UNAMITY
Baricitinib 2 mg film-coated tablets
Baricitinib 4 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Unamity 2 mg film-coated tablets
Unamity 4 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Unamity 2 mg film-coated tablets
Each film-coated tablet contains 2 mg baricitinib

Unamity 4 mg film-coated tablets
Each film-coated tablet contains 4 mg baricitinib

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Unamity 2 mg film-coated tablets
Light pink, 9 x 7.5 mm oblong tablets, debossed with “Lilly” on one side and “2” on the other.

Unamity 4 mg film-coated tablets
Medium pink, 8.5 mm round tablets, debossed with “Lilly” on one side and “4” on the other.

The tablets contain a recessed area on each side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Baricitinib is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to one or more disease-modifying anti-rheumatic drugs. Baricitinib may be used as monotherapy or in combination with methotrexate.

Atopic dermatitis

Baricitinib is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

Alopecia areata

Baricitinib is indicated for the treatment of severe alopecia areata in adult patients (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of the conditions for which this medicinal product is indicated.

Posology

Rheumatoid arthritis
The recommended dose of Baricitinib 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 (see section 5.1).

Atopic dermatitis
The recommended dose of Baricitinib 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 should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering (see section 5.1).

Baricitinib can be used with or without topical corticosteroids. The efficacy of baricitinib can be enhanced when given with topical corticosteroids (see section 5.1). Topical calcineurin inhibitors may be used, but should be reserved for sensitive areas only, such as the face, neck, intertriginous and genital areas.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 8 weeks of treatment.

Alopecia areata
The recommended dose of baricitinib is 4 mg once daily. A dose of 2 mg once daily may be appropriate for patients such as those aged ≥ 75 years and 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 (see section 5.1).

Once a stable response has been achieved, it is recommended to continue treatment for at least several months, in order to avoid relapse. The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 36 weeks of treatment.

Treatment initiation
Treatment should not be initiated in patients with an absolute lymphocyte count (ALC) less than 0.5 x 10^9 cells/L, an absolute neutrophil count (ANC) less than 1 x 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 (see section 4.4).

Co-administration with OAT3 inhibitors
The recommended dose is 2 mg once daily in patients taking Organic Anion Transporter 3 (OAT3) inhibitors with a strong inhibition potential, such as probenecid (see section 4.5).

Special populations

Renal impairment
The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 mL/min. Baricitinib is not recommended for use in patients with creatinine clearance < 30 mL/min (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. Baricitinib is not recommended for use in patients with severe hepatic impairment (see section 5.2).

Elderly
Clinical experience in patients ≥ 75 years is very limited and in these patients a starting dose of 2 mg is appropriate.

Paediatric population
The safety and efficacy of baricitinib in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Method of administration

Oral use.
Baricitinib is to be taken once daily with or without food and may be taken at any time of the day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Infections

Baricitinib is associated with an increased rate of infections such as upper respiratory tract infections compared to placebo (see section 4.8). In rheumatoid arthritis clinical studies, in treatment naïve patients, combination with methotrexate resulted in increased frequency of infections compared to baricitinib monotherapy.

The risks and benefits of treatment with baricitinib should be carefully considered prior to initiating therapy in patients with active, chronic or recurrent infections (see section 4.2). If an infection develops, the patient should be monitored carefully and therapy should be temporarily interrupted if the patient is not responding to standard therapy. Treatment should not be resumed until the infection resolves.

Tuberculosis
Patients should be screened for tuberculosis (TB) before starting therapy. Baricitinib should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of treatment in patients with previously untreated latent TB.

Haematological abnormalities

Absolute Neutrophil Count (ANC) < 1 x 10^9 cells/L, Absolute Lymphocyte Count (ALC) < 0.5 x 10^9 cells/L, and haemoglobin < 8 g/dL were reported in less than 1% of patients in clinical trials.

Treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 10^9 cells/L, ALC < 0.5 x 10^9 cells/L or haemoglobin < 8 g/dL observed during routine patient management (see section 4.2).

The risk of lymphocytosis is increased in elderly patients with rheumatoid arthritis. Rare cases of lymphoproliferative disorders have been reported.

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster, herpes simplex), were reported in clinical studies (see section 4.8). In rheumatoid arthritis clinical studies, herpes zoster was reported more commonly in patients ≥ 65 years of age who had previously been treated with both biologic and conventional disease-modifying antirheumatic drugs (DMARDs). If a patient develops herpes zoster, treatment should be temporarily interrupted until the episode resolves.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with baricitinib. Patients with evidence of active hepatitis B or C infection were excluded from clinical trials. Patients, who were positive for hepatitis C antibody but negative for hepatitis C virus RNA, were allowed to participate. Patients with hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were also allowed to participate; such patients should be monitored for expression of hepatitis B virus (HBV) DNA. If HBV DNA is detected, a liver specialist should be consulted to determine if treatment interruption is warranted.

Vaccination

No data are available on the response to vaccination with live vaccines in patients receiving baricitinib. Use with live, attenuated vaccines during, or immediately prior to baricitinib therapy is not recommended. Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines.

Lipids

Dose dependent increases in blood lipid parameters were reported in patients treated with baricitinib (see section 4.8). Elevations in low density lipoprotein (LDL) cholesterol decreased to pre-treatment levels in response to statin therapy. Lipid parameters should be assessed approximately 12 weeks following initiation of therapy and thereafter patients should be managed according to international clinical guidelines for hyperlipidaemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Hepatic transaminase elevations

Dose dependent increases in blood alanine transaminase (ALT) and aspartate transaminase (AST) activity were reported in patients treated with baricitinib (see section 4.8).

Increases in ALT and AST to ≥ 5 and ≥ 10 x upper limit of normal (ULN) were reported in clinical trials. In rheumatoid arthritis clinical studies in treatment-naïve patients, combination with methotrexate resulted in increased frequency of hepatic transaminase elevations compared with baricitinib monotherapy (see section 4.8).

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, treatment should be temporarily interrupted until this diagnosis is excluded.

Malignancy

The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medicinal products may increase the risk of malignancies including lymphoma.
The clinical data are insufficient to assess the potential incidence of malignancies following exposure to baricitinib. Long-term safety evaluations are ongoing.

Venous thromboembolism

Cases of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib (see section 4.8). Baricitinib should be used with caution in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation. If clinical features of DVT/PE occur, treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Laboratory monitoring

Table 1. Laboratory measures and monitoring guidance

Laboratory Measure	**Action**	**Monitoring guidance**
Lipid parameters	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC < 1 x 10^9 cells/L and may be restarted once ANC return above this value	Before treatment initiation and thereafter according to routine patient management
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC < 0.5 x 10^9 cells/L and may be restarted once ALC return above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb < 8 g/dL and may be restarted once Hb return above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	

Immunosuppressive medicinal products

Combination with biological DMARDs, biological immunomodulators or other Janus kinase (JAK) inhibitors is not recommended, as a risk of additive immunosuppression cannot be excluded.

In rheumatoid arthritis, data concerning use of baricitinib with potent immunosuppressive medicinal products (e.g., azathioprine, tacrolimus, ciclosporin) are limited and caution should be exercised when using such combinations (see section 4.5).

In atopic dermatitis and alopecia areata, combination with ciclosporin or other potent immunosupressants has not been studied and is not recommended (see section 4.5).

Hypersensitivity

In post-marketing experience, cases of drug hypersensitivity associated with baricitinib administration have been reported. If any serious allergic or anaphylactic reaction occurs, treatment should be discontinued immediately.

Diverticulitis

Cases of diverticulitis and gastrointestinal perforation have been reported in clinical trials and from postmarketing sources (see section 4.8). Baricitinib should be used with caution in patients with diverticular disease and especially in patients chronically treated with concomitant medicinal products associated with an increased risk of diverticulitis: nonsteroidal anti-inflammatory drugs, corticosteroids, and opioids. Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Immunosuppressive medicinal products
Combination with biological DMARDs, biological immunomodulators or other JAK inhibitors has not been studied. In rheumatoid arthritis, use of baricitinib with potent immunosuppressive medicinal products such as azathioprine, tacrolimus, or ciclosporin was limited in clinical studies, and a risk of additive immunosuppression cannot be excluded. In atopic dermatitis and alopecia areata, combination with ciclosporin or other potent immunosuppressants has not been studied and is not recommended (see section 4.4).

Potential for other medicinal products to affect the pharmacokinetics of baricitinib

Transporters
In vitro, baricitinib is a substrate for organic anionic transporter (OAT)3, P-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and multidrug and toxic extrusion protein (MATE)2-K. In a clinical pharmacology study, dosing of probenecid (an OAT3 inhibitor with strong inhibition potential) resulted in approximately a 2-fold increase in $AUC_{(0-\infty)}$ with no change in t_{max} or C_{max} of baricitinib. Consequently, the recommended dose in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid, is 2 mg once daily (see section 4.2). No clinical pharmacology study has been conducted with OAT3 inhibitors with less inhibition potential. The prodrug leflunomide rapidly converts to teriflunomide which is a weak OAT3 inhibitor and therefore may lead to an increase in baricitinib exposure. Since dedicated interaction studies have not been conducted, caution should be used when leflunomide or teriflunomide are given concomitantly with baricitinib. Concomitant use of the OAT3 inhibitors ibuprofen and diclofenac may lead to increased exposure of baricitinib, however their inhibition potential of OAT3 is less compared to probenecid and thus a clinically relevant interaction is not expected. Coadministration of baricitinib with ciclosporin (Pgp/BCRP inhibitor) or methotrexate (substrate of several transporters including OATP1B1, OAT1, OAT3, BCRP, MRP2, MRP3, and MRP4) resulted in no clinically meaningful effects on baricitinib exposure.

Cytochrome P450 enzymes
In vitro, baricitinib is a cytochrome P450 enzyme (CYP)3A4 substrate although less than 10 % of the dose is metabolised via oxidation. In clinical pharmacology studies, coadministration of baricitinib with ketoconazole (strong CYP3A inhibitor) resulted in no clinically meaningful effect on the PK of baricitinib.

Coadministration of baricitinib with fluconazole (moderate CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampicin (strong CYP3A inducer) resulted in no clinically meaningful changes to baricitinib exposure.

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

Potential for baricitinib to affect the pharmacokinetics of other medicinal products

Transporters
In vitro, baricitinib is not an inhibitor of OAT1, OAT2, OAT3, organic cationic transporter (OCT) 2, OATP1B1, OATP1B3, BCRP, MATE1 and MATE2-K at clinically relevant concentrations. Baricitinib may be a clinically relevant inhibitor of OCT1, however there are currently no known selective OCT1 substrates for which clinically significant interactions might be predicted. In clinical pharmacology studies there were no clinically meaningful effects on exposure when baricitinib was coadministered with digoxin (Pgp substrate) or methotrexate (substrate of several transporters).

Cytochrome P450 enzymes
In clinical pharmacology studies, coadministration of baricitinib with the CYP3A substrates simvastatin, ethinyl oestradiol, or levonorgestrel resulted in no clinically meaningful changes in the PK of these medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity which can affect early embryonic development. There are no adequate data from the use of baricitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Baricitinib was teratogenic in rats and rabbits. Animal studies indicate that baricitinib may have an adverse effect on bone development *in utero* at higher doses.

Baricitinib is contraindicated during pregnancy (see section 4.3). 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 baricitinib the parents should be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether baricitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of baricitinib in milk (see section 5.3).

A risk to newborns/infants cannot be excluded and baricitinib should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies in animals suggest that treatment with baricitinib has the potential to decrease female fertility while on treatment, but there was no effect on male spermatogenesis (see section 5.3).

4.7 Effects on ability to drive and use machines

Baricitinib has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In the integrated data from rheumatoid arthritis, atopic dermatitis, and alopecia areata clinical trials, the most commonly reported adverse reactions with baricitinib are increased LDL cholesterol (26.0 %), upper respiratory tract infections (16.9 %), headache (5.2%), herpes simplex (3.2%) and urinary tract infection (2.9%). Serious pneumonia and serious herpes zoster occurred uncommonly in patients with rheumatoid arthritis.

Tabulated list of adverse reactions

Rheumatoid arthritis
A total of 3,770 patients were treated with Unamity in rheumatoid arthritis clinical studies representing 10,127 patient-years of exposure. Of these, 2960 patients with rheumatoid arthritis were exposed to Unamity for at least 1 year.

Seven placebo-controlled studies were integrated (1,142 patients on 4 mg once daily and 1,215 patients on placebo) to evaluate the safety of Unamity in comparison with placebo for up to 16 weeks after treatment initiation.

Atopic dermatitis
A total of 2,531 patients were treated with Unamity in atopic dermatitis clinical studies representing a total of 2,247 patient-years of exposure. Of these, 1,106 patients with atopic dermatitis were exposed to Unamity for at least 1 year.

Five placebo-controlled studies were integrated (489 patients on 4 mg once daily and 743 patients on placebo) to evaluate the safety of Unamity in comparison with placebo for up to 16 weeks after treatment initiation.

Alopecia areata
A total of 1,244 patients were treated with Unamity in alopecia areata clinical studies representing a total of 1,668 patient-years of exposure. Of these, 948 patients with alopecia areata were exposed to Unamity for at least 1 year. Two placebo-controlled studies were integrated (540 patients on 4 mg once daily and 371 patients on placebo) to evaluate the safety of Unamity in comparison with placebo for up to 36 weeks after treatment initiation.

Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to < /1,000), very rare (<1/10,000). The frequencies in Table 2 are based on integrated data from clinical trials and/or postmarketing setting across rheumatoid arthritis, atopic dermatitis, and alopecia areata indications unless stated otherwise; where notable differences in frequency between indications are observed, these are presented in the footnotes below the table.

Table 2. Adverse reactions

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections	Herpes zoster[b] Herpes simplex Gastroenteritis	

		Urinary tract infections Pneumonia[d] Folliculitis[g]	
Blood and lymphatic system disorders		Thrombocytosis >600 x 10^9 cells/L[a, d]	Neutropaenia <1 x 10^9 cells/L[a]
Immune system disorders			Swelling of the face, Urticaria
Metabolism and nutrition disorders	Hypercholesterolaemia[a]		Hypertriglyceridaemia[a]
Nervous system disorders		Headache	
Vascular disorders			Deep Vein Thrombosis[b]
Respiratory, thoracic, mediastinal disorders			Pulmonary embolism[f]
Gastrointestinal disorders		Nausea[d] Abdominal pain[d]	Diverticulitis
Hepatobiliary disorders		ALT increased ≥3 x ULN[a, d]	AST increased ≥3 x ULN[a, e]
Skin and subcutaneous tissue disorders		Rash Acne[c]	
Investigations		Creatine phosphokinase increased >5 x ULN[a, c]	Weight increased

a. Includes changes detected during laboratory monitoring (see text below).
b. Frequency for herpes zoster and deep vein thrombosis is based on rheumatoid arthritis clinical trials.
c. In rheumatoid arthritis clinical trials, the frequency of acne and creatine phosphokinase increased > 5 x ULN was uncommon
d. In atopic dermatitis clinical trials, the frequency of nausea and ALT ≥3 x ULN was uncommon. In alopecia areata clinical trials, the frequency of abdominal pain was uncommon. In atopic dermatitis and alopecia areata clinical trials, the frequency of pneumonia and thrombocytosis > 600 x 10^9 cells/L was uncommon.
e. In alopecia areata clinical trials, the frequency of AST ≥ 3 x ULN was common.
f. Frequency for pulmonary embolism is based on rheumatoid arthritis and atopic dermatitis clinical trials.
g. Folliculitis was observed in alopecia areata clinical trials. It was usually localized in the scalp region associated with hair regrowth.

Description of selected adverse reactions

Gastrointestinal disorders
In rheumatoid arthritis clinical studies, in treatment-naïve patients, through 52 weeks, the frequency of nausea was greater for the combination treatment of methotrexate and baricitinib (9.3 %) compared to methotrexate alone (6.2 %) or baricitinib alone (4.4 %). In the integrated data from rheumatoid arthritis, atopic dermatitis and alopecia areata clinical trials, nausea was most frequent during the first 2 weeks of treatment.

Cases of abdominal pain were usually mild, transient, not associated with infectious or inflammatory gastrointestinal disorders, and did not lead to treatment interruption.

Infections
In the integrated data from rheumatoid arthritis, atopic dermatitis and alopecia areata clinical trials, most infections were mild to moderate in severity. In studies which included both doses, infections were reported in 31.0 %, 25.7 % and 26.7 % of patients in the 4 mg, 2 mg and placebo groups, respectively. In rheumatoid arthritis clinical studies, combination with methotrexate resulted in increased frequency of infections compared to baricitinib monotherapy. Frequency of herpes zoster was common in rheumatoid arthritis, very rare in atopic dermatitis and uncommon in alopecia areata. In atopic dermatitis clinical trials, there were less skin infections requiring antibiotic treatment with baricitinib than with placebo.

The incidence of serious infections with baricitinib was similar to placebo. The incidence of serious infections remained stable during long term exposure. The overall incidence rate of serious infections in the clinical trial programme was 3.2 per 100 patient-years in rheumatoid arthritis, 2.1 in atopic dermatitis and 0.8 in alopecia areata. Serious pneumonia and serious herpes zoster occurred uncommonly in patients with rheumatoid arthritis.

Hepatic transaminase elevations
Dose dependent increases in blood ALT and AST activity were reported in studies extended over week 16. Elevations in mean ALT/AST remained stable over time. Most cases of hepatic transaminase elevations ≥ 3 x ULN were asymptomatic and transient.

In patients with rheumatoid arthritis, the combination of baricitinib with potentially hepatotoxic medicinal products, such as methotrexate, resulted in increased frequency of these elevations.

Lipid elevations
In the integrated data from rheumatoid arthritis, atopic dermatitis and alopecia areata clinical trials, baricitinib treatment was associated with dose-dependent increases in lipid parameters including total cholesterol, LDL cholesterol, and high density lipoprotein (HDL) cholesterol. There was no change in the LDL/HDL ratio. Elevations were observed at 12 weeks and remained stable thereafter at a higher value than baseline including in the long-term extension study in rheumatoid arthritis. Mean total and LDL cholesterol increased through week 52 in patients with atopic dermatitis and alopecia areata. In rheumatoid arthritis clinical trials, baricitinib treatment was associated with dose-dependent increases in triglycerides. There was no increase in triglycerides levels in atopic dermatitis and alopecia areata clinical trials.

Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy.

Creatine phosphokinase (CPK)
Baricitinib treatment was associated with dose-dependent increases in CPK. Mean CPK was increased at week 4 and remained at a higher value than baseline thereafter. Across indications, most cases of CPK elevations > 5 x ULN were transient and did not require treatment discontinuation.

In clinical trials, there were no confirmed cases of rhabdomyolysis.

Neutropaenia
Mean neutrophil counts decreased at 4 weeks and remained stable at a lower value than baseline over time. There was no clear relationship between neutropaenia and the occurrence of serious infections. However, in clinical studies, treatment was interrupted in response to ANC < 1 x 10^9 cells/L.

Thrombocytosis
Dose-dependent increases in mean platelet counts were observed and remained stable at a higher value than baseline over time.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions immediately.

4.9 Overdose

Single doses up to 40 mg and multiple doses of up to 20 mg daily for 10 days have been administered in clinical trials without dose-limiting toxicity. No specific toxicities were identified. Pharmacokinetic data of a single dose of 40 mg in healthy volunteers indicate that more than 90 % of the administered dose is expected to be eliminated within 24 hours. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA37

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.

Pharmacodynamic effects

Inhibition of IL-6 induced STAT3 phosphorylation
Administration of baricitinib resulted in a dose dependent inhibition of IL-6 induced STAT3 phosphorylation in whole blood from healthy subjects with maximal inhibition observed 2 hours after dosing which returned to near baseline by 24 hours.

Immunoglobulins
Mean serum IgG, IgM, and IgA values decreased by 12 weeks after starting treatment, and remained stable at a lower value than baseline through at least 104 weeks. For most patients, changes in immunoglobulins occurred within the normal reference range.

Lymphocytes

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

C-reactive protein
In patients with rheumatoid arthritis, decreases in serum C-reactive protein (CRP) were observed as early as 1 week after starting treatment and were maintained throughout dosing.

Creatinine
In clinical trials, baricitinib induced a mean increase in serum creatinine levels of 3.8 µmol/L after two weeks of treatment, which remained stable thereafter. This may be due to inhibition of creatinine secretion by baricitinib in the renal tubules. Consequently, 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 reactions. In alopecia areata, mean serum creatinine continued to increase up to week 52. In atopic dermatitis and alopecia areata, baricitinib was associated with a decrease in cystatin C (also used to estimate glomerular filtration rate) at week 4, with no further decreases thereafter.

Skin biopsies and in vitro skin models
Elevated pSTAT3 levels are associated with increased inflammation in atopic dermatitis. In lesional skin of patients with atopic dermatitis, baricitinib reduced phosphorylated STAT3 (pSTAT3) expression in epidermal keratinocytes at week 4 and week 16 reflecting disease improvement.

In a human skin equivalent model treated with pro-inflammatory cytokines (i.e., IL-4, IL-13, IL-31), baricitinib reduced pathological changes consistent with atopic dermatitis, reduced epidermal keratinocyte pSTAT3 expression, and increased the expression of filaggrin, a protein that plays a role in skin barrier function and in the pathogenesis of atopic dermatitis.

Vaccine study

The influence of baricitinib on the humoral response to non-live vaccines was evaluated in 106 rheumatoid arthritis patients under stable treatment with baricitinib 2 or 4 mg, receiving inactivated pneumococcal or tetanus vaccination. The majority of these patients (n = 94) were co-treated with methotrexate. For the total population, pneumococcal vaccination resulted in a satisfactory IgG immune response in 68 % (95 % CI: 58.4 %, 76.2 %) of the patients. In 43.1 % (95 % CI: 34 %, 52.8 %) of the patients, a satisfactory IgG immune response to tetanus vaccination was achieved.

Clinical efficacy

Rheumatoid arthritis

The efficacy and safety of baricitinib once daily were assessed in 4 Phase III randomised, double-blind, multicentre studies in adult patients with moderate to severe active rheumatoid arthritis diagnosed according to the ACR/EULAR 2010 criteria (Table 3). Patients over 18 years of age were eligible to participate. The presence of at least 6 tender and 6 swollen joints was required at baseline. All patients who completed these studies were eligible to enrol in a long term extension study for up to 4 years continued treatment.

The RA-BEGIN Study in MTX-naïve patients is supportive for the target population of patients with an inadequate response to other DMARDs (section 4.1).

Table 3: Clinical trial summary

Study name (Duration)	**Population** (Number)	**Treatment arms**	**Summary of key outcome measures**

RA-BEGIN (52 weeks)	MTX-naïve[1] (584)	• Baricitinib 4 mg QD • Baricitinib 4 mg QD + MTX • MTX	• Primary endpoint: ACR20 at week 24 • Physical function (HAQ-DI) • Radiographic progression (mTSS) • Low disease activity and Remission (SDAI)
RA-BEAM (52 weeks)	MTX-IR[2] (1305)	• Baricitinib 4 mg QD • Adalimumab 40 mg SC Q2W • Placebo All patients on background MTX	• Primary endpoint: ACR20 at week 12 • Physical function (HAQ-DI) • Radiographic progression (mTSS) • Low disease activity and Remission (SDAI) • Morning Joint Stiffness
RA-BUILD (24 weeks)	cDMARD-IR[3] (684)	• Baricitinib 4 mg QD • Baricitinib 2 mg QD • Placebo On background cDMARDs[5] if on stable cDMARD at study entry	• Primary endpoint: ACR20 at week 12 • Physical function (HAQ-DI) • Low disease activity and remission (SDAI) • Radiographic progression (mTSS) • Morning Joint Stiffness
RA-BEACON (24 weeks)	TNF-IR[4] (527)	• Baricitinib 4 mg QD • Baricitinib 2 mg QD • Placebo On background cDMARDs[5]	• Primary endpoint: ACR20 at week 12 • Physical function (HAQ-DI) • Low disease activity and Remission (SDAI)

Abbreviations: QD = Once daily; Q2W = Once every 2 weeks; SC = Subcutaneously; ACR = American College of Rheumatology; SDAI = Simplified Disease Activity Index; HAQ-DI = Health Assessment Questionnaire-Disability Index; mTSS = modified Total Sharp Score

[1] Patients who had received less than 3 doses of Methotrexate (MTX); naïve to other conventional or biologic DMARDs

[2] Patients who had an inadequate response to MTX (+/- other cDMARDs); biologic-naïve

[3] Patients who had an inadequate response or were intolerant to ≥ 1 cDMARDs; biologic- naïve

[4] Patients who had an inadequate response or were intolerant to ≥ 1 bDMARDs; including at least one TNF inhibitor

[5] Most common concomitant cDMARDs included MTX, hydroxychloroquine, leflunomide and sulfasalazine

Clinical response

In all studies, patients treated with baricitinib 4 mg once daily had statistically significantly higher ACR20, ACR50 and ACR70 response at 12 weeks compared to placebo, MTX or adalimumab (Table 4). Time to onset of efficacy was rapid across measures with significantly greater responses seen as early as week 1. Continued, durable response rates were observed, with ACR20/50/70 responses maintained for at least 2 years including the long-term extension study.

Treatment with baricitinib 4 mg, alone or in combination with cDMARDs, resulted in significant improvements in all individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment and CRP, compared to placebo or MTX monotherapy.

In RA-BEAM, treatment with baricitinib resulted in significant improvement in patient and physician global assessments, HAQ-DI, pain assessment and CRP at weeks 12, 24 and 52 compared to adalimumab.

In placebo-controlled trials in which MTX was not required, 501 subjects randomized to baricitinib 2 mg or 4 mg received MTX as background therapy, and 303 received conventional DMARDs other than MTX (approximately half with MTX and half without). The most common concomitant DMARDs in these subjects were MTX (79% of patients), hydroxychloroquine (19%), leflunomide (11%), and sulphasalazine (9%). No relevant differences regarding efficacy and safety were observed in subgroups defined by types of concomitant DMARDs used in combination with baricitinib.

Remission and low disease activity
A statistically significantly greater proportion of patients treated with baricitinib 4 mg compared to placebo or MTX achieved remission, (SDAI $\leq$ 3.3 and CDAI $\leq$ 2.8) or low disease activity or remission (DAS28 ESR or DAS28 hsCRP $\leq$ 3.2 and DAS28 ESR or DAS28 hsCRP < 2.6), at weeks 12 and 24 (Table 4).

Greater rates of remission compared to placebo were observed as early as week 4. Remission and low disease activity rates were maintained for at least 2 years.

Table 4: Response, remission and physical function

Study	RA-BEGIN MTX-naïve patients			RA-BEAM MTX-IR patients			RA-BUILD cDMARD-IR patients			RA-BEACON TNF-IR patients		
Treatment group	MTX	BARI 4 mg	BARI 4 mg + MTX	PBO	BARI 4 mg	ADA 40 mg Q2W	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg
N	210	159	215	488	487	330	228	229	227	176	174	177
ACR20:												
Week 12	59 %	79 %***	77 %***	40 %	70 %***†	61 %***	39 %	66 %***	62 %***	27 %	49 %***	55 %***
Week 24	62 %	77 %**	78 %***	37 %	74 %***†	66 %***	42 %	61 %***	65 %***	27 %	45 %***	46 %***
Week 52	56 %	73 %***	73 %***		71 %††	62 %						
ACR50:												
Week 12	33 %	55 %***	60 %***	17 %	45 %***††	35 %***	13 %	33 %***	34 %***	8 %	20 %**	28 %***
Week 24	43 %	60 %**	63 %***	19 %	51 %***	45 %***	21 %	41 %***	44 %***	13 %	23 %*	29 %***
Week 52	38 %	57 %***	62 %***		56 %†	47 %						
ACR70:												
Week 12	16 %	31 %***	34 %***	5 %	19 %***†	13 %***	3 %	18 %***	18 %***	2 %	13 %***	11 %**
Week 24	21 %	42 %***	40 %***	8 %	30 %***†	22 %***	8 %	25 %***	24 %***	3 %	13 %***	17 %***
Week 52	25 %	42 %***	46 %***		37 %	31 %						
DAS28-hsCRP ≤ 3.2:												
Week 12	30 %	47 %***	56 %***	14 %	44 %***††	35 %***	17 %	36 %***	39 %***	9 %	24 %***	32 %***
Week 24	38 %	57 %***	60 %***	19 %	52 %***	48 %***	24 %	46 %***	52 %***	11 %	20 %*	33 %***
Week 52	38 %	57 %***	63 %***		56 %†	48 %						
SDAI ≤ 3.3:												
Week 12	6 %	14 %*	20 %***	2 %	8 %***	7 %***	1 %	9 %***	9 %***	2 %	2 %	5 %
Week 24	10 %	22 %**	23 %***	3 %	16 %***	14 %***	4 %	17 %***	15 %***	2 %	5 %	9 %**
Week 52	13 %	25 %**	30 %***		23 %	18 %						
CDAI ≤ 2.8:												
Week 12	7 %	14 %*	19 %***	2 %	8 %***	7 %**	2 %	10 %***	9 %***	2 %	3 %	6 %
Week 24	11 %	21 %**	22 %**	4 %	16 %***	12 %***	4 %	15 %***	15 %***	3 %	5 %	9 %*
Week 52	16 %	25 %*	28 %**		22 %	18 %						
HAQ-DI Minimum Clinically Important Difference (decrease in HAQ-DI score of ≥ 0.30):												
Week 12	60 %	81 %***	77 %***	46 %	68 %***	64 %***	44 %	60 %***	56 %**	35 %	48 %*	54 %***
Week 24	66 %	77 %*	74 %	37 %	67 %***†	60 %***	37 %	58 %***	55 %***	24 %	41 %***	44 %***
Week 52	53 %	65 %*	67 %**		61 %	55 %						

Note: Proportions of responders at each time point based on those initially randomised to treatment (N). Patients who discontinued or received rescue therapy were considered as non-responders thereafter.

Abbreviations: ADA = adalimumab; BARI = baricitinib; MTX = methotrexate; PBO = Placebo

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ vs. placebo (vs. MTX for study RA-BEGIN)

† $p \leq 0.05$; †† $p \leq 0.01$; ††† $p \leq 0.001$ vs. adalimumab

Radiographic response

The effect of baricitinib on progression of structural joint damage was evaluated radiographically in studies RA-BEGIN, RA-BEAM and RA-BUILD and assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score.

Treatment with baricitinib 4 mg resulted in a statistically significant inhibition of progression of structural joint damage (Table 5). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with baricitinib 4 mg compared to placebo at weeks 24 and 52.

Table 5. Radiographic changes

Study	**RA-BEGIN** MTX-naïve patients			**RA-BEAM** MTX-IR patients			**RA-BUILD** 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
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***			
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***			
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 %**			

Abbreviations: ADA = adalimumab; BARI = baricitinib; MTX = methotrexate; PBO = Placebo
[a] Placebo data 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 RA-BEGIN)

Physical function response and health-related outcomes
Treatment with baricitinib 4 mg, alone or in combination with cDMARDs, resulted in a significant improvement in physical function compared to all comparators (placebo, MTX, adalimumab), as measured by HAQ-DI, at 12, 24 and 52 weeks. The proportion of patients achieving a clinically significant improvement (HAQ-DI ≥ 0.30) was also higher with baricitinib compared to placebo or MTX at week 12 (Table 4). Improvements were seen as early as week 1 and, in studies RA-BEGIN and RA-BEAM, this was maintained for up to 52 weeks.

Treatment with baricitinib 4 mg, alone or in combination with cDMARDs, resulted in a significant improvement in pain compared to all comparators (placebo, MTX, adalimumab), as measured on a 0-100 visual analogue scale, at 12 weeks. Statistically significant pain reduction was seen as early as week 1 and in studies RA-BEGIN and RA-BEAM this was maintained for up to 52 weeks.

In RA-BEAM and RA-BUILD, treatment with baricitinib 4 mg resulted in a significant improvement in the mean duration and severity of morning joint stiffness compared to placebo or adalimumab as assessed using daily electronic patient diaries for 12 weeks.

In all studies, baricitinib-treated patients reported improvements in patient-reported quality of life, as measured by the Short Form (36) Health Survey (SF-36) Physical Component Score and fatigue, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F).

Baricitinib 4 mg vs. 2 mg
Differences in efficacy between the 4 mg and the 2 mg doses were most notable in the bDMARD-IR population (RA-BEACON), in which statistically significant improvements in the ACR components of swollen joint count, tender joint count and ESR were shown for baricitinib 4 mg compared to placebo at week 24 but not for baricitinib 2 mg compared to placebo. In addition, for both study RA-BEACON and RA-BUILD, onset of efficacy was faster and the effect size was generally larger for the 4 mg dose groups compared to 2 mg.

In a long-term extension study, patients from Studies RA-BEAM, RA-BUILD and RA-BEACON who achieved sustained low disease activity or remission (CDAI ≤ 10) after at least 15 months of treatment with baricitinib 4 mg once daily were re-randomized 1:1 in a double-blind manner to continue 4 mg once daily or reduce dose to 2 mg once daily. The majority of patients maintained low disease activity or remission based on CDAI score:

- At week 12: 234/251 (93 %) continuing 4 mg vs. 207/251 (82 %) reduced to 2 mg ($p \leq 0.001$)
- At week 24: 163/191 (85 %) continuing 4 mg vs. 144/189 (76 %) reduced to 2 mg ($p \leq 0.05$)
- At week 48: 57/73 (78 %) continuing 4 mg vs. 51/86 (59 %) reduced to 2 mg ($p \leq 0.05$)

The majority of patients who lost their low disease activity or remission status after dose reduction could regain disease control after the dose was returned to 4 mg.

Atopic dermatitis

The efficacy and safety of baricitinib as monotherapy or in combination with topical costicosteroids (TCS) were assessed in 3 Phase III randomised, double-blind, placebo-controlled, 16 weeks studies (BREEZE-AD1, -AD2 and -AD7). The studies included 1568 patients with moderate to severe atopic dermatitis defined by Investigator's Global Assessment (IGA) score ≥ 3, an Eczema Area and Severity Index (EASI) score ≥ 16, and a body surface area (BSA) involvement of ≥ 10 %. Eligible patients were over 18 years of age and had previous inadequate response or were intolerant to topical medication. Patients were permitted to receive rescue treatment (which included topical or systemic therapy), at which time they were considered non-responders. All patients who completed these studies were eligible to enrol in a long term extension study (BREEZE AD-3) for up to 2 years of continued treatment.

Clinical Study Summary

Study Name (Duration)	**No. of Patients Treated**(N)	**Background Treatment**[a]	**Treatment arms (QD)**	**Outcome Measures**
BREEZE AD-1 (16 weeks)	624	None	BARI 4 mg BARI 2 mg BARI 1 mg Placebo	• **Primary endpoint:** IGA 0 or 1[b] at week 16 • Improvement of ≥ 50, 75% or 90 % in Eczema Area and Severity Index from baseline (EASI 50, 75, 90) • Improvement of ≥ 75 % in SCORing Atopic Dermatitis (SCORAD) scale • Itch Numerical Rating Scale (NRS) ≥ 4-point improvement • Impact of itch on sleep as measured by Atopic Dermatitis Sleep Scale (ADSS) • Skin pain severity as measured by Skin Pain Numerical Rating Scale (NRS) • Patient-Oriented Eczema Measure (POEM) • Dermatology Life Quality Index (DLQI) • Hospital Anxiety and Depression Scale (HADS)
BREEZE AD-2 (16 weeks)	615	None		
BREEZE AD-7 (16 weeks)	329	TCS; TCI as needed	BARI 4 mg BARI 2 mg Placebo	

BARI = baricitinib; QD = Once daily; TCI = Topical Calcineurin Inhibitor; TCS = Topical Corticosteroid

[a] Patients used emollients throughout the study

[b] Investigators Global Assessment score of 0 ("clear") or 1 ("almost clear") with a reduction of ≥2 points on a 5-point severity scale of 0 to 4

Baseline Characteristics

In the monotherapy studies (BREEZE-AD1 and BREEZE-AD2), across all treatment groups, the mean age was 35.2, the mean weight was 73.3 kg, 37.7 % were female, 63.5 % were Caucasian, 30 % were Asian and 0.2 % were black. In these studies, 54 % of patients had a baseline IGA score of 3 (moderate AD), 46 % of patients had a baseline IGA of 4 (severe AD) and 59.9 % of patients had received prior systemic treatment for atopic dermatitis. The baseline mean EASI score was 32.2, the baseline mean BSA score was 52.3, the baseline weekly averaged pruritus NRS was 6.6, the baseline mean SCORAD score was 67.8, the baseline mean POEM score was 20.6, the baseline mean DLQI was 14.0, the baseline mean HADS depression score was 5.0, and the baseline mean HADS anxiety score was 6.1.

In the combination TCS study (BREEZE-AD7), across all treatment groups, the mean age was 33.8, the mean weight was 72.9 kg, 34.3 % were female, 45.6 % were Caucasian, 51.1 % were Asian. In this study, 54.9 % of patients had a baseline IGA score of 3, 45.1 % of patients had a baseline IGA of 4 and 66.4 % of patients received prior systemic treatment. The baseline mean EASI score was 29.6, the baseline mean BSA score was 50.3, the baseline weekly averaged pruritus NRS was 7.1, the baseline mean SCORAD score was 67.2, the baseline mean POEM score was 21.1, the baseline mean DLQI was 14.9, the baseline mean HADS depression score was 5.5, and the baseline mean HADS anxiety score was 6.6.

Clinical Response

16-week Monotherapy Studies (BREEZE-AD1 and BREEZE-AD2)

In BREEZE-AD1 and BREEZE-AD2, a significantly greater proportion of patients randomised to baricitinib 4 mg achieved an IGA 0 or 1 response, EASI75, or an improvement of ≥ 4 points on the Itch NRS compared to placebo at week 16 (Table 6).

A significantly greater proportion of patients randomised to baricitinib 4 mg achieved a rapid improvement in the Itch NRS compared to placebo (defined as ≥ 4-point improvement as early as Day 2; $p \leq 0.05$). The improvement in Itch NRS occurred in conjunction with the improvement of objective skin signs of atopic dermatitis.

Figures 1 and 2 respectively show the mean percent change from baseline in EASI and in Itch NRS, respectively up to week 16.

Treatment effects in subgroups (weight, age, gender, race, disease severity and previous treatment, including immunosuppressants) in BREEZE-AD1 and BREEZE-AD2 were consistent with the results in the overall study population.

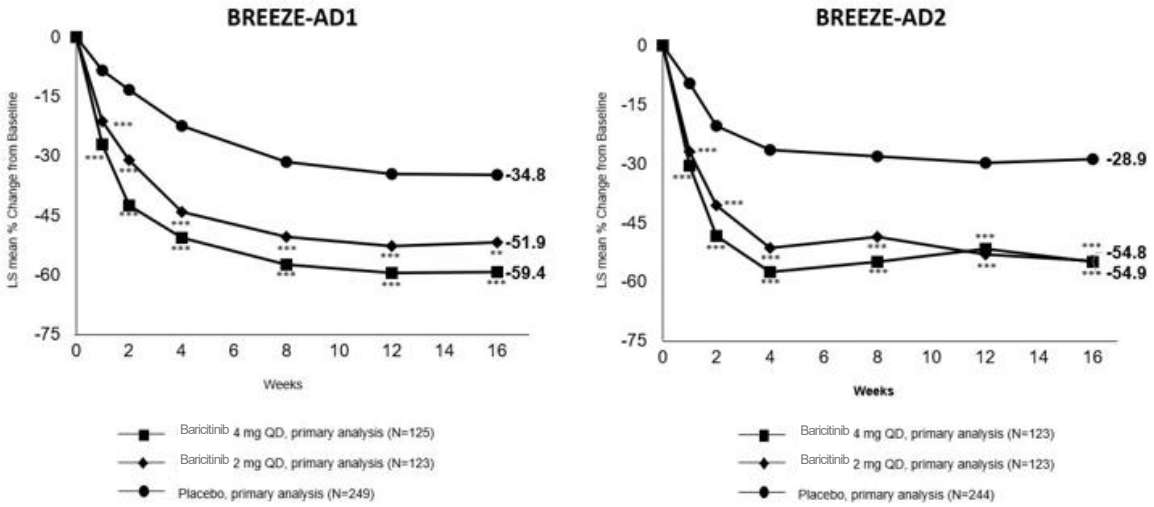
Table 6. Efficacy of baricitinib monotherapy at week 16 (FAS[a])

Study	**BREEZE- AD1**			**BREEZE-AD2**		
Treatment Group	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg
N	N = 249	N = 123	N = 125	N = 244	N = 123	N = 123
IGA 0 or 1, % responders[b, c]	4.8 %	11.4 %*	16.8 %***	4.5 %	10.6 %*	13.8 %***
EASI-50, % responders[c]	15.3 %	30.1 %***	41.6 %***	12.3 %	27.6 %***	29.3 %***
EASI-75, % responders[c]	8.8 %	18.7 %**	24.8 %***	6.1 %	17.9 %***	21.1 %***
EASI-90, % responders[c]	4.8 %	10.6 %*	16.0 %***	2.5 %	8.9 %**	13.0 %***
SCORAD75, % responders[c]	1.2 %	7.3 %**	10.4 %***	1.6 %	7.3 %**	11.4 %***
Itch NRS (≥ 4 point improvement), % responders[c],[d]	7.2 %	12.0 %	21.5 %***	4.7 %	15.1 %**	18.7 %***
BSA LS mean % change from baseline (SE)[e]	-14.80 % (1.82)	-20.14 % (2.16)	-25.96 %*** (1.93)	-12.82 % (2.07)	-22.12 %** (2.37)	-23.98 %*** (2.17)

BARI = baricitinib; PBO = Placebo
*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo.

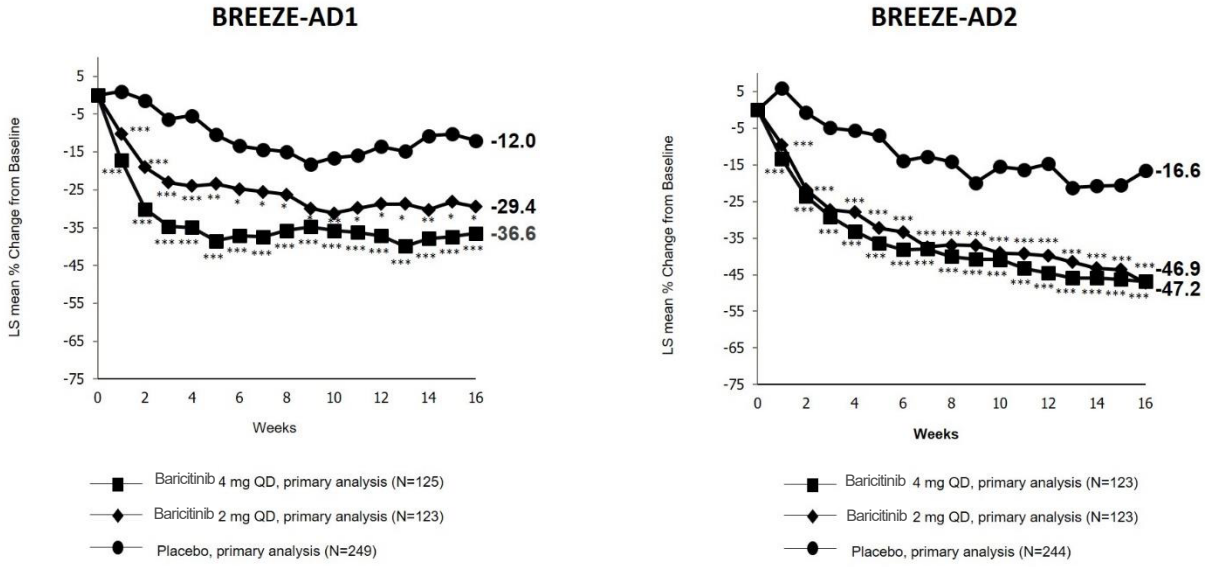
[a] Full analysis set (FAS) including all randomised patients.
[b] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on 0-4 IGA scale.
[c] Non-Responder Imputation: Patients who received rescue treatment or with missing data were considered as non-responders.
[d] Results shown in subset of patients eligible for assessment (patients with itch NRS ≥ 4 at baseline).
[e] Data collected after rescue therapy or after permanent study drug discontinuation were considered missing. LS means are from MMRM analyses which incorporates multiple imputation for missing data.

Figure 1. Mean percent change from baseline in EASI in BREEZE-AD1 and BREEZE-AD2 (FAS)[a]



LS = Least squares; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo
[a] Full analysis set (FAS) including all patients randomised. Data collected after rescue therapy or after permanent study drug discontinuation were considered missing. LS means are from MMRM analyses which incorporates multiple imputation for missing data.

Figure 2. Mean percent change from baseline in Itch NRS in BREEZE-AD1 and BREEZE-AD2 (FAS)[a]



LS = Least squares; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo
[a] Full analysis set (FAS) including all patients randomised. Data collected after rescue therapy or after permanent study drug discontinuation were considered missing. LS means are from MMRM analyses which incorporates multiple imputation for missing data.

16-week Combination TCS Study (BREEZE-AD7)

In BREEZE-AD7, a significantly greater proportion of patients randomised to baricitinib 4 mg + TCS achieved an IGA 0 or 1 response, EASI-75, or an improvement of ≥ 4 points on the itch NRS compared to placebo at week 16 (Table 7).

A significantly greater proportion of patients randomised to baricitinib 4 mg achieved a rapid improvement in the Itch NRS compared to placebo (defined as ≥ 4-point improvement as early as Week 2; $p < .001$). The improvement in Itch NRS occurred in conjunction with the improvement of objective skin signs of atopic dermatitis.

Figures 3 and 4 respectively show the mean percent change from baseline in EASI and in Itch NRS, respectively up to week 16.

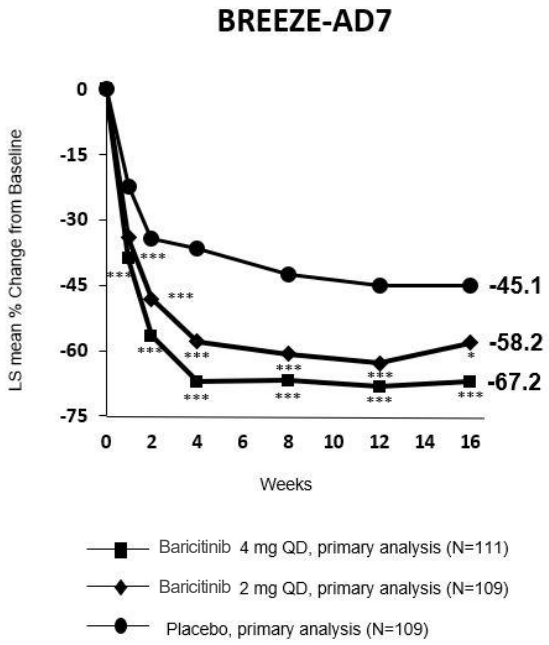
Treatment effects in subgroups (weight, age, gender, race, disease severity and previous treatment, including immunosuppressants) in BREEZE-AD7 were consistent with the results in the overall study population.

Table 7. Efficacy of baricitinib in combination with TCS[a] at week 16 (FAS)[b]

Study	**BREEZE- AD7**		
Treatment group	PBO[a]	BARI 2 mg [a]	BARI 4 mg [a]
N	109	109	111
IGA 0 or 1, % responders[c, d]	14.7 %	23.9 %	30.6 %**
EASI-50, % responders[d]	41.3 %	64.2 %***	70.3 %***
EASI-75, % responders[d]	22.9 %	43.1 %**	47.7 %***
EASI-90, % responders[d]	13.8 %	16.5 %	24.3 %*
SCORAD75, % responders[d]	7.3 %	11.0 %	18.0 %*
Itch NRS (≥ 4-point improvement), % responders [d, e]	20.2 %	38.1 %**	44.0 %***
BSA LS mean change from baseline (SE)[f]	-18.03 % (1.89)	-27.00 %*** (1.83)	29.73 %*** (1.81)

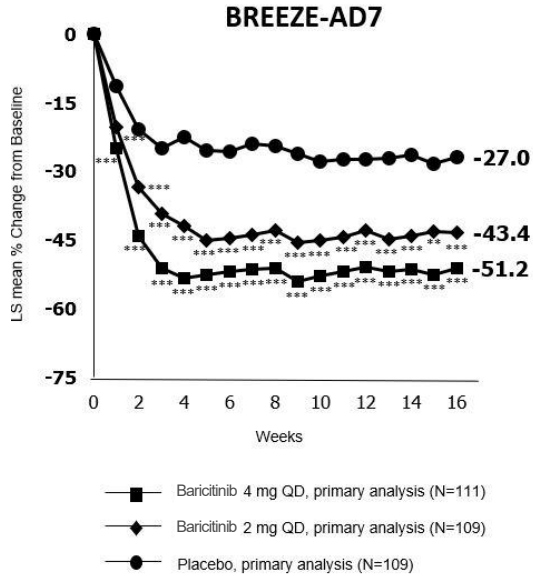
BARI = baricitinib; PBO = Placebo
*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo
[a] All patients were on background topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.
[b] Full analysis set (FAS) includes all randomised patients.
[c] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.
[d] Non-Responder Imputation: Patients who received rescue treatment or with missing data were considered as non-responders.
[e] Results shown in subset of patients eligible for assessment (patients with itch NRS ≥ 4 at baseline)
[f] Data collected after rescue therapy or after permanent study drug discontinuation were considered missing. LS means are from MMRM analyses which incorporates multiple imputation for missing data.

Figure 3. Mean percent change from baseline in EASI in BREEZE-AD7 (FAS) [a]



LS = Least squares; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo
[a] Full analysis set (FAS) including all patients randomised. Data collected after rescue therapy or after permanent study drug discontinuation are considered missing. LS means are from MMRM analyses which incorporates multiple imputation for missing data.

Figure 4. Mean percent change from baseline in Itch NRS in BREEZE-AD7 (FAS)[a]

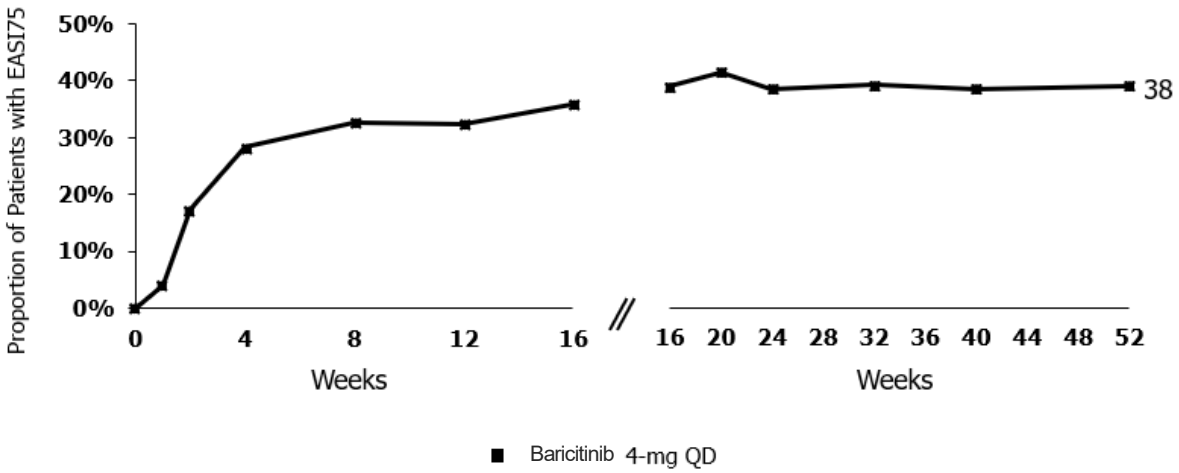


LS = Least squares; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo
[a] Full analysis set (FAS) including all patients randomised. Data collected after rescue therapy or after permanent study drug discontinuation are considered missing. LS means are from MMRM analyses which incorporates multiple imputation for missing data.

Maintenance of response

To evaluate maintenance of response, subjects treated with baricitinib for 16 weeks in BREEZE-AD1 and BREEZE-AD2 were eligible to enroll in a long term extension study BREEZE-AD3 to an additional 36-week of treatment, for a cumulative 52-week study treatment. Continued, durable response was observed. Figure 5 shows the percentage of patients with EASI 75 from baseline in BREEZE-AD3 up to week 52.

Figure 5. EASI 75 Persistence over time for baricitinib 4 mg in BREEZE-AD3 up to Week 52[a]



[a] Non-Responder Imputation was used. Patients who received rescue treatment (other than topical treatment) or with missing data were considered as non-responders. Data for week 52 are shown for the evaluable population.

Quality of life/patient-reported outcomes in atopic dermatitis

In both monotherapy studies (BREEZE-AD1 and BREEZE-AD2) and in the concomitant TCS study (BREEZE-AD7), baricitinib 4 mg significantly improved patient-reported outcomes, including itch, sleep (as measured by ADSS, POEM and SCORAD), skin pain (skin pain NRS) and quality of life (DLQI) at 16 weeks compared to placebo. In addition, anxiety and depression symptoms as measured by the HADS total score were significantly reduced in the baricitinib groups compared to placebo at 16 weeks (See Table 8).

Table 8. Quality of life/patient-reported outcomes results of baricitinib monotherapy and baricitinib in combination with TCS at week 16 (FAS) [a]

	Monotherapy						TCS Combination		
Study	**BREEZE-AD1**			**BREEZE-AD2**			**BREEZE-AD7**		
Treatment group	PBO	BARI 2mg	BARI 4mg	PBO	BARI 2mg	BARI 4mg	PBO + TCS	BARI 2 mg + TCS	BARI 4 mg + TCS
N	249	123	125	244	123	123	109	109	111
Change in ADSS, mean(SE)[b,c]	-0.84 (0.15)	-1.04 (0.17)	-1.42** (0.16)	-0.50 (0.12)	-1.03** (0.13)	-1.13*** (0.13)	-0.51 (0.15)	-1.33*** (0.15)	-1.42*** (0.15)
Change in Skin Pain NRS, mean(SE)[b]	-0.84 (0.24)	-1.58 (0.29)	-1.93** (0.26)	-0.86 (0.26)	2.61*** (0.30)	-2.49*** (0.28)	-2.06 (0.23)	-3.22 *** (0.22)	-3.73*** (0.23)
Change in POEM, mean(SE)[b]	-2.68 (0.76)	-6.26** (0.91)	-7.84** (0.80)	-1.48 (0.84)	-7.06*** (0.96)	-7.56*** (0.88)	-5.60 (0.76)	-8.50** (0.74)	-10.83*** (0.73)
POEM ≥ 4-point improvement, % responders[d, e]	14.2%	29.3%***	42.4%***	9.2%	23.8%***	30.6%***	46.7	65.7**	70.6***
Change in DLQI, mean(SE)[b]	-2.46 (0.57)	-4.30* (0.68)	-6.76*** (0.60)	-3.35 (0.62)	-7.44*** (0.71)	-7.56*** (0.66)	-5.58 (0.61)	-7.50* (0.58)	-8.89*** (0.58)
DLQI ≥ 4-point improvement, % responders[d, e]	16.3%	26.8%*	47.4%***	13.4%	26.3%**	33.9%***	52.9	61.2	73.3***
Change in HADS, mean(SE)[b]	-1.22 (0.48)	-3.22** (0.58)	-3.56*** (0.52)	-1.25 (0.57)	-2.82 (0.66)	-3.71** (0.62)	-3.18 (0.56)	-4.75* (0.54)	-5.12* (0.54)
HADS Anxiety Score <8 response rate, (%)[d, e]	12.0	18.4	41.0***	11.4	20.0	25.6*	45.5	54.8	56.1
HADS Depression Score <8 response rate, (%)[d, e]	13.0	17.4	35.7*	5.5	19.4*	16.0	30.3	66.7*	51.5

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo

[a] Full analysis set (FAS) including all randomised patients.
[b] Results shown are LS mean change from baseline (SE). Data collected after rescue therapy or after permanent medicinal product discontinuation were considered missing. LS means are from MMRM analyses which incorporates multiple imputation for missing data.
[c] ADSS Item 2: Mean number of night time awakenings due to itch
[d] Non-Responder Imputation: Patients who received rescue treatment or with missing data were considered as non-responders.
[e] Results shown in subset of patients eligible for assessment. For DLQI and POEM improvement, only patients with baseline severity of 4 or more points were included in the analysis. For HADS anxiety, and HADS Depression only patients with baseline severity of 8 or more points were included in the analysis.

Alopecia Areata

The efficacy and safety of baricitinib once daily were assessed in one adaptive Phase II/III study (BRAVE-AA1) and one Phase III study (BRAVE-AA2). The Phase III portion of BRAVE-AA1 study and the Phase III BRAVE-AA2 study were randomised, double blind, placebo-controlled, 36-week studies with extension phases up to 200 weeks. In both phase III studies, patients were randomised to placebo, 2 mg or 4 mg baricitinib in a 2:2:3 ratio. Eligible patients were adults between 18 years and 60 years of age for male patients, and between 18 years and 70 years of age for female

patients, with a current episode of more than 6 months of severe alopecia areata (hair loss encompassing ≥ 50 % of the scalp). Patients with a current episode of more than 8 years were not eligible unless episodes of regrowth had been observed on the affected areas of the scalp over the past 8 years. The only permitted concomitant alopecia areata therapies were finasteride (or other 5 alpha reductase inhibitors), oral or topical minoxidil and bimatoprost ophthalmic solution for eyelashes, if at a stable dose at study entry.

Both studies assessed as primary outcome the proportion of subjects who achieved a SALT (Severity of Alopecia Tool) score of ≤20 (80% or more scalp coverage with hair) at week 36. Additionally, both studies evaluated clinician assessment of eyebrow and eyelash hair loss using a 4-point scale (ClinRO Measure for Eyebrow Hair Loss™, ClinRO Measure for Eyelash Hair Loss™).

Baseline Characteristics
The Phase III portion of BRAVE-AA1 study and the Phase III BRAVE-AA2 study included 1 200 adult patients. Across all treatment groups, the mean age was 37.5 years, 61% of patients were female. The mean duration of alopecia areata from onset and the mean duration of current episode of hair loss were 12.2 and 3.9 years, respectively. The median SALT score across the studies was 96 (this equals 96 % scalp hair loss), and approximately 44% of patients were reported as alopecia universalis. Across the studies, 69% of patients had significant or complete eyebrow hair loss at baseline and 58% had significant or complete eyelash hair loss, as measured by ClinRO Measures for eyebrow and eyelash scores of 2 or 3. Approximately 90% of patients had received at least one treatment for alopecia areata at some point before entering the studies, and 50 % at least one systemic immunosuppressant. The use of authorised concomitant alopecia areata treatments was reported by only 4.3 % of patients during the studies.

Clinical Response
In both studies, a significantly greater proportion of patients randomised to baricitinib 4 mg once daily achieved a SALT ≤20 at week 36 compared to placebo, starting as early as week 8 in study BRAVE-AA1 and week 12 in study BRAVE-AA2. Consistent efficacy was seen across most of the secondary endpoints (Table 9). Figure 6 shows the proportion of patients achieving SALT ≤20 from baseline up to week 36.

Treatment effects in subgroups (gender, age, weight, eGFR, race, geographic region, disease severity, current alopecia areata episode duration) were consistent with the results in the overall study population at week 36.

Table 9. Efficacy of baricitinib through week 36 for pooled studies (Pooled Week 36 Efficacy Population[a])

	BRAVE-AA1 (phase III part of a phase II/III study) and BRAVE-AA2 (phase III study) Pooled Data*		
	Placebo N=345	Baricitinib 2 mg N=340	Baricitinib 4 mg N=515
SALT ≤ 20 at week 36	4.1 %	19.7 %**	34.0 %**
SALT ≤ 20 at week 24	3.2 %	11.2 %	27.4 %**
ClinRO Measure for Eyebrow Hair Loss of 0 or 1 at week 36 with a ≥ 2 point improvement from baseline[b]	3.8 %	15.8 %	33.0 %**
ClinRO Measure for Eyelash Hair Loss of 0 or 1 at week 36 with a ≥ 2 point improvement from baseline[b]	4.3 %	12.0 %	33.9 %**

Change in Skindex-16 adapted for alopecia areata emotions domain, mean (SE)[c]	-11.33 (1.768)	-19.89 (1.788)	-23.81 (1.488)
Change in Skindex-16 adapted for alopecia areata functioning domain, mean (SE)[c]	-9.26 (1.605)	-13.68 (1.623)	-16.93 (1.349)

ClinRO = clinician-reported outcome; SE = standard error

[a] Pooled Week 36 Efficacy Population: All patients enrolled in the Phase III portion of Study BRAVE-AA1 and in Study BRAVE-AA2.

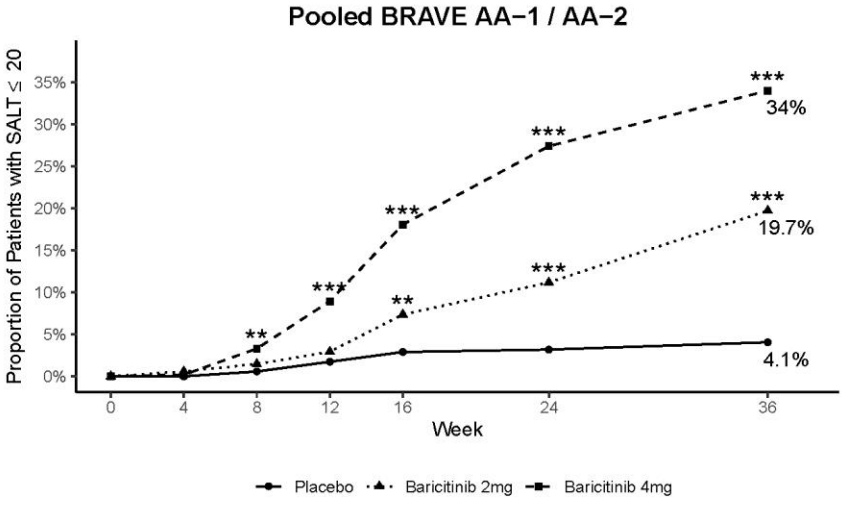
* The results of the pooled analysis are in line with those of the individual studies

** Statistically significant with adjustment for multiplicity in the graphical testing scheme within each individual study.

[b] Patients with ClinRO Measure for Eyebrow Hair loss score of ≥ 2 at baseline: 236 (Placebo), 240 (Baricitinib 2 mg), 349 (Baricitinib 4 mg). Patients with ClinRO Measure for Eyelash Hair loss score of ≥ 2 at baseline: 186 (Placebo), 200 (Baricitinib 2 mg), 307 (Baricitinib 4 mg). Both ClinRO Measures use a 4-point response scale ranging from 0 indicating no hair loss to 3 indicating no notable eyebrow/eyelashes hair.

[c] Sample sizes for analysis on Skindex-16 adapted for alopecia areata at Week 36 are n= 256 (Placebo), 249 (Baricitinib 2 mg), 392 (Baricitinib 4 mg).

Figure 6: Proportion of patients with SALT ≤20 through week 36



**p-value for baricitinib versus placebo ≤0.01; ***p-value for baricitinib versus placebo ≤0.001.

Efficacy up to week 52

The proportion of patients treated with baricitinib achieving a SALT ≤ 20 continued to increase after week 36, reaching 39.0 % of patients on baricitinib 4 mg at week 52. The results for the baseline disease severity and episode duration subpopulations at week 52 were consistent with those observed at week 36 and with the results in the overall study population.

Dose tapering substudy

In the study BRAVE-AA2, patients who had received baricitinib 4 mg once daily since the initial randomization and achieved SALT ≤ 20 at week 52 were re-randomised in a double-blind manner to continue 4 mg once daily or reduce dose to 2 mg once daily. The results show that 96 % of the

patients who remained on baricitinib 4 mg and 74 % of the patients who were re-randomised to baricitinib 2 mg maintained their response at week 76.

5.2 Pharmacokinetic properties

Following oral administration of baricitinib, a dose-proportional increase in systemic exposure was observed in the therapeutic dose range. The PK of baricitinib is linear with respect to time.

Absorption

Following oral administration, baricitinib is rapidly absorbed with a median t_{max} of approximately 1 hour (range 0.5 - 3.0 h) and an absolute bioavailability of approximately 79 % (CV = 3.94 %). Food intake led to a decreased exposure by up to 14 %, a decrease in C_{max} by up to 18 % and delayed t_{max} by 0.5 hours. Administration with meals was not associated with a clinically relevant effect on exposure**.**

Distribution

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

Biotransformation

Baricitinib metabolism is mediated by CYP3A4, with less than 10 % of the dose identified as undergoing biotransformation. No metabolites were quantifiable in plasma. In a clinical pharmacology study, baricitinib was excreted predominately as the unchanged active substance in urine (69 %) and faeces (15 %) and only 4 minor oxidative metabolites were identified (3 in urine; 1 in faeces) constituting approximately 5 % and 1 % of the dose, respectively. *In vitro*, baricitinib is a substrate for CYP3A4, OAT3, Pgp, BCRP and MATE2-K, and may be a clinically relevant inhibitor of the transporter OCT1 (see section 4.5). Baricitinib is not an inhibitor of the transporters OAT1, OAT2, OAT3, OCT2, OATP1B1, OATP1B3, BCRP, MATE1 and MATE2-K at clinically relevant concentrations.

Elimination

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

Mean apparent clearance (CL/F) and half-life in patients with rheumatoid arthritis was 9.42 L/hr (CV = 34.3 %) and 12.5 hrs (CV = 27.4 %), respectively. C_{max} and AUC at steady state are 1.4- and 2.0–fold higher, respectively, in subjects with rheumatoid arthritis compared to healthy subjects.

Mean apparent clearance (CL/F) and half-life in patients with atopic dermatitis was 11.2 L/hr (CV = 33.0%) and 12.9 hrs (CV = 36.0%), respectively. C_{max} and AUC at steady state in patients with atopic dermatitis are 0.8-fold those seen in rheumatoid arthritis.

Mean apparent clearance (CL/F) and half-life in patients with alopecia areata was 11.0 L/hr (CV = 36.0 %) and 15.8 hrs (CV = 35.0 %), respectively. C_{max} and AUC at steady state in patients with alopecia areata are 0.9-fold those seen in rheumatoid arthritis.

Renal impairment

Renal function was found to significantly affect baricitinib exposure. The mean ratios of AUC in patients with mild and moderate renal impairment to patients with normal renal function are 1.41 (90 % CI: 1.15-1.74) and 2.22 (90 % CI: 1.81-2.73), respectively. The mean ratios of C_{max} in patients with mild and moderate renal impairment to patients with normal renal function are 1.16 (90 %CI: 0.92-1.45) and 1.46 (90 %CI: 1.17-1.83), respectively. See section 4.2 for dose recommendations.

Hepatic impairment

There was no clinically relevant effect on the PK of baricitinib in patients with mild or moderate hepatic impairment. The use of baricitinib has not been studied in patients with severe hepatic impairment.

Elderly

Age ≥ 65 years or ≥ 75 years has no effect on baricitinib exposure (C_{max} and AUC).

Paediatric population

The safety, efficacy and pharmacokinetics of baricitinib have not yet been established in a paediatric population (see section 4.2).

Other intrinsic factors
Body weight, sex, race, and ethnicity did not have a clinically relevant effect on the PK of baricitinib. The mean effects of intrinsic factors on PK parameters (AUC and C_{max}) were generally within the inter-subject PK variability of baricitinib. Therefore, no dose adjustment is needed based on these patient factors.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Decreases in lymphocytes, eosinophils and basophils as well as lymphoid depletion in organs/tissues of the immune system were observed in mice, rats and dogs. Opportunistic infections related to demodicosis (mange) were observed in dogs at exposures approximately 7 times the human exposure. Decreases in red blood cell parameters were observed in mice, rats and dogs at exposures approximately 6 to 36 times the human exposure. Degeneration of the sternal growth plate was observed in some dogs, at low incidence and also in control animals, but with a dose-effect relationship regarding severity. At present it is not known whether this is clinically relevant.

In rat and rabbit reproductive toxicology studies, baricitinib was shown to reduce foetal growth/weight and produce skeletal malformations (at exposures of approximately 10 and 39 times the human exposure, respectively). No adverse foetal effects were observed at exposures 2 times the human exposure based on AUC.

In a combined male/female rat fertility study, baricitinib decreased overall mating performance (decreased fertility and conception indices). In female rats there were decreased numbers of corpora lutea and implantation sites, increased pre-implantation loss, and/or adverse effects on intrauterine survival of the embryos. Since there were no effects on spermatogenesis (as assessed by histopathology) or semen/sperm endpoints in male rats, the decreased overall mating performance was likely the result of these female effects.

Baricitinib was detected in the milk of lactating rats. In a pre- and postnatal development study, decreased pup weights and decreased postnatal survival were observed at exposures 4 and 21 times, respectively, the human exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores

cellulose, microcrystalline
croscarmellose sodium
magnesium stearate
mannitol

Film coating

iron oxide red (E172)
lecithin (soya) (E322)
macrogol
poly (vinyl alcohol)
talc
titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Polyvinylchloride/aluminium/oriented polyamide - aluminium perforated unit dose blisters in cartons of 4 x 7 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 PRESENTATION

Unamity 2 mg film-coated tablets, 28 film-coated tablets Reg. No.: DKIxxxxxxxxxx

Unamity 4 mg film-coated tablets, 28 film-coated tablets Reg. No.: DKIxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Manufactured by:
Lilly del Caribe, Inc.
12.6 Km, 65th Infantry Road
Carolina
00985 Puerto Rico

Packed and released by:
Lilly S.A.
Avda.de la Industria, 30
Alcobendas
28108 Madrid
SPAIN

Registered by:
PT Pyridam Farma Tbk.
Kabupaten Cianjur, Indonesia

UNAMITY
Baricitinib 2 mg tablet salut selaput
Baricitinib 4 mg tablet salut selaput
Informasi untuk pasien

Bacalah leaflet ini dengan seksama sebelum Anda menggunakan obat ini karena leaflet ini berisi informasi yang penting untuk Anda.
- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya kembali.
- Jika Anda mempunyai pertanyaan lebih lanjut, silahkan bertanya kepada dokter atau apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Hal ini dapat membahayakan mereka, meski jika gejala penyakit yang dialami sama dengan Anda.
- Jika Anda mengalami efek samping, bicaralah dengan dokter atau apoteker Anda. Termasuk jika Anda mengalami efek samping yang tidak tercantum di leaflet ini. Silahkan lihat bagian 4.

Apa isi leaflet ini:

1. Apa itu Unamity dan apa kegunaannya

Unamity mengandung zat aktif baricitinib. Merupakan kelompok obat yang disebut penghambat Janus kinase, yang membantu mengurangi peradangan.

Radang sendi rematik
Unamity digunakan untuk mengobati pasien dewasa dengan radang sendi rematik sedang sampai berat, suatu penyakit peradangan pada sendi, jika terapi sebelumnya tidak bekerja dengan cukup baik. Unamity dapat digunakan sendiri atau bersama-sama dengan beberapa obat lain, seperti metotreksat.

Unamity bekerja dengan mengurangi aktivitas enzim dalam tubuh yang disebut 'Janus kinase', yang berperan dalam peradangan. Dengan mengurangi aktivitas enzim ini, Unamity membantu mengurangi rasa nyeri, kekakuan dan bengkak pada persendian, kelelahan, dan membantu memperlambat kerusakan tulang dan tulang rawan pada persendian. Hal ini dapat membantu Anda melakukan aktivitas normal sehari-hari dan dengan demikian meningkatkan kualitas hidup yang berhubungan dengan kesehatan bagi para pasien dengan radang sendi rematik.

Radang kulit atopik
Unamity digunakan untuk mengobati orang dewasa dengan radang kulit atopik sedang hingga berat, juga dikenal sebagai eksim atopik. Unamity dapat digunakan bersamaan dengan obat-obatan eksim yang Anda oleskan ke kulit atau dapat digunakan sendiri.

Unamity bekerja dengan mengurangi aktivitas enzim dalam tubuh yang disebut 'Janus kinase', yang berperan dalam peradangan. Dengan mengurangi aktivitas enzim ini, Unamity membantu memperbaiki kondisi kulit Anda dan mengurangi rasa gatal. Selain itu, Unamity membantu meningkatkan kualitas tidur

Anda (karena gatal) dan kualitas hidup secara keseluruhan. Unamity juga telah terbukti memperbaiki gejala nyeri kulit, kecemasan, dan depresi yang berhubungan dengan radang kulit atopik.

Alopecia areata
Unamity digunakan untuk mengobati orang dewasa dengan alopecia areata parah, suatu penyakit autoimun yang ditandai dengan peradangan, kerontokan rambut tanpa jaringan parut di kulit kepala, wajah, dan terkadang di area tubuh lain yang dapat berulang dan progresif.

Unamity bekerja dengan mengurangi aktivitas enzim dalam tubuh yang disebut 'Janus kinase', yang berperan dalam peradangan. Dengan mengurangi aktivitas enzim ini, Unamity membantu rambut untuk tumbuh kembali di kulit kepala, wajah, dan area tubuh lainnya yang terkena penyakit.

2. Apa yang perlu Anda ketahui sebelum menggunakan Unamity

Jangan gunakan Unamity
- Jika Anda alergi terhadap baricitinib atau kandungan lain dari obat ini (terdaftar di bagian 6).
- Jika Anda hamil atau menduga mungkin Anda hamil

Peringatan dan perhatian
Bicaralah dengan dokter atau apoteker Anda sebelum dan selama menggunakan Unamity jika Anda:
- mengalami infeksi, atau jika Anda sering terkena infeksi. Beritahu dokter Anda jika Anda mengalami gejala seperti demam, luka, merasa lebih lelah dari biasanya atau masalah gigi karena ini bisa jadi merupakan tanda-tanda infeksi. Unamity dapat mengurangi kemampuan tubuh Anda untuk melawan infeksi dan dapat membuat infeksi yang ada menjadi lebih buruk atau meningkatkan kemungkinan Anda mendapatkan infeksi baru
- sedang atau pernah menderita TBC sebelumnya. Anda mungkin perlu pemeriksaan untuk TBC sebelum Anda diberikan Unamity. Beritahu dokter Anda jika Anda menderita batuk terus-menerus, demam, keringat malam dan penurunan berat badan selama penggunaan Unamity karena ini bisa jadi merupakan tanda-tanda dari TBC
- pernah mengalami infeksi herpes (herpes zoster), karena penggunaan Unamity dapat menyebabkan kekambuhan kembali. Beritahu dokter Anda jika Anda mengalami ruam kulit yang nyeri dengan lepuh selama penggunaan Unamity karena ini bisa jadi merupakan tanda-tanda herpes zoster
- sedang atau pernah menderita Hepatitis B atau C
- akan mendapatkan vaksin. Anda tidak boleh mendapatkan jenis vaksin (hidup) tertentu selama menggunakan Unamity.
- menderita kanker, karena dokter Anda akan perlu memutuskan apakah Anda tetap dapat diberikan Unamity
- memiliki fungsi hati yang buruk
- sebelumnya memiliki gumpalan darah di pembuluh darah kaki Anda (trombosis vena dalam) atau paru-paru (emboli paru). Beritahu dokter Anda jika Anda mengalami pembengkakan kaki yang nyeri, nyeri dada, atau sesak napas karena ini bisa jadi merupakan tanda penggumpalan darah di pembuluh darah.
- pernah mengalami diverticulitis (suatu jenis radang pada usus besar) atau luka di perut atau usus (lihat bagian 4)

Jika Anda merasakan salah satu dari efek samping serius berikut, Anda harus langsung memberi tahu dokter:
- Sesak dada

- Mengi
- Pusing yang berat
- Bengkak pada bibir, lidah, atau tenggorokan
- Gatal-gatal (gatal atau ruam kulit)
- sakit perut yang parah terutama disertai dengan demam, mual dan muntah.

Anda mungkin perlu pemeriksaan darah sebelum memulai menggunakan Unamity, atau saat Anda menggunakan Unamity, untuk memeriksa apakah Anda memiliki jumlah sel darah merah yang rendah (anemia), jumlah sel darah putih yang rendah (neutropenia atau limfopenia), kadar lemak darah yang tinggi (kolesterol) atau kadar enzim hati yang tinggi, untuk memastikan bahwa pengobatan dengan Unamity tidak menyebabkan masalah.

Anak-anak dan Remaja

Jangan berikan obat ini untuk anak-anak dan remaja dibawah 18 tahun karena belum ada data untuk penggunaan pada kelompok usia ini.

Obat-obatan lain dan Unamity
Beritahu dokter atau apoteker Anda jika sedang menggunakan, baru-baru ini menggunakan atau mungkin akan menggunakan obat lain.

Secara khusus, beritahu dokter atau apoteker Anda sebelum menggunakan Unamity jika Anda menggunakan obat-obatan lain seperti:
- probenecid (untuk asam urat), karena obat ini dapat meningkatkan kadar Unamity dalam darah Anda. Jika Anda menggunakan probenecid, dosis Unamity yang disarankan adalah 2 mg sehari
- obat anti-rematik suntik
- obat suntik yang menekan sistem kekebalan tubuh. Termasuk yang disebut terapi biologis yang ditargetkan (antibodi)
- obat-obatan yang digunakan untuk mengendalikan respons kekebalan tubuh, seperti azathioprine, tacrolimus atau siklosporin
- obat-obatan lain golongan penghambat Janus kinase
- obat-obatan yang dapat meningkatkan risiko divertikulitis seperti obat-obat antiinflamasi nonsteroid (biasanya digunakan untuk mengobati kondisi nyeri dan/atau peradangan pada otot atau sendi) dan/atau opioid (digunakan untuk mengobati nyeri parah), dan/atau kortikosteroid (biasanya digunakan untuk mengobati kondisi peradangan) (lihat bagian 4)

Kehamilan and Menyusui
Jika Anda sedang hamil atau menyusui, menduga diri Anda hamil atau berencana untuk hamil, mintalah saran dokter atau apoteker Anda sebelum menggunakan obat ini.

Anda harus menggunakan metode kontrasepsi yang efektif untuk menghindari kehamilan selama penggunaan dengan Unamity dan untuk setidaknya satu minggu setelah penggunaan Unamity terakhir. Anda harus memberi tahu dokter Anda jika Anda hamil karena Unamity tidak boleh digunakan selama kehamilan.

Anda tidak boleh menggunakan Unamity saat menyusui karena tidak diketahui apakah obat ini dikeluarkan melalui ASI. Anda dan dokter Anda harus memutuskan apakah Anda akan menyusui atau menggunakan Unamity. Anda tidak boleh melakukan keduanya bersamaan.

Mengemudi dan menggunakan mesin
Unamity tidak berpengaruh pada kemampuan mengemudi dan menggunakan mesin.

Unamity mengandung natrium
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per tablet, pada dasarnya "bebas natrium".

3. Bagaimana cara menggunakan Unamity

Pengobatan harus dimulai oleh dokter yang berpengalaman dalam mendiagnosis dan mengobati kondisi Anda. Selalu gunakan obat ini tepat seperti yang dikatakan dokter atau apoteker Anda. Tanyakan kepada dokter atau apoteker Anda jika Anda tidak yakin.

Radang sendi rematik, radang kulit atopic dan alopecia areata
Dosis yang dianjurkan adalah 4 mg sekali sehari. Dokter Anda dapat memberi Anda dosis lebih rendah yaitu 2 mg sekali sehari, terutama jika Anda berusia diatas 75 tahun atau jika Anda memiliki peningkatan risiko infeksi. Jika obatnya bekerja dengan baik, dokter Anda dapat memutuskan untuk mengurangi dosis.

Jika fungsi ginjal Anda menurun, dosis Unamity yang disarankan adalah 2 mg sekali sehari.

Unamity adalah obat minum. Anda harus menelan tablet Anda dengan air.
Anda dapat menelan tablet dengan atau tanpa makanan. Untuk membantu memudahkan Anda mengingat minum Unamity, minumlah di waktu yang sama setiap hari.

Jika Anda menggunakan Unamity lebih banyak dari yang diperlukan
Jika Anda menggunakan Unamity lebih banyak dari yang seharusnya, hubungi dokter Anda. Anda bisa mengalami beberapa efek samping yang dijelaskan pada bagian 4.

Jika Anda lupa menggunakan Unamity
- Jika Anda melewatkan satu dosis, minumlah segera setelah Anda ingat.
- Jika Anda lupa dosis Anda sepanjang hari, lewati saja dosis yang terlewat dan gunakan hanya satu dosis seperti biasa pada hari berikutnya.
- Jangan gunakan dosis ganda untuk menebus tablet yang terlupakan.

Jika Anda berhenti menggunakan Unamity
Jangan berhenti meminum Unamity kecuali dokter Anda memberitahu Anda untuk berhenti meminumnya.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Efek samping serius

Infeksi seperti herpes zoster dan radang paru, yang dapat terjadi pada hingga 1 dari 10 orang:

Segera beritahu dokter Anda atau cari bantuan medis jika Anda mengalami gejala-gejala berikut, yang bisa jadi merupakan tanda-tanda:
- Herpes zoster: ruam kulit yang nyeri dengan lepuh dan demam (hal ini sangat jarang terjadi pada radang kulit atopik dan jarang terjadi pada alopecia areata)
- Radang paru: batuk terus-menerus, demam, sesak napas, dan kelelahan (hal ini jarang terjadi pada radang kulit atopik dan alopecia areata)

Radang paru serius dan herpes zoster serius jarang terjadi.

Efek samping lainnya

Sangat umum terjadi (dapat terjadi pada lebih dari 1 dari 10 orang):
- infeksi tenggorokan dan hidung
- kadar lemak darah (kolesterol) tinggi pada pemeriksaan darah

Umum terjadi (dapat terjadi pada hingga 1 dari 10 orang):
- cold sores (herpes simpleks)
- infeksi yang menyebabkan sakit perut atau diare (gastroenteritis)
- infeksi saluran kemih
- jumlah trombosit yang tinggi (sel yang berperan dalam pembekuan darah), pada pemeriksaan darah (jarang terjadi pada radang kulit atopik dan alopecia areata)
- sakit kepala
- rasa tidak enak di perut (mual; jarang terjadi pada radang kulit atopik)
- sakit perut (jarang terjadi pada alopecia areata)
- kadar enzim hati yang tinggi, pada pemeriksaan darah (jarang terjadi pada radang kulit atopik)
- ruam
- jerawat (jarang terjadi pada radang sendi rematik)
- peningkatan enzim creatine kinase, pada pemeriksaan darah (jarang terjadi pada radang sendi rematik)
- peradangan (pembengkakan) folikel rambut terutama di daerah kulit kepala yang berhubungan dengan pertumbuhan kembali rambut (diamati pada alopecia areata)

Jarang terjadi (dapat terjadi pada hingga 1 dari 100 orang):
- jumlah sel darah putih yang rendah (neutrofil), pada pemeriksaan darah
- kadar lemak darah (triglycerides) yang tinggi pada pemeriksaan darah
- kadar enzim hati yang tinggi, pada pemeriksaan darah (umum terjadi pada alopecia areata)
- berat badan meningkat
- bengkak pada wajah
- gatal-gatal/kaligata/biduran
- gumpalan darah pada pembuluh darah paru
- gumpalan darah pada pembuluh darah kaki atau panggul, yang disebut Deep Vein Thrombosis (DVT)
- diverticulitis (peradangan yang nyeri pada kantung kecil di lapisan usus Anda)

Pelaporan efek samping
Jika Anda mengalami efek samping apapun, beritahu dokter atau apoteker Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara menyimpan Unamity

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada blister dan karton setelah 'EXP'. Tanggal kedaluwarsa mengacu pada hari terakhir di bulan tersebut.

Jangan membuang obat apa pun melalui saluran pembuangan air atau limbah rumah tangga. Tanyakan apoteker Anda cara membuang obat yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lain

Apa kandungan Unamity

- Zat aktifnya adalah baricitinib. Setiap tablet mengandung 2 atau 4 miligram baricitinib.

- Bahan-bahan lainnya adalah: mikrokristalin selulosa, croscarmellose sodium (lihat bagian 2 “Unamity mengandung natrium), magnesium stearate, manitol, iron oxide red (E172), lecithin (soya) (E322), makrogol, poli (vinil alkohol), talc dan titanium dioksida (E171).

Seperti apa wujud Unamity dan isi kemasannya
Unamity 2 mg tablet salut selaput berwarna pink muda, tablet lonjong berukuran 9 x 7.5 mm, dengan tulisan "Lilly" di satu sisi dan "2" di sisi lainnya.

Unamity 4 mg tablet salut selaput berwarna pink sedang, tablet bundar berukuran 8.5 mm, dengan tulisan "Lilly" di satu sisi dan "4" di sisi lain.

Tablet berbentuk bundar dan memiliki sisi cekung untuk membantu Anda mengambilnya.

Unamity 2 mg dan 4 mg tersedia dalam kemasan Dus, 4 blister @ 7 tablet salut selaput.

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Kabupaten Cianjur, Indonesia

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Spain

HARUS DENGAN RESEP DOKTER

Unamity 2 mg tablet salut selaput, 4 blister @ 7 tablet salut selaput Reg. No.: DKIxxxxxxxxxxx
Unamity 4 mg tablet salut selaput, 4 blister @ 7 tablet salut selaput Reg. No.: DKIxxxxxxxxxxx