures in the protocol. To address this issue, educational material, including a patient alert card, will be made available in order to emphasiz the contra-indication and addressing that child-wish should be discussed with patients. In addition to the contra-

indication, additional wording has been added to section 4.6 of the SmPC that women of childbearing potential have to use effective contraception during and after treatment. If a patient becomes pregnant while taking Olumiant the parents should be informed of the potential risk to the foetus. At present stage, these measures are considered adequate by CHMP, and no PPP is requested. No signal of teratogenicity in humans was observed thus far, though the numbers are too small to exclude such a risk at present stage.
Furthermore, an European treatment guidance by the EULAR is available, addressing that rheumatologists should be aware of the risks of DMARDs at conception and during pregnancy.
As the target population also includes younger women, the need for contraception will also be addressed in the alert card.

3.5. Uncertainties and limitations about unfavourable effects

Malignancies

The incidence rates of malignancies and NMSC of baricitinib were in line with what has been reported for other DMARDs or RA populations. Also the SIR of all malignancies or lymphoma was within the range of expectations. Pre-clinical studies did not indicate that baricitinib is carcinogenic. However, the confidence interval of the estimates are wide, and 2 cases of lymphoma emerged in a relatively short time frame of 4.5 months of follow-up (920.3 PY). However further data regarding the risk of malignancies will be generated in post-marketing (see RMP section).

Lipids

The consequences of increased LDL-C levels by baricitinib are not fully clear, as these exceeded the effects of standard care with controls MTX and adalimumab on lipids. It may take multiple years before CV events due to hypercholesterolaemia develop. Moreover, the general target population may be at higher risk of CV disorders than the selected study populations. Lipid increments will be further followed in a PASS.

PK interactions

There are uncertainties regarding interaction at the level of P-glycoprotein, OAT2 and OCT1 transporters, which will be addressed post-marketing.

Pregnancy

In two animal models, baricitinib showed skeletal anomalies in developing foetus, with relatively low safety margin (NOAEL < 2 times therapeutic level). No signal of teratogenicity was observed in the limited number of exposed pregnancies (n=15) in the trial setting, though the exposed population is too small to draw conclusions regarding the risks of baricitinib for the foetus.

Elderly

In patients aged ≥65 years, a 5 times higher incidence rate of h.zoster was observed in the 4-mg than in the 2-mg dose group in the bDMARD-IR patients' population (13.5% versus 2.4%). Limited data were available in very elderly 75 years (n=77). A recommendation for dose reduction in patients over 74 years has been included in the SmPC.

3.6. Effects Table

Table 52. Effects Table for baricitinib for treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to disease-modifying anti-rheumatic drugs (including conventional or biologic DMARDs)

DMARD-naïve RA patients (First Line)Effect	Short Description	Unit	Treatment		Control	Uncertainties / Strength of evidence	References
Favourable effects							
			BARI 4 mg	**BARI + MTX**	**MTX**	SoE: superior to MTX mono-therapy regarding ACR20scores, remission, and physical function. The treatment effects were persistent over 52 weeks. Un: MTX monotherapy is not considered an optimal comparator in naïve patients. Un: Only the combination BARI+MTX, and not BARI monotherapy, was superior to MTX regarding the prevention of radiographic progression of joint damage.	Study JADZ
PE ACR20	-20% improvement from BL , W24	%	76.7	78.1	61.9		
ACR20	W52	%	73.0	72.6	55.7		
DAS28hsCRP< 2.6	Remission W24	%	40.3	40.5	23.8		
	W52	%	44.0	48.8	23.8		
CDAI ≤ 2.8	Remission W24	%	21.4	22.3	11.0		
	W52	%	25.2	28.4	15.7		
Boolean	Remission W52	%	17.0	20.9	11.4		
HAQ-DI >=0.3	Physical function W24	%	77.4	74.4	65.7		
	W52	%	64.8	66.5	53.3		
mTSS ≤0	No X-ray progress	%	69	80	66		
Unfavourable effects							
Infections W52		%	43.4	50.2	38.1	Unfavourable for BARI, highest risk of the combination	Study JADZ
Serious infections W52		%	3.8	2.3	3.8	Similar risks among treatments	
h.zoster W52		%	2.5	2.3	1.0	Unfavourable for baricitinib	
Nausea W24		%	4.4	7.4	5.2	The combination was less tolerated	
Vomiting W24		%	2.5	0.5	1.9	Similar risks among treatments	
ALT > 5 x ULN W52		%	0.6	1.4	1.0	increased risk of the combination	
LDL-C > 4.1 W24		%	22.4	18.2	7.1	Unfavourable for BARI	

MTX-IR patients (Second Line)

Effect	Short Description	Unit	Treatment		Control	Uncertainties / Strength of evidence	References
Favourable effects							
			BARI 4 mg	**PCO**	**ADA**		
PE ACR20	-20% BL signs & symptoms W24 W52	%	 73.9 71.3	36.7	 66.4 61.3	SoE: Both BARI 4 mg and ADA were superior to placebo in all domains. BARI 4 mg was superior to ADA regarding ACR20 /ACR50/ACR70, LDA and HAQ-DI. Non-inferiority was shown for remission and prevention of radiographic bone damage.	Study JADV
DAS28hsCRP≤ 3.2	LDA W24 W52	%	 52.4 55.6	19.1	 47.9 48.2		
CDAI ≤10.0	LDA W24 W52	%	 49.9 56.9	19.7	 47.6 49.4		
HAQ-DI >=0.3	Physical function W24 W52	%	 66.7 61.4	37.1	 59.7 54.8		
mTSS ≤0	No X-ray progress W24 W52	%	 81 79	70	 83 81		
Unfavourable effects							
Infections W24 Infections W52		%	36.1 47.8	27.5 NA	33.3 43.9	Similar risk for BARI and ADA	Study JADV
Serious infections W52		%	2.1	NA	1.5	Slightly increased risk for BARI as compared to ADA	
h. zoster W24 h. zoster W52		%	1.5 2.3	0.4 NA	1.2 1.5	Modestly increased risk for BARI as compared to ADA	
ALT > 5 x ULN W24		%	0.6	1.0	0.9	No increased risk vs ADA	
LDL-C > 4.1 W24		%	16.8	3.8	9.2	Unfavourable for BARI	

Abbreviations: ADA= adalimumab, ALT= alanine aminotransferase , BL=baseline, CDAI= Clinical Disease Activity Index, HAQ-DI = Health Assessment Questionnaire-Disability Index, LDL-C= low-density lipoprotein cholesterol, mTSS = modified Total Sharp Score, PE=primary endpoint, progress= progression, ULN=upper level of normal, W=Week

Notes: LDL-C category shift from normal at baseline to high (>4.1 µmol/L)

bDMARD-IR patients

Effect	Short Description	Unit	Treatment		Control	Uncertainties / Strength of evidence	References
Favourable effects							
			BARI 4 mg	**BARI 2 mg**	**placebo**	SoE: Both the 2 and 4 mg dose were superior to placebo after 24 weeks regarding improvement in signs and symptoms (ACR), percentage responders disease state targets (LDA and remission) and physical function. More clinical meaningful treatment effects were shown for the 4 mg regarding LDA and remission, as compared to the 2 mg dose.	Study JADW
ACR20	-20% from BL Signs & symptoms W24	%	44.8	46.3	27.3		
DAS28hsCRP≤ 3.2	LDA W24	%	33.3	20.1	11.4		
CDAI ≤10.0	LDA W24	%	31.1	23.0	15.3		
HAQ-DI >=0.3	Physical function W24	%	43.5	41.4	23.9		
Unfavourable effects							
h. zoster % [per 100 py] W24		%	4.0 [9.55]	1.1 [2.86]	1.1 #[3.04]	Dose dependent risk	Study JADW

Effect	Short Description	Unit	Treatment		Control	Uncertainties / Strength of evidence	References
LDL-C W24		%	24.6	18.4	11.3	Dose dependent risk	
ALT > 5 x ULN W24		%	0.8	0.6	0.4	Dose dependent risk	

Abbreviations: BL=baseline, CDAI= Clinical Disease Activity Index, LDL-C= low-density lipoprotein cholesterol, HAQ-DI = Health Assessment Questionnaire-Disability Index, PE=primary endpoint, W=Week

Notes: #H.zoster incidence overall the highest in the more extensive pre-treated study population bDMARD-IR patient versus naïve or MTX-IR patients (table 5.1.a a& b). LDL-C category shift from normal at baseline to high (>4.1 µmol/L)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Important favourable effects

Baricitinib as an oral treatment was efficacious to reduce disease activity in patients with moderate-severe active RA to a clinically relevant extent.

In all 4 trials in different disease stages, varying from DMARD-naïve RA patients to treatment-experienced patients with an inadequate response to multiple biologic DMARDs, the primary endpoint ACR20 at Week 12-24 was met. Also maintenance of efficacy has been demonstrated in 12 months trials, which is important in a chronic disorder like RA.

ACR20 represents a relative small improvement of 20% of signs and symptoms from baseline. From epidemiological databases and long-term follow-up studies it is known, that sustained reduction of disease activity below an established target -remission or Low Disease Activity according to DAS28- prevents structural joint damage and deterioration of physical function. Baricitinib showed superior efficacy regarding DAS28-CRP remission/LDA compared to placebo and active control adalimumab and MTX. Recently, it was noted in the literature that for drugs with a specific effect on acute phase reactant, like baricitinib, DAS28-CRP may overestimate remission response. LDA and remission targets as defined by SDAI/CDAI, endpoints which are less biased by the effect on acute phase reactant, were also superior for baricitinib, as compared to placebo and active controls.

Furthermore, clinical relevance of ACR20 is supported by other endpoints, such as prevention of structural damage by X-ray, improvement of physical function (HAQ-DI), fatigue, morning stiffness and several QOL scales.

There is a need for new treatment options of patients with an inadequate response to multiple classes of DMARDs. Baricitinib fulfils this need, as shown in subgroup analyses in this special patients' group where baricitinib was superior to placebo in achieving LDA.

Currently, limited alternative *oral* treatment options are available for patients irresponsive to MTX, the first choice of treatment, and biologic DMARDS will be used often in these patients. Biologics have the risk of drug-antibody formation, and subsequent loss of efficacy and infusion reactions, which are not apparent for baricitinib. Patients may prefer oral drugs over parental administrations. Another favourable aspect of baricitinib as compared to biologicals is its considerable shorter PK and PD half-life. Treatment interruption in case of an adverse drug reaction is more abrupt than for biologicals. In addition, baricitinib would be the only oral treatment option that will be registered for patients irresponsive to a bDMARD thus far.

In general, the studies were adequately designed. However, in Study JADZ in naïve patients, MTX monotherapy was chosen as comparator which is not considered optimal to modern standards. As MTX has to be titrated for reason of tolerability, the onset of effect is relatively slow. A combination of corticosteroids and other synthetic DMARDs, as recommended in the EULAR treatment guideline in accordance to the treatment-to-target principle, would have been a more optimal comparator. However, since this was not discussed at the scientific advices when designing the studies and as the CHMP approved the study design, this issue forms no major objection. Although the treatment effect of baricitinib may have been somewhat inflated in this study in naïve patients, the response to baricitinib is still considered robust and clinically meaningful on its own.

Importance unfavourable effects

The drop-out rates of baricitinib due to any adverse event were overall modest, though higher than the active controls MTX and adalimumab. Common Adverse Drug Reactions were infections, liver enzyme abnormalities, and hyperlipidaemia. Important Adverse Drug Reactions that were more frequently reported for baricitinib than the active controls were infections by herpes zoster and hyperlipidaemia.

Viral reactivation and H.zoster is a particular risk due to the mode of action of JAK inhibitors, baricitinib included. It was argued that most cases (95%) were uncomplicated and the minority of these cases were reported as SAE (14%). However, herpes zoster may induce post-herpetic neuralgia, which could be long-lasting and bothersome for patients. Baricitinib caused persistent increments of lipids including LDL-cholesterol. Lipid increments were also observed for the active controls MTX and adalimumab, however, to considerable lesser extent than for baricitinib. There was no increased incidence of MACE for baricitinib as compared to placebo or active controls. The trial population constituted a selected population at low risk of cardiovascular events, as compared to the general target population of RA patients, where the incidence of CV events is reported to be as twice as high as the normal reference population.

Thus far, the incidence rates of malignancies and NMSC of baricitinib were in line with what has been reported for other DMARDs or RA populations. Also the SIR of all malignancies or lymphoma was within the range of expectations.

3.7.2. Balance of benefits and risks

Baricitinib showed a relevant and persistent clinical response, in a study population representative for the target population. At the standard dose of 4 mg, baricitinib was superior to adalimumab regarding LDA and fatigue. Baricitinib in combination with MTX also prevented structural joint damage.

For the second-line target population of RA patients not responding to synthetic DMARDs, very limited *oral* alternative treatments are available. Biologic DMARDs have risks such as antibody formation and infusion reaction, which is not present for oral synthetic drugs like baricitinib. Some patients may prefer oral treatment over injections. Baricitinib fulfils the need for patients with an inadequate response to multiple biologic DMARDs.

The incidence of herpes zoster of baricitinib was increased compared to adalimumab in the trial, and historical data of TNF-inhibitors and tocilizumab. However, alternative treatment options like TNF-I have shown an increased risk of disseminated tuberculosis, and rituximab has been associated with PML, which is not the case for baricitinib. Several risk minimisation measures have been put in place, such as a dose reduction to 2 mg in patients at risk (i.e. patients with history of recurrent infections and elderly > 75 y) and interruption of treatment in the case reactivated herpes zoster. In the trials, treatment was immediately

withdrawn once symptoms of h.zoster infection occurred, and this may have contributed that complications such as facial palsy and systemic features were limited. A patient alert card will be available, which may help to early diagnose the patients in real-life clinical setting. Taking these measures into consideration, the benefits of baricitinib outweigh the risk of h.zoster.

Hypercholesterolaemia was higher for baricitinib than for the active control adalimumab. To date, this did not lead to increased incidence of MACE. In the SmPC, a recommendation for continuous monitoring was included, which is considered sufficiently adequate to address the risk at present stage. As the effect on lipids was dose dependent, the advice of tapering from the 4 mg dose to the 2 mg dose in stable patients might further mitigate this risk.

Uncertainties regarding the risk of lymphoma will be addressed in a PASS comprising US/EU registries, which is considered adequate . Furthermore, a warning has been included in SmPC about the potential risk and required vigilance of lymphoma for the attention of the prescriber which is considered adequate for marketing authorisation.

Naïve patients

Baricitinib also showed an earlier and superior response to MTX regarding ACR-EULAR remission in naïve patients. However, the benefit-risk balance should be envisioned in the context of available alternative treatment options in each treatment setting, and this is different for naïve patients versus patients irresponsive to one or multiple DMARDs. Several well-established *oral* treatments are available for naïve patients. The response to MTX monotherapy was still considerable, and would have been better if this was combined with low-dose steroids, as now recommended in European treatment guidelines. In clinical practice, MTX may be poorly tolerated. However, baricitinib monotherapy showed no benefits towards MTX regarding drop-out due to intolerance. Superiority regarding the prevention of structural damage was only demonstrated when baricitinib was combined with MTX. However, tolerance towards the combination was worse in naïve patients, as compared to patients who received baricitinib add-on to prior treatment of MTX.

Starting baricitinib in newly diagnosed patients will lead to prolonged exposure to this new drug. At present stage, there are too many uncertainties regarding the long-term safety of baricitinib in terms of malignancies, and cardiovascular complications due to hyperlipidaemia, to allow a first-line indication. It is anticipated that more safety data will become available for baricitinib from the second line treatment setting, where the B/R balance of baricitinib is considered positive. A PASS and a registry, both in the US and Europe, have been included in the RMP.

It is noted that several biologic DMARDs have been registered for the first-line treatment, despite their drawbacks, albeit for a limited indication of *severe* RA patients. However, the first-line indications of bDMARDs were only approved after broad experience was obtained in the real-life clinical setting, following authorisation for a second line treatment. Such a strategy is also being applied for baricitinib.

For baricitinib 4 mg monotherapy, discontinuation rates were marginally increased as compared to MTX monotherapy in naïve patients (6.9% versus 5.2%). Naïve patients poorly tolerated the combination MTX+ baricitinib (drop-out rate 10.7% after 52 weeks, of which 7% in the first 6 months), mainly because of hepatotoxic events and infections.

Combination with cDMARDs

It was initially proposed that Baricitinib could be given as add-on to other conventional synthetic DMARDs than MTX. However, as the majority of the study population used MTX as background therapy, and considering the heterogeneity of the other synthetic DMARDs that were used regarding safety and efficacy,

the CHMP was of the opinion that there isn't enough data to support the broad indication "monotherapy or in combination with conventional synthetic DMARDs". The indication was restricted to MTX use (or monotherapy), and reference is made to other sections of the SmPC regarding information on the use in combination with hydroxychloroquine, leflunomide, and sulphasalazine (section 5.1). Warnings were included regarding the combination wiith potent immunosuppressive medicinal products such as azathioprine, tacrolimus, or ciclosporin, which is considered appropriate.

3.7.3. Additional considerations on the benefit-risk balance

Additional risk minimisations

Because of its mode of action, baricitinib may induce neutropenia and cause infections. Most infections were upper respiratory tract infections, gastro-enteritis and urinary tract infections. Serious infections were rare which occurred in similar rates as compared to placebo or active controls. In contrast to biologicals, the half-life of baricitinib is short, and treatment withdrawal is recommended once infections occur. This was also applied in the trials, and overall, the incidence of serious infections was low and manageable. Routine monitoring of neutropenia is proposed, which may further mitigate the risk.

Abnormal liver function tests were also frequently reported. The incidence rates of severe events were similar or even lower than active controls MTX monotherapy and adalimumab, and most cases were transient. It is, however, noted that the combination of MTX + baricitinib in naive patients, was poorly tolerated regarding hepatotoxic and gastric events versus monotherapies of either drug. This has been addressed in the SmPC. No cases of DILI were reported. Continuous monitoring is recommended in the SmPC, which is considered adequate.

3.8. Conclusions

The overall B/R of Olumiant is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Olumiant is favourable in 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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Olumiant in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The main objectives of the programme are to make the prescribers aware of the risks associated with the product's use, and to highlight specific risk minimisation measures to be performed before and during the treatment with Olumiant.

The MAH shall ensure that, in each Member State where Olumiant is marketed, all healthcare professionals who are expected to prescribe Olumiant are provided with the physician educational material, which should contain:

- The Summary of Product Characteristics
- The Package Leaflet including the Patient Alert Card
- The guide for healthcare professionals to support counselling of the patient

- Additional Patient Alert Cards

The guide for healthcare professionals shall contain the following key elements:

- That Olumiant increases the potential risk of infections. Patients should be instructed to seek immediate medical attention, if signs or symptoms suggesting infection appear.
- That Olumiant use should be stopped in case of herpes zoster or any other infection that doesn't respond to standard treatment until the event resolves. Patients should not be immunised using live attenuated vaccines shortly before or during treatment with Olumiant.
- Prescribers should screen the patients for viral hepatitis before commencing Olumiant treatment. Active tuberculosis should also be ruled out.
- That Olumiant use is associated with hyperlipidaemia; prescribers should monitor the patient's lipid parameters and manage the hyperlipidaemia, if detected.
- That Olumiant is contraindicated in pregnancy as pre-clinical data showed reduced foetal growth and malformations. Physicians should advise women of child bearing potential to use contraception during treatment and for a week after its ending. If a planned pregnancy is considered, Olumiant treatment should be stopped.
- The purpose and use of the Patient Alert Card

The patient alert card shall contain the following key messages:

- That treatment with Olumiant may increase the risk of infections, and viral reactivation.
- Signs or symptoms of infections including general symptoms, and specifically tubercolosis and herpes zoster signs and symptoms; and a warning for the patients to seek immediate medical attention if signs or symptoms suggesting infection appear
- That Olumiant should not be taken while pregnant and that women should inform their doctor should they become (or wish to become) pregnant
- That the patient may need to have their cholesterol level checked during treatment
- Contact details of the prescriber
- That the Patient Alert Card should be carried by the patient at any time and to share it with other healthcare professionals involved in their treatment.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that baricitinib is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.