Patient Safety Information Card

The marketing of Olumiant 2 and 4 mg is subject to a risk management plan (RMP), including a 'Patient safety information card'. The 'Patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment.

Please explain to the patient the need to review the card before starting treatment.

HCP Guide

This product is marketed with an HCP guide, providing important safety information.

Please ensure you are familiar with this material, as it contains important safety information.

1. NAME OF THE MEDICINAL PRODUCT

Olumiant 2 mg
Olumiant 4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Olumiant 2 mg film-coated tablets

Each film-coated tablet contains 2 mg baricitinib.

Olumiant 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)

Olumiant 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.

Olumiant 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

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).

Atopic dermatitis

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

Alopecia areata

Olumiant 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 recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections (see section 4.4). A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2 mg once daily dose. 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).

Atopic dermatitis

The recommended dose of baricitinib is 4 mg once daily. A dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections (see section 4.4). A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2 mg once daily dose. 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 is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections (see section 4.4). A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2 mg once

daily dose. 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).

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 aged ≥ 75 years is very limited.

Pediatric 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

Baricitinib should only be used if no suitable treatment alternatives are available in patients: - 65 years of age and older; - patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers); - patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Use of JAK inhibitors in patients 65 years of age and older

Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised study of tofacitinib (another JAK inhibitor), baricitinib should only be used in these patients if no suitable treatment alternatives are available.

Infections

Serious and sometimes fatal infections have been reported in patients receiving other JAK inhibitors.

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, combination with methotrexate resulted in increased frequency of infections compared to baricitinib monotherapy.

The risks and benefits of treatment should be carefully considered prior to initiating baricitinib 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.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients over 65 years of age, baricitinib should only be used if no suitable treatment alternatives are available.

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 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 synthetic conventional 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 immunizations in agreement with current immunization 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.

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, 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

Immunomodulatory medicinal products may increase the risk of malignancies including lymphoma. Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including baricitinib.

In a large randomized active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors.

In patients over 65 years of age, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available.

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Venous thromboembolism

In a retrospective observational study of baricitinib in rheumatoid arthritis patients, a higher rate of venous thromboembolic events (VTE) was observed compared to patients treated with TNF inhibitors (see section 4.8).

In a large randomized active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) baricitinib should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, baricitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder.

Patients should be re-evaluated periodically during baricitinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue baricitinib in patients with suspected VTE, regardless of dose or indication.

Major adverse cardiovascular events (MACE)

In a retrospective observational study of baricitinib in rheumatoid arthritis patients, a higher rate of MACE was observed compared to patients treated with TNF inhibitors.

In a large randomized active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke ,was observed with tofacitinib (another JAK inhibitor) compared with TNF inhibitors.

Therefore, in patients over 65 years of age, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available.

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 other than methotrexate (e.g., azathioprine, tacrolimus, ciclosporin) are limited. Caution should be exercised when using such combinations (see section 4.5).

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

Hypersensitivity

In post-marketing experience, cases of 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.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of JAK inhibitors, including baricitinib, in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

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

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 infections (2.9%). Serious pneumonia and serious herpes zoster occurred uncommonly in patients with rheumatoid arthritis.

Tabulated list of adverse reactions

Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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: L04AF02

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.

In vitro skin models
In an *in vitro* human skin model treated with pro-inflammatory cytokines (i.e., IL-4, IL-13, IL-31), baricitinib 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). 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 7 years additional treatment.

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] (1,305)	• 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: IR = inadequate responder; 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, methotrexate (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, MTX or adalimumab.

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 ≤ 3.3 and CDAI ≤ 2.8) or low disease activity or remission (DAS28-ESR or DAS28-hsCRP ≤ 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. Data from the long-term extension study up to 6 years follow-up indicate durable low disease activity/remission rates.

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; IR = inadequate responder; 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	BARI4 mg	BARI4 mg + MTX	PBO[a]	BARI4 mg	ADA 40 mg Q2W	PBO	BARI2 mg	BARI4 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***			
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; IR = inadequate responder; 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 (HAQ-DI) and pain (0-100 visual analogue scale) compared to all comparators (placebo, MTX, adalimumab). Improvements were 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.

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-inadequate responder (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-randomised 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: 451/498 (91 %) continuing 4 mg vs. 405/498 (81 %) reduced to 2 mg (p ≤ 0.001)
- At week 24: 434/498 (87 %) continuing 4 mg vs. 372/498 (75 %) reduced to 2 mg (p ≤ 0.001)
- At week 48: 400/498 (80 %) continuing 4 mg vs. 343/498 (69 %) reduced to 2 mg (p ≤ 0.001)
- At week 96: 347/494 (70 %) continuing 4 mg vs. 297/496 (60 %) reduced to 2 mg (p ≤ 0.001)

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 corticosteroids (TCS) were assessed in 3 Phase III randomised, double-blind, placebo-controlled, 16 week studies (BREEZE-AD1, -AD2, and -AD7). The studies included 1,568 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 medicinal products. Patients were permitted to receive rescue treatment (which included topical or systemic therapy), at which time they were considered non-responders. At baseline of study BREEZE-AD7, all patients were on concomitant topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors. 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.

The Phase III randomised, double-blind, placebo-controlled BREEZE-AD4 study evaluated the efficacy of baricitinib in combination with topical corticosteroids over 52 weeks in 463 patients with moderate to severe atopic dermatitis with failure, intolerance, or contraindication to oral ciclosporin treatment.

Baseline characteristics

In the placebo-controlled Phase III studies (BREEZE-AD1, -AD2, -AD7, and -AD4), across all treatment groups, 37 % were female, 64 % were Caucasian, 31 % were Asian and 0.6 % were Black, and the mean age was 35.6 years. In these studies, 42 % to 51 % of patients had a baseline IGA of 4 (severe atopic dermatitis), and 54 % to 79 % of patients had received prior systemic treatment for atopic dermatitis. The baseline mean EASI score ranged from 29.6 to 33.5, the baseline weekly averaged Itch Numerical Rating Scale (NRS) ranged from 6.5 to 7.1, the baseline mean Dermatology Life Quality Index (DLQI) ranged from 13.6 to 14.9, and the baseline mean Hospital Anxiety and Depression Scale (HADS) Total score ranged from 10.9 to 12.1.

Clinical response

16-week monotherapy (BREEZE-AD1, -AD2) and TCS combination (BREEZE-AD7) studies
A significantly larger proportion of patients randomised to baricitinib 4 mg achieved an IGA 0 or 1 response (primary outcome), EASI75, or an improvement of ≥ 4 points on the Itch NRS compared to placebo at week 16 (Table 6). Figure 1 shows the mean percent change from baseline in EASI up to week 16.

A significantly greater proportion of patients randomised to baricitinib 4 mg achieved a ≥ 4-point improvement in the Itch NRS compared to placebo (within the first week of treatment for BREEZE-AD1 and AD2, and as early as week 2 for BREEZE-AD7; $p < 0.002$).

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

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

	Monotherapy						TCS Combination		
Study	**BREEZE- AD1**			**BREEZE-AD2**			**BREEZE- AD7**		
Treatment Group	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg	PBO + TCS	BARI 2 mg + TCS	BARI 4 mg + TCS
N	249	123	125	244	123	123	109	109	111
IGA 0 or 1, % responders[b, c]	4.8	11.4**	16.8**	4.5	10.6**	13.8**	14.7	23.9	30.6**
EASI-75, % responders[c]	8.8	18.7**	24.8**	6.1	17.9**	21.1**	22.9	43.1*	47.7**
Itch NRS (≥ 4 point improvement), % responders[c, d]	7.2	12.0	21.5**	4.7	15.1**	18.7**	20.2	38.1*	44.0**

BARI = Baricitinib; PBO = Placebo

* statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.

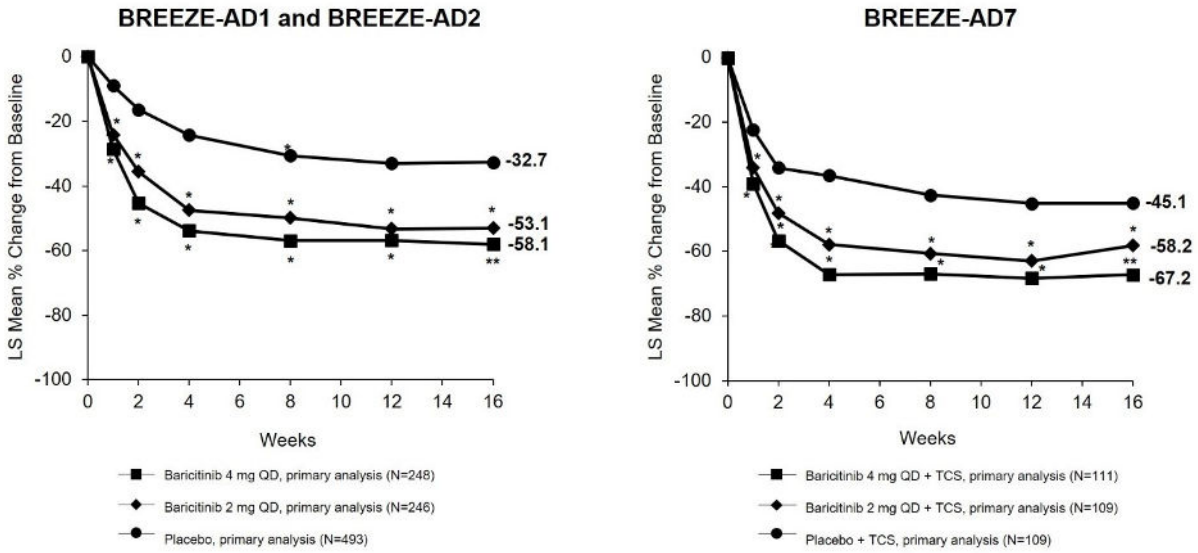
[a] Full analysis set (FAS) including all randomised patients.

[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).

Figure 1. Mean percent change from baseline in EASI (FAS)[a]



LS = Least squares; * statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.

[a] Full analysis set (FAS) including all patients randomised. Data collected after rescue therapy or after permanent medicinal product discontinuation were considered missing. LS means are from Mixed Model with Repeated Measures (MMRM) analyses.

Maintenance of response

To evaluate maintenance of response, 1,373 subjects treated with baricitinib for 16 weeks in BREEZE-AD1 (N = 541), BREEZE-AD2 (N = 540) and BREEZE-AD7 (N = 292) were eligible to enrol in a long term extension study BREEZE-AD3. Data are available up to 68 weeks of cumulative treatment for patients from BREEZE-AD1 and BREEZE-AD2, and up to 32 weeks of cumulative

treatment for patients from BREEZE-AD7. Continued response was observed in patients with at least some response (IGA 0, 1 or 2) after initiating baricitinib.

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 NRS, sleep (ADSS), skin pain (skin pain NRS), quality of life (DLQI) and symptoms of anxiety and depression (HADS) that were uncorrected for multiplicity, at 16 weeks compared to placebo (See Table 7).

Table 7. 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 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg	PBO + TCS	BARI 2 mg + TCS	BARI 4 mg + TCS
N	249	123	125	244	123	123	109	109	111
ADSS Item 2 ≥ 2-point improvement, % responders[c,d]	12.8	11.4	32.7*	8.0	19.6	24.4*	30.6	61.5*	66.7*
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 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)
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)

BARI = Baricitinib; PBO = Placebo

* statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.

[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 Mixed Model with Repeated Measures (MMRM) analyses.

[c] ADSS Item 2: Number of night time awakenings due to itch.

[d] Nonresponder imputation: patients who received rescue treatment or with missing data were considered as nonresponders. Results shown in subset of patients eligible for assessment (patients with ADSS Item 2 ≥ 2 at baseline).

Clinical response in patients with experience with or a contra-indication to ciclosporin treatment (BREEZE-AD4 study)

A total of 463 patients were enrolled, who had either failed (n = 173), or had an intolerance (n = 75), or contraindication (n = 126) to oral ciclosporin. The primary endpoint was the proportion of patients achieving EASI-75 at week 16. The primary and some of the most important secondary endpoints at week 16 are summarised in Table 8.

Table 8: Efficacy of baricitinib in combination with TCS[a] at week 16 in BREEZE-AD4 (FAS)[b]

Study	**BREEZE- AD4**		
Treatment group	PBO[a]	BARI 2 mg[a]	BARI 4 mg[a]
N	93	185	92
EASI-75, % responders[c]	17.2	27.6	31.5**
IGA 0 or 1, % responders[c, e]	9.7	15.1	21.7*
Itch NRS (≥ 4 point improvement), % responders[c, f]	8.2	22.9*	38.2**
Change in DLQI mean (SE)[d]	-4.95 (0.752)	-6.57 (0.494)	-7.95* (0.705)

BARI = Baricitinib; PBO = Placebo

* statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.

[a] All patients were on concomitant topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.

[b] Full analysis set (FAS) includes all randomised patients.

[c] Non-Responder Imputation: Patients who received rescue treatment or with missing data were considered as non-responders.

[d] Data collected after rescue therapy or after permanent medicinal product discontinuation were considered missing. LS means are from Mixed Model with Repeated Measures (MMRM) analyses.

[e] 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.

[f] Results shown in subset of patients eligible for assessment (patients with itch NRS ≥ 4 at baseline).

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 2 shows the proportion of patients achieving SALT ≤ 20 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.

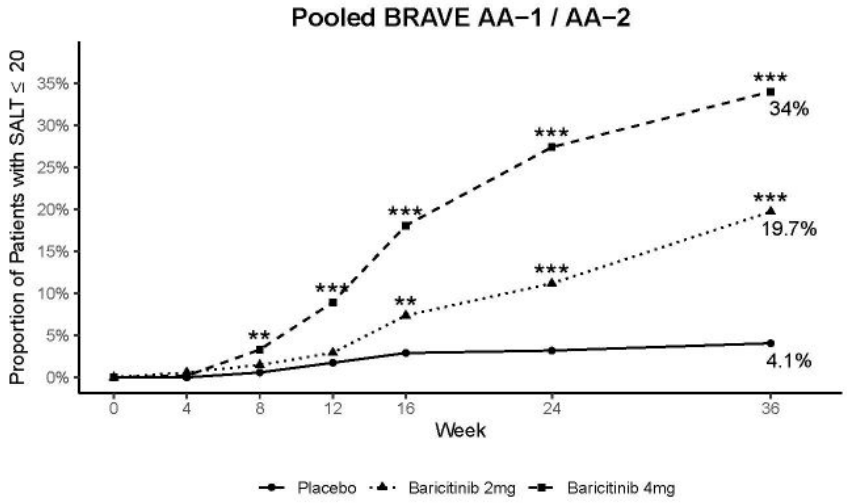
* The results of the pooled analysis are in line with those of the individual studies

** 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 2: 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.

Pediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with baricitinib in one or more subsets of the pediatric population in chronic idiopathic arthritis, atopic dermatitis and alopecia areata (see section 4.2 for information on pediatric use).

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).

Pediatric population

The safety, efficacy and pharmacokinetics of baricitinib have not yet been established in a pediatric 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
- mannitol
- croscarmellose sodium
- magnesium stearate (vegetable)

Film coating, color mixture pink 85G140008 (2 mg) /85G140009 (4 mg):

- polyvinyl alcohol
- titanium dioxide
- macrogol
- talc
- lecithin
- iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium blisters in cartons of 14, 28, 35, 56, 84 or 98 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. License Holder
Eli Lilly Israel Limited
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8. Manufacturer:
Eli Lilly & Company, USA
Lilly Technology Center, Indianapolis, Indiana 46285, USA

9. License Number
Olumiant 2 mg - 161-15-35738-00
Olumiant 4 mg - 161-16-35739-00

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