▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – OLUMIANT® (BARICITINIB)

WARNINGS

Based on the results from a post-marketing safety study of another JAK inhibitor, OLUMIANT should only be used if no suitable treatment alternatives are available in patients:

- **with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors such as current or past long-time smokers.**
- **with malignancy risk factors (e.g. current malignancy or history of malignancy).**
- **65 years of age and older.**

See section 4.4 Special warnings and precautions for use: Mortality, Major adverse cardiovascular events (MACE), Thrombosis, Malignancy, Infections and Use in the elderly.

1 NAME OF THE MEDICINE

Baricitinib

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 List of excipients

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

OLUMIANT 2 mg film-coated tablets
Light pink, oblong, debossed with “Lilly” script on one side and “2” on the other.

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

The tablets contain a recessed area on each face of the tablet surface.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rheumatoid Arthritis

OLUMIANT is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately, or who are intolerant, to one or more DMARDs.

OLUMIANT can be taken as monotherapy or in combination with cDMARDs, including methotrexate (MTX).

Atopic Dermatitis

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

Alopecia Areata

OLUMIANT is indicated for the treatment of severe alopecia areata (AA) in adult patients in whom other treatments have failed or are not appropriate and no spontaneous improvement is observed (see section 5.1 Pharmacodynamic properties, Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

OLUMIANT is given orally with or without food.

Rheumatoid Arthritis

Therapy with OLUMIANT should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

The recommended dose of OLUMIANT is 4 mg once daily. OLUMIANT may be used as monotherapy or in combination with cDMARDS.

A dose of 2 mg once daily may be acceptable for patients with an inadequate response to cDMARDs who have moderate disease severity, limited risk of progressive joint damage and moderate impairment of physical function (see section 5.1 Pharmacodynamic properties, Clinical trials; section 4.4 Special warnings and precautions, Use in hepatic impairment, Use in renal impairment, Effects on laboratory tests).

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.

Combination with other JAK inhibitors has not been studied and is not recommended.

Atopic Dermatitis

Therapy with OLUMIANT should be initiated and supervised by a dermatologist or physician with expertise in the management of atopic dermatitis.

The recommended dose of OLUMIANT is 2 mg once daily (see section 5.1 Pharmacodynamic properties, Clinical trials on Atopic Dermatitis; section 4.4 Special warnings and precautions, Use in hepatic impairment, Use in renal impairment, Effects on laboratory tests).

A dose of 4 mg once daily may also be considered for patients who have not achieved sustained control of disease activity with 2 mg once daily. Dose tapering to 2 mg once daily should be considered once the patient has achieved sustained control of disease with 4 mg once daily.

Treatment should be discontinued in patients who show no evidence of therapeutic benefit after 8 weeks of treatment with 4 mg.

OLUMIANT may be used as monotherapy or in combination with topical corticosteroids. Topical calcineurin inhibitors may be used.

Combination with biologic immunomodulators, other JAK inhibitors, cyclosporine or other potent immunosuppressants has not been studied in patients with atopic dermatitis and is not recommended.

Alopecia Areata

Therapy with OLUMIANT should be initiated and supervised by a dermatologist or physician with expertise in the management of alopecia areata. Prior to commencement of therapy, specific consideration of the likely benefits and risks and discussion with the patient must occur.

The recommended dose of OLUMIANT is 4 mg once daily.

A starting dose of 2 mg once daily may be considered according to prescriber preferences and patient factors.

In patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy, patients aged ≥ 65 years and patients with a history of chronic or recurrent infections, a starting dose of 2 mg once daily is recommended (see section 4.4 Special warnings and precautions for use). 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 if likely benefit outweighs the risk.

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 Pharmacodynamic properties).

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.

Discontinue treatment in patients who show no or minimal evidence of therapeutic benefit after 36 weeks of treatment. Treatment can be stopped earlier than 36 weeks if no benefit is seen and at the discretion of the treating doctor.

Combination with biologic immunomodulators, other JAK inhibitors, cyclosporine or other potent immunosuppressants has not been studied in patients with alopecia areata and is not

recommended. There are no data on combining OLUMIANT with topical or intralesional therapies for alopecia areata.

Dose Modifications in Patients with Renal Impairment

The recommended dose of OLUMIANT in patients with moderate, Stage 3 renal impairment, (estimated glomerular filtration rate (GFR) 30 - ≤60 mL/min/1.73 m^2) is 2 mg once daily. OLUMIANT is not recommended for use in patients with severe and end stage renal impairment Stage 4 & 5 (estimated GFR of <30 mL/min/1.73 m^2) (see section 4.4 Special warnings and precautions for use, Use in renal impairment).

Subjects with creatinine clearance of <40 mL/min at baseline were excluded from participating in the Phase 3 baricitinib studies.

Dose Modifications Due to Drug Interactions

The recommended dose of OLUMIANT in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid, is 2 mg once daily (see section 4.5 Interactions with other medicines and other forms of interactions).

Managing Dose Interruptions or Adjustments

Table 1 Laboratory Measures and Monitoring Guidance

Laboratory Measure	Action	Monitoring Guidance
Lipid parameters	Patients should be managed according to local clinical guidelines for hyperlipidaemia	Week 0 and 12 weeks after initiation of treatment and thereafter according to local clinical guidelines for hyperlipidaemia
Absolute neutrophil count (ANC)	Treatment should be interrupted if ANC <1x 10^9 cells/L and may be restarted once ANC returns above this value	Before treatment initiation and thereafter according to routine patient management
Absolute lymphocyte count (ALC)	Treatment should be interrupted if ALC <0.5x 10^9 cells/L and may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb <8 g/dL and may be restarted once Hb returns above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	

4.3 CONTRAINDICATIONS

OLUMIANT is contraindicated in patients with known hypersensitivity to baricitinib or any of the excipients in the product.

OLUMIANT must not be used in combination with bDMARDs.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Mortality

In a large, randomised, post-marketing safety study in rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor comparing tofacitinib (another JAK inhibitor) to tumour necrosis factor (TNF) inhibitors, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with tofacitinib. Mortality was mainly due to cardiovascular events, infections and malignancies. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OLUMIANT (see the Boxed Warnings and section 4.4 Special warnings and precautions for use, MACE, Thrombosis, Malignancy, Infections and Serious Infections).

Major adverse cardiovascular events (MACE)

MACE have been reported in patients receiving OLUMIANT.

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

In a large randomised post-marketing safety 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 compared to TNF inhibitors. MACE, including events of myocardial infarction, were more common in older patients and in patients who were current or past smokers.

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

Thrombosis

Serious and sometimes fatal events of thrombosis, including deep vein thrombosis (DVT), arterial thrombosis and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors, including baricitinib.

In a large randomised post-marketing safety 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 increased risk for these thrombotic events was observed with tofacitinib compared to TNF inhibitors.

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

In patients with cardiovascular or malignancy risk factors (see also section 4.4 Special warnings and precautions for use, Major adverse cardiovascular events (MACE) and Malignancy), OLUMIANT should only be used if no suitable treatment alternatives are available.

Avoid OLUMIANT in patients with an increased risk of thrombosis or in whom risk factors are identified. 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 OLUMIANT treatment to assess for changes in VTE risk.

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

For venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), 5 patients (0.5%) treated with baricitinib 4 mg reported events during the 24-week, randomised, placebo-controlled time period of the 6 Phase 2 and Phase 3 RA studies; no events were reported with the 2 mg dose or placebo during this time period. During the 0 to 52 week treatment period, venous thromboses were reported in 2 patients (0.6 per 100 patient years) treated with baricitinib 2 mg and 7 patients (0.8 per 100 patient years) treated with baricitinib 4 mg. In an analysis of extended data from the all baricitinib RA exposure population, 3770 patients (12151 patient years of observation) with RA, 57 patients experienced a VTE with an exposure-adjusted IR of 0.47 per 100 PY.

During the 16-week placebo-controlled period of atopic dermatitis studies, 1 patient treated with baricitinib 4 mg reported a VTE. In an analysis of extended data from all the baricitinib AD exposure population, including 2531 patients (2247 patient years of observation) with AD, an additional 2 patients reported VTE (one patient receiving 4 mg reported PE and one patient receiving 2 mg reported DVT). The overall IR was 0.13 per 100 PY.

No VTE events were reported up to 52 weeks of treatment in the alopecia areata clinical trial programme. During longer term treatment, events of DVT and PE have been observed.

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 randomised post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one 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 65 years of age and older, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy) OLUMIANT 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.

In the placebo-controlled phase 2/3 clinical studies in rheumatoid arthritis patients, with data up to 24 weeks, 2 malignancies (excluding NMSC) were diagnosed in 2 patients receiving baricitinib 4 mg, compared to 2 malignancies (excluding NMSC) in patients in the placebo group. There were no cases of lymphoma reported during the placebo-controlled studies. In the all baricitinib exposure population of 3464 patients (4214 patient-years of exposure) with RA, 31 patients were diagnosed with malignancies (excluding NMSC), with an exposure-adjusted IR of 0.7 per 100 PY.

Infections

OLUMIANT treatment is associated with an increased rate of infections such as upper respiratory tract infections. The risks and benefits of treatment should be carefully considered prior to initiating OLUMIANT in patients with chronic, active, or recurrent infection.

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 65 years of age and older-OLUMIANT should only be used if no suitable treatment alternatives are available.

If an infection develops, monitor carefully and interrupt OLUMIANT therapy if the patient is not responding to standard therapy; do not resume OLUMIANT until the infection resolves.

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including OLUMIANT and other JAK inhibitors (see section 4.8 Adverse effects (Undesirable effects), Adverse Reactions, Infections.

The most common serious infections reported with OLUMIANT included herpes zoster and cellulitis. Among opportunistic infections, oesophageal candidiasis, pneumocystis pneumonia, and multidermatomal herpes zoster were reported with OLUMIANT.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OLUMIANT.

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 65 years of age and older, OLUMIANT should only be used if no suitable treatment alternatives are available.

A patient who develops a new infection during treatment with OLUMIANT should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated and the patient should be closely monitored.

If a patient develops a serious infection, administration of OLUMIANT should be interrupted until the infection is controlled.

Tuberculosis

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

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g. herpes zoster including cases that were disseminated beyond the primary or adjacent dermatomes) were reported in clinical studies with OLUMIANT. If a patient develops herpes zoster, OLUMIANT treatment should be interrupted until the episode resolves.

The impact of OLUMIANT on chronic viral hepatitis reactivation is unknown. 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 permitted to enrol. Patients with hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were permitted to enrol; such patients should be monitored for expression of hepatitis B virus (HBV) DNA. Should HBV DNA be detected, consult with a hepatologist.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with OLUMIANT.

Immunisations

No data are available on the response to vaccination with live vaccines in patients receiving OLUMIANT.

Use with live, attenuated vaccines during, or immediately prior to, OLUMIANT therapy is not recommended. Prior to initiating OLUMIANT, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. The interval between live vaccinations and initiation of OLUMIANT therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

The influence of baricitinib on the humoral response to non-live vaccines was evaluated in 106 RA patients under stable treatment with baricitinib 2 or 4 mg, receiving inactivated pneumococcal 13-valent conjugate vaccine or tetanus vaccination. The majority of these patients (n=94) were co-treated with methotrexate. For the total population, excluding one patient who had pneumococcal 13-valent conjugate vaccine prior to entry to the study, pneumococcal conjugate vaccination resulted in a satisfactory IgG immune response (a ≥2-fold increase from baseline in ≥6 pneumococcal serotypes) in 68.6% (95% CI: 59.1%, 76.8%) of the patients. In 43.1% (95% CI: 34.0%, 52.8%) of the patients, a satisfactory IgG immune response (a ≥4-fold increase from baseline in patients with a baseline anti-tetanus IgG concentration ≥0.1 IU/mL) to tetanus vaccination was achieved.

Diverticulitis

Cases of diverticulitis and gastrointestinal perforations have been reported in clinical trials and from post marketing sources. Diverticulitis may cause gastrointestinal perforation. OLUMIANT should be used with caution in patients with diverticular disease and especially in patients chronically treated with concomitant medications associated with an increased risk of diverticulitis such as 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 to prevent gastrointestinal perforation.

Long term use

For alopecia areata, there are no data on safety and efficacy beyond 2 years.

Use in hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment. The use of OLUMIANT has not been studied in patients with severe hepatic impairment and is therefore not recommended.

Use in renal impairment

Renal function was found to significantly affect OLUMIANT exposure. The recommended dose of OLUMIANT in patients with moderate, Stage 3 renal impairment, (estimated GFR 30 - ≤60 mL/min/1.73 m^2) is 2 mg once daily. OLUMIANT is not recommended for use in patients with Stage 4 & 5 severe & end stage renal impairment (estimated GFR of <30 mL/min/1.73 m^2). (See Table 1 section 4.2 Dose and method of administration). Patients with a creatinine clearance <40 mL/min were excluded from the Phase 3 studies therefore caution is advised in patients with creatinine clearance 30 - <40 mL/min.

Use in the elderly

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

Safety information in patients ≥75 years is limited compared to younger patients and this should be taken into consideration when choosing the dose for these patients.

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

Males > 60 and females > 70 years old were excluded from the Alopecia Areata clinical trials. Consider the contribution of age-related or other causes of hair loss before treating.

Paediatric use

The safety and effectiveness of OLUMIANT have not been established in patients under 18 years of age.

Effects on laboratory tests

Neutropenia

Absolute neutrophil counts (ANC) <1000 cells/mm^3 were uncommonly reported in clinical trials. Avoid initiation or interrupt OLUMIANT treatment in patients with an ANC <1000 cells/mm^3 (See Table 1 section 4.2 Dose and method of administration).

Lymphopenia

Absolute lymphocyte counts (ALC) <500 cells/mm^3 were uncommonly reported in clinical trials. Avoid initiation or interrupt OLUMIANT treatment in patients with an ALC <500 cells/mm^3 (See Table 1 section 4.2 Dose and method of administration).

Haemoglobin

Decreases in haemoglobin levels to <8 g/dL were reported uncommonly with baricitinib treatment. Avoid use of OLUMIANT treatment in patients with haemoglobin <8 g/dL (See Table 1 section 4.2 Dose and method of administration).

Lipids

Increases in lipid parameters were very common in the OLUMIANT treated patients in clinical trials. 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 OLUMIANT therapy. During 12 weeks of treatment, 33.7% of patients treated with OLUMIANT 4 mg, 20.3% of patients treated with OLUMIANT 2 mg and 11.3% of patients treated with placebo developed LDL-C ≥3.36 mmol/L (see section 4.8 Adverse effects (undesirable effects), Adverse Reactions, Lipids). Patients should be managed according to local clinical guidelines for hyperlipidaemia (See Table 1 section 4.2 Dose and method of administration). The effect of these lipid parameter elevations on long-term cardiovascular morbidity and mortality has not been determined.

Aminotransferases

Increases to ≥5 and ≥10x upper limit of normal (ULN) were uncommonly observed for both alanine transaminase (ALT) and aspartate transaminase (AST) in patients treated with OLUMIANT in clinical trials. If increases in ALT or AST are observed, and drug induced liver injury is suspected, OLUMIANT should be interrupted until this diagnosis is excluded (See Table 1 section 4.2 Dose and method of administration).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential for OLUMIANT to affect other drugs

Cytochrome P450 Enzymes

In vitro, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6). In clinical pharmacology studies, coadministration of baricitinib with the CYP3A substrates simvastatin, ethinyl estradiol, or levonorgestrel resulted in no clinically meaningful changes in the pharmacokinetics (C_{max} and $AUC_{(0-\infty)}$) of these drugs.

Transporters

In vitro, baricitinib did not inhibit the transporters P-glycoprotein (Pgp) or organic anion transporting polypeptide (OATP) 1B1. In vitro, baricitinib does inhibit organic anionic transporter (OAT) 1, OAT2, OAT3, organic cationic transporter (OCT)1, OCT2, OATP1B3, breast cancer resistance protein (BRCP) and multidrug and toxic extrusion protein (MATE)1 and MATE2-K, but clinically meaningful changes

to drugs that are substrates for these transporters are unlikely. In clinical pharmacology studies there were no clinically meaningful effects when baricitinib was coadministered with digoxin (Pgp substrate) or methotrexate (substrate of several transporters).

Potential for other drugs to affect OLUMIANT

Cytochrome P450 Enzymes

In vitro, baricitinib is a CYP3A4 substrate. In clinical pharmacology studies, coadministration of baricitinib with ketoconazole (CYP3A inhibitor) resulted in no clinically meaningful effect. Coadministration of baricitinib with fluconazole (CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampicin (CYP3A inducer) resulted in no clinically meaningful changes in the pharmacokinetics (C_{max} and $AUC_{(0-\infty)}$) of baricitinib.

Transporters

In vitro, baricitinib is a substrate for OAT3, Pgp, BCRP and MATE2-K. In a clinical pharmacology study, probenecid (OAT3 inhibitor with strong inhibition potential) dosing resulted in approximately a 2-fold increase in $AUC_{(0-\infty)}$ with no effect on C_{max} or T_{max} of baricitinib. Simulations with diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential) predicted minimal effect on baricitinib exposure. Coadministration of baricitinib with cyclosporine (Pgp/BCRP inhibitor) or methotrexate (substrate of several transporters) resulted in no clinically meaningful effects on baricitinib exposure.

Medicines used for VTE

No clinical drug-drug interaction (DDI) studies with anticoagulants have been conducted. Based on the low DDI potential of baricitinib via enzymes and transporters, clinically meaningful DDI are not anticipated for coadministration of baricitinib with medicines commonly used for prophylaxis or treatment of VTE.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a combined male/female rat fertility study, baricitinib decreased overall mating performance and male copulation index following dosing at approximately 56x the maximum recommended human exposure (AUC) and induced a dose-related trend towards reduced male fertility index following dosing at approximately 12x the maximum recommended human exposure (AUC).

Baricitinib treatment also significantly decreased female conception index following dosing at approximately 85x human exposure at the maximum recommended dose (AUC) and induced a dose related trend towards decreased fertility index following dosing at approximately 24x the maximum recommended human exposure (AUC). In female rats there were decreased numbers of corpora lutea and implantation sites and increased pre-implantation loss following dosing at approximately 85x human exposure at the maximum recommended dose (AUC). Following dosing at approximately 24x the maximum recommended human exposure (AUC), reduced mean number of viable embryos/dam, reduced mean viable embryos and increased mean post-implantation loss occurred. The no-observed-effects-level (NOEL) for fertility and impaired early embryonic development was approximately 4x human exposure at the maximum recommended dose (AUC).

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

Women of childbearing potential should take appropriate precautions to avoid becoming pregnant during treatment with OLUMIANT and for at least 1 week after the final treatment.

Use in pregnancy

Pregnancy Category D

Effects on human foetal development are not known. Based on limited data in rats, baricitinib-associated radioactivity readily crosses the placenta (foetal:maternal ratio approximately 2; n=1). In a rat embryofoetal development study, dosing with baricitinib at maternotoxic doses (approximately ≥10x the human maximum recommended dose; AUC) caused increased incidences of adverse malformations (bent limb bones, rib malformations). An increased incidence of foetal rib variations were also noted at even higher maternal exposures (approximately 55x human exposure at the maximum recommended human dose; AUC). In a rabbit embryofoetal development study, dosing of rabbits at ≤30x human exposure at the maximum recommended dose (AUC comparison) was not associated with foetal malformations or variations. However, maternal dosing at approximately 30x human exposure at the maximum recommended dose (AUC comparison) was associated with a decreased mean number of live foetuses/litter (7% decrease), an increased number of late in utero deaths, and decreased foetal weight.

Although the human relevance of the findings in animal studies is uncertain, the JAK/STAT pathway is involved in cell adhesion and cell polarity, which can affect early embryonic development.

OLUMIANT should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Women of childbearing potential should take appropriate precautions to avoid becoming pregnant during treatment with OLUMIANT and for at least 1 week after the final treatment.

Use in lactation

It is unknown whether baricitinib is present in human milk. Baricitinib was detected in the milk of lactating rats. Following maternal PO dosing at 2-22x human exposure at the maximum recommended dose (AUC), the maximum plasma levels in pups occurred at 8 hours (last time point measured) post-dose of the dam.

Breastfeeding is not recommended during OLUMIANT treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to assess driving ability or sedation. There are no known effects on the ability to drive and use machines associated with the use of OLUMIANT.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Events Reported in Clinical Trials

Rheumatoid Arthritis

The safety of OLUMIANT in patients with rheumatoid arthritis (RA) was evaluated in a clinical program consisting of one phase 1 multi-dose study (n=53), three phase 2 multi-dose studies (n=573), four phase 3 multicentre, randomised, double-blind, controlled studies (n=3100), and an ongoing long term extension study.

Tables 2 and 3 list the adverse events (regardless of causality) occurring in ≥1% of patients treated with OLUMIANT during the double-blind, RA controlled studies.

Table 2 Summary of Adverse Events reported by ≥0.1% of patients treated with OLUMIANT (all causalities) – double-blind, placebo-controlled studies up to 16 weeks.

Events	Trials Evaluating OLUMIANT 4 mg (6 Trials) (up to 16 weeks)		Trials Evaluating OLUMIANT 2 mg and OLUMIANT 4 mg (4 Trials) (up to 16 weeks)		
	Placebo + cDMARDs n=1070 (%)	OLUMIANT 4 mg + cDMARDs n=997 (%)	Placebo + cDMARDs n=551 (%)	OLUMIANT 2 mg + cDMARDs n=479 (%)	OLUMIANT 4 mg + cDMARDs n=479 (%)
Blood and lymphatic system disorders					
Anaemia	22 (2.1)	20 (2.0)	8 (1.5)	8 (1.7)	6 (1.3)
Gastrointestinal disorders					
Nausea	17 (1.6)	28 (2.8)	11 (2.0)	13 (2.7)	14 (2.9)
Diarrhoea	35 (3.3)	24 (2.4)	21 (3.8)	16 (3.3)	12 (2.5)
Dyspepsia	8 (0.7)	14 (1.4)			
Constipation	15 (1.4)	11 (1.1)	9 (1.6)	8 (1.7)	5 (1.0)
Vomiting	6 (0.6)	13 (1.3)	4 (0.7)	11 (2.3)	5 (1.0)
Abdominal pain[a]	15 (1.4)	21 (2.1)	8 (1.5)	18 (3.8)	9 (1.9)
General disorders and administration site conditions					
Fatigue	14 (1.3)	11 (1.1)	8 (1.5)	7 (1.5)	8 (1.7)
Pyrexia			3 (0.5)	6 (1.3)	6 (1.3)
Oedema peripheral			8 (1.5)	5 (1.0)	2 (0.4)
Hepatobiliary disorders					
Hepatic function abnormal			1 (0.2)	5 (1.0)	2 (0.4)
Infections and infestations					
Nasopharyngitis	51 (4.8)	53 (5.3)	26 (4.7)	16 (3.3)	25 (5.2)
Upper respiratory tract infection	39 (3.6)	46 (4.6)	25 (4.5)	27 (5.6)	31 (6.5)
Bronchitis	30 (2.8)	31 (3.1)	19 (3.4)	12 (2.5)	14 (2.9)
Urinary tract infection	29 (2.7)	34 (3.4)	14 (2.5)	17 (3.5)	16 (3.3)
Pharyngitis	14 (1.3)	23 (2.3)	4 (0.7)	10 (2.1)	13 (2.7)
Gastroenteritis	9 (0.8)	16 (1.6)	4 (0.7)	7 (1.5)	12 (2.5)
Influenza	10 (0.9)	18 (1.8)	6 (1.1)	6 (1.3)	9 (1.9)

Herpes zoster	4 (0.4)	14 (1.4)	2 (0.4)	5 (1.0)	9 (1.9)
Sinusitis	12 (1.1)	10 (1.0)	6 (1.1)	10 (2.1)	6 (1.3)
Oral herpes	4 (0.4)	10 (1.0)			
Rhinitis			1 (0.2)	6 (1.3)	1 (0.2)
Cystitis			5 (0.9)	7 (1.5)	1 (0.2)
Injury, poisoning and procedural complications					
Contusion			7 (1.3)	6 (1.3)	2 (0.4)
Investigations					
Blood creatine phosphokinase increased	6 (0.6)	35 (3.5)	3 (0.5)	11 (2.3)	24 (5.0)
Alanine aminotransferase increased	10 (0.9)	15 (1.5)	6 (1.1)	5 (1.0)	8 (1.7)
Aspartate aminotransferase increased	5 (0.5)	14 (1.4)	4 (0.7)	2 (0.4)	10 (2.1)
Weight increased	5 (0.5)	6 (0.6)	2 (0.4)	4 (0.8)	4 (0.8)
Metabolism and nutrition disorders					
Hypercholesterolaemia	14 (1.3)	28 (2.8)	7 (1.3)	7 (1.5)	16 (3.3)
Hyperlipidaemia	8 (0.7)	19 (1.9)	6 (1.1)	5 (1.0)	9 (1.9)
Dyslipidaemia	5 (0.5)	10 (1.0)	2 (0.4)	6 (1.3)	5 (1.0)
Musculoskeletal and connective tissue disorders					
Arthralgia	17 (1.6)	17 (1.7)	10 (1.8)	8 (1.7)	11 (2.3)
Rheumatoid arthritis	23 (2.1)	14 (1.4)	10 (1.8)	5 (1.0)	10 (2.1)
Back pain	26 (2.4)	12 (1.2)	18 (3.3)	14 (2.9)	7 (1.5)
Muscle spasms			3 (0.5)	6 (1.3)	5 (1.0)
Myalgia			1 (0.2)	4 (0.8)	5 (1.0)
Nervous system disorders					
Headache	32 (3.0)	38 (3.8)	22 (4.0)	30 (6.3)	20 (4.2)
Dizziness	8 (0.7)	14 (1.4)	4 (0.7)	7 (1.5)	7 (1.5)
Psychiatric disorders					
Insomnia			3 (0.5)	5 (1.0)	2 (0.4)
Reproductive system and breast disorders					
Erectile dysfunction[b]			0	0	1 (1.1)
Respiratory, thoracic and mediastinal disorders					
Cough	17 (1.6)	19 (1.9)	9 (1.6)	9 (1.9)	13 (2.7)
Oropharyngeal pain	5 (0.5)	12 (1.2)	3 (0.5)	9 (1.9)	11 (2.3)
Pulmonary embolism	0	3 (0.3)	(0)	(0)	2 (0.4)
Skin and subcutaneous tissue disorders					
Alopecia			5 (0.9)	0	9 (1.9)
Acne	0	8 (0.8)	0	1 (0.2)	5 (1.0)
Rash[c]	28 (2.6)	18 (1.8)	15 (2.7)	9 (1.9)	9 (1.9)
Swelling of the face	1 (0.1)	4 (0.4)	(0)	(0)	1 (0.2)
Urticaria	1 (0.1)	2 (0.2)	(0)	2 (0.4)	2 (0.4)
Vascular disorders					
Hypertension	17 (1.6)	21 (2.1)	6 (1.1)	16 (3.3)	15 (3.1)
Deep Vein Thrombosis	0	2 (0.2)	0	0	0

[a] Includes abdominal pain, abdominal pain lower, abdominal pain upper.
[b] denominator adjusted because event is specific to males: N=93 (placebo), N=93 (OLUMIANT 2 mg), N=88 (OLUMIANT 4 mg)
[c]Includes rash, dermatitis, dermatitis contact, eczema, dermatitis allergic, rash maculo-papular, rash pruritic, rash pustular, drug eruption, rash erythematous, rash macular

Table 3 Summary of Adverse Events reported by ≥1% of patients treated with OLUMIANT (all causalities) – double-blind, active-controlled study up to 24 weeks (RA-BEGIN).

	Trial Evaluating OLUMIANT 4 mg (1 Trial) (up to 24 weeks)		
Events	**Methotrexate n=210 (%)**	**OLUMIANT 4 mg n=159 (%)**	**OLUMIANT4 mg + methotrexate n=215 (%)**
Blood and lymphatic system disorders			
Anaemia	2 (1.0)	2 (1.3)	4 (1.9)
Iron deficiency anaemia	0	1 (0.6)	3 (1.4)
Thrombocytosis	0	3 (1.9)	2 (0.9)
Cardiac disorders			
Coronary artery disease	0	2 (1.3)	0
Eye disorders			
Vision blurred	0	0	3 (1.4)
Cataract	1 (0.5)	2 (1.3)	1 (0.5)
Gastrointestinal disorders			
Nausea	11 (5.2)	7 (4.4)	16 (7.4)
Dyspepsia	0	2 (1.3)	8 (3.7)
Constipation	2 (1.0)	1 (0.6)	5 (2.3)
Stomatitis	1 (0.5)	1 (0.6)	4 (1.9)
Abdominal discomfort	1 (0.5)	1 (0.6)	3 (1.4)
Diarrhoea	9 (4.3)	3 (1.9)	3 (1.4)
Gastrooesophageal reflux disease	1 (0.5)	0	3 (1.4)
Abdominal pain upper	4 (1.9)	3 (1.9)	1 (0.5)
Vomiting	4 (1.9)	4 (2.5)	1 (0.5)
General disorders and administration site conditions			
Pyrexia	4 (1.9)	1 (0.6)	6 (2.8)
Fatigue	4 (1.9)	4 (2.5)	5 (2.3)
Drug intolerance	2 (1.0)	2 (1.3)	0
Oedema peripheral	1 (0.5)	3 (1.9)	0
Hepatobiliary disorders			
Hepatic function abnormal	4 (1.9)	1 (0.6)	6 (2.8)
Infections and infestations			
Nasopharyngitis	11 (5.2)	11 (6.9)	14 (6.5)
Upper respiratory tract infection	13 (6.2)	7 (4.4)	10 (4.7)
Urinary tract infection	2 (1.0)	4 (2.5)	10 (4.7)
Pharyngitis	3 (1.4)	2 (1.3)	5 (2.3)

Sinusitis	2 (1.0)	1 (0.6)	5 (2.3)
Gastroenteritis	2 (1.0)	3 (1.9)	4 (1.9)
Influenza	1 (0.5)	4 (2.5)	4 (1.9)
Vulvovaginal candidiasis[b]	1 (0.7)	0	4 (2.6)
Bronchitis	3 (1.4)	2 (1.3)	3 (1.4)
Cystitis	0	1 (0.6)	3 (1.4)
Herpes zoster	1 (0.5)	3 (1.9)	3 (1.4)
Tonsillitis	1 (0.5)	2 (1.3)	1 (0.5)
Onychomycosis	1 (0.5)	2 (1.3)	0
Investigations			
Blood creatine phosphokinase increased	0	4 (2.5)	9 (4.2)
Alanine aminotransferase increased	2 (1.0)	1 (0.6)	9 (4.2)
Aspartate aminotransferase increased	1 (0.5)	0	4 (1.9)
Blood alkaline phosphatase increased	1 (0.5)	1 (0.6)	4 (1.9)
Low density lipoprotein increased	1 (0.5)	1 (0.6)	3 (1.4)
Liver function test abnormal	1 (0.5)	2 (1.3)	2 (0.9)
Blood cholesterol increased	0	2 (1.3)	1 (0.5)
Platelet count increased	0	2 (1.3)	1 (0.5)
Weight increased	2 (1.0)	3 (1.9)	1 (0.5)
White blood cell count increased	0	2 (1.3)	0
Metabolism and nutrition disorders			
Dyslipidaemia	2 (1.0)	2 (1.3)	6 (2.8)
Hyperlipidaemia	0	3 (1.9)	5 (2.3)
Hypercholesterolaemia	3 (1.4)	4 (2.5)	4 (1.9)
Musculoskeletal and connective tissue disorders			
Back pain	3 (1.4)	2 (1.3)	5 (2.3)
Muscle spasms	1 (0.5)	2 (1.3)	6 (2.8)
Osteoarthritis	0	2 (1.3)	1 (0.5)
Nervous system disorders			
Headache	1 (0.5)	4 (2.5)	5 (2.3)
Dizziness	4 (1.9)	0	3 (1.4)
Sciatica	0	3 (1.9)	0
Depression	3 (1.4)	6 (3.8)	1 (0.5)
Reproductive system and breast disorders			
Benign prostatic hyperplasia[a]	0	0	1 (1.7)
Respiratory, thoracic and mediastinal disorders			
Cough	11 (5.2)	4 (2.5)	4 (1.9)
Oropharyngeal pain	1 (0.5)	2 (1.3)	2 (0.9)
Dyspnea	4 (1.9)	2 (1.3)	0
Rhinorrhea	0	2 (1.3)	0
Skin and subcutaneous tissue disorders			
Alopecia	4 (1.9)	1 (0.6)	5 (2.3)
Acne	0	2 (1.3)	2 (0.9)
Dermatitis contact	2 (1.0)	2 (1.3)	2 (0.9)

Vascular disorders			
Hypertension	5 (2.4)	1 (0.6)	9 (4.2)

[a] denominator adjusted because event is specific to males: N=62 (MTX), N=38 (OLUMIANT 4 mg), N=59 (OLUMIANT 4 mg + MTX)
[b] denominator adjusted because event is specific to females: N=148 (MTX), N=121 (OLUMIANT4 mg), N=156 (OLUMIANT 4 mg + MTX)

Venous thromboembolism

Events of VTE, including DVT and PE, have been reported in clinical trials (see section 4.4 Special warnings and precautions for use , Thrombosis).

Treatment-Naïve Patients

RA-BEGIN evaluated 584 patients with moderate to severe RA who had no or limited exposure to MTX and who were naïve to other DMARDs. The safety profile observed in the OLUMIANT treatment groups was consistent with the overall safety profile of OLUMIANT across all treatment settings. Up to week 52, similar proportions of patients in each of the 3 treatment groups experienced a treatment-emergent adverse event: MTX alone 71.9%, OLUMIANT 4 mg monotherapy 71.1%, and OLUMIANT 4 mg + MTX 77.7%. Likewise, similar proportions of patients experienced serious adverse events (SAEs): MTX alone 9.5%, OLUMIANT 4 mg monotherapy 7.5%, and OLUMIANT 4 mg + MTX 7.9%. Adverse events leading to discontinuation of study drug were most frequent in patients taking baricitinib in combination with MTX: MTX alone 5.2%, OLUMIANT 4 mg monotherapy 5.7%, and OLUMIANT 4 mg +MTX 10.7%. The most common reason for treatment discontinuation was infections or infestations. Three patient deaths were reported during the study, all in the MTX alone group.

Methotrexate Inadequate Responders

RA-BEAM evaluated 1305 patients with moderate to severe RA who had had an inadequate response to methotrexate and had not been treated with biologic DMARDs. Patients in this study were randomised to receive placebo, baricitinib or adalimumab. The safety profile observed in the baricitinib treatment groups was consistent with the overall safety profile of baricitinib across all treatment settings. Up to week 24, a higher proportion of patients in the 2 active treatment groups experienced a treatment-emergent adverse event: placebo 60.5%, baricitinib 4 mg 71.3%, and adalimumab 67.9%. Higher proportions of patients experienced serious adverse events (SAEs) in the placebo (4.5%) and baricitinib 4 mg (4.7%) treatment groups compared to adalimumab (1.8%). Adverse events leading to discontinuation of study drug were most frequent in patients taking baricitinib 4 mg (5.1%) compared to placebo (3.5%) and adalimumab (2.1%). The most common reason for treatment discontinuation was infections or infestations.

Atopic Dermatitis

A total of 2531 patients were treated with OLUMIANT in clinical studies in atopic dermatitis representing a total of 2247 patient years of exposure. Of these 1106 atopic dermatitis patients were exposed to OLUMIANT for at least one year.

Five placebo controlled studies were integrated (489 patients on 4 mg once daily, 576 patients on 2 mg once daily and 743 patients on placebo) to evaluate the safety of OLUMIANT in comparison to placebo for up to 16 weeks after treatment initiation.

Table 4 Adverse Events in Placebo-Controlled Trials: Up to 16 Weeks

System Organ Class/ Preferred term	Placebo n=743 (%*)	OLUMIANT 2 mg n= 576 (%*)	OLUMIANT 4 mg n= 489 (%*)
Gastrointestinal disorders			
Nausea	8 (0.8)	14 (1.8)	4 (0.8)
Abdominal pain[a]	18 (2.2)	21 (3.0)	20 (3.6)
Infections			
Upper respiratory tract infections[b]	124 (14.1)	114 (16.0)	103 (17.5)
Herpes simplex[c]	22 (2.7)	25 (3.6)	35 (6.1)
Herpes zoster	3 (0.3)	6 (0.8)	0
Urinary tract infection	8 (0.8)	9 (1.1)	11 (2.0)
Investigations			
Weight increased	0	3 (0.5)	4 (0.7)
Nervous system disorders			
Headache	28 (3.3)	37 (5.9)	35 (6.3)
Vascular disorders			
Deep vein thrombosis	0	0	0
Respiratory, thoracic, mediastinal disorders			
Pulmonary embolism	0	0	1 (0.1)
Skin and subcutaneous tissue disorders			
Rash[d]	12 (1.2)	9 (1.3)	8 (1.3)
Acne[e]	7 (0.7)	9 (1.3)	10 (1.5)
Swelling of the face[f]	3 (0.3)	4 (0.5)	3 (0.6)
Urticaria	4 (0.5)	3 (0.4)	2 (0.4)
Laboratory Parameters[g]			
Creatine Phosphokinase >5 x ULN	14 (1.9)	14 (2.5)	16 (3.3)
LDL cholesterol ≥130 mg/dL	34 (6.3)	52 (12.0)	48 (13.2)
Triglycerides ≥500 mg/dL	5 (0.8)	3 (0.6)	3 (0.7)
ALT ≥3 x ULN	7 (0.8)	3 (0.4)	1 (0.2)
AST ≥3 x ULN	7 (0.8)	5 (0.6)	3 (0.5)
Neutropenia <1000 cells/mm^3	0	1 (0.2)	1 (0.2)
Thrombocytosis >600,000 cells/mm^3	0	7 (1.2)	3 (0.6)

* Study size adjusted percentage.

[a] Includes abdominal pain, abdominal pain lower, abdominal pain upper.

[b] Includes acute sinusitis, chronic sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection.

[c] Includes eczema herpeticum, herpes simplex, Kaposi's varicelliform eruption, genital herpes, genital herpes simplex, ophthalmic herpes simplex, oral herpes.

[d] Includes dermatitis, dermatitis allergic, dermatitis contact, drug eruption, eczema, rash, rash maculo-papular, rash pustular.

[e] Includes acne, acne varioliformis, dermatitis acneiform.

[f] Includes eye swelling, eyelid oedema, face oedema, lip swelling, swelling face, swelling of eyelid.

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

Alopecia Areata

A total of 1244 patients were treated with OLUMIANT in clinical studies in alopecia areata representing a total of 1362 patient-years of exposure. Of these 845 patients were exposed to OLUMIANT for at least one year.

Two placebo-controlled studies were integrated (540 patients on 4 mg once daily, 365 patients on 2 mg once daily and 371 patients on placebo) to evaluate the safety of OLUMIANT in comparison to placebo for up to 36 weeks after treatment administration as well as during long-term therapy.

Up to 36 weeks, the proportion of patients that experienced treatment emergent adverse events in the 3 treatment groups were placebo (56.9%), OLUMIANT 2mg (60.5%) and OLUMIANT 4mg (63.1%). The proportion of patients that experienced serious adverse events were placebo (1.6%), OLUMIANT 2mg (2.2%) and OLUMIANT 4mg (2.6%). The proportion of patients that experienced adverse events leading to treatment discontinuation were placebo (1.6%), OLUMIANT 2mg (2.2%) and OLUMIANT 4mg (2.2%). Whilst most events were mild or moderate in severity, a higher proportion of patients in the placebo (3.0%) and OLUMIANT 4 mg (3.9%) treatment groups reported severe treatment-emergent adverse events compared to OLUMIANT 2 mg (1.6%).

Table 5 lists the adverse events (regardless of causality) occurring in ≥1% of patients treated with OLUMIANT during the double-blind, controlled AA studies.

Table 5 Adverse Events reported by ≥1% of patients treated with OLUMIANT (all causalities) during double-blind, placebo-controlled studies up to 36 weeks

Events	Placebo N=371 n (%)	OLUMIANT 2 mg N=365 n (%)	OLUMIANT4 mg N=540 n (%)
Upper respiratory tract infection	26 (7.0)	24 (6.6)	41 (7.6)
Nasopharyngitis	19 (5.1)	16 (4.4)	37 (6.9)
Headache	20 (5.4)	20 (5.5)	36 (6.7)
Acne	4 (1.1)	21 (8.5)	30 (5.6)
Blood creatine phosphokinase increased	5 (1.3)	3 (0.8)	23 (4.3)
Urinary tract infection	5 (1.3)	3 (0.8)	23 (4.3)
Hypertension	9 (2.4)	2 (0.5)	14 (2.6)
Influenza	7 (1.9)	6 (1.6)	14 (2.6)
Pruritus	8 (2.2)	1 (0.3)	12 (2.4)
Cough	7 (1.9)	5 (1.4)	12 (2.2)
Fatigue	4 (1.1)	3 (0.8)	12 (2.2)
Folliculitis	3 (0.8)	5 (1.4)	12 (2.2)
Nausea	6 (1.6)	10 (2.7)	11 (2.0)
Back pain	12 (3.2)	6 (1.6)	10 (1.9)
Arthralgia	8 (2.2)	7 (1.9)	9 (1.7)
Diarrhoea	8 (2.2)	2 (0.5)	9 (1.7)
Dyslipidaemia	3 (0.8)	0	9 (1.7)
Dyspepsia	4 (1.1)	4 (1.1)	8 (1.5)
Oropharyngeal pain	3 (0.8)	5 (1.4)	8 (1.5)
Viral upper respiratory tract infection	6 (1.6)	8 (2.2)	8 (1.5)

Anaemia	1 (0.3)	1 (0.3)	7 (1.3)
Blood cholesterol increased	2 (0.5)	4 (1.1)	7 (1.3)
Hypercholesterolaemia	3 (0.8)	5 (1.4)	7 (1.3)
Oral herpes	9 (2.4)	6 (1.6)	7 (1.3)
Transaminases increased	1 (0.3)	1 (0.3)	7 (1.3)
Alanine aminotransferase increased	3 (0.8)	2 (0.5)	6 (1.1)
Bronchitis	1 (0.3)	3 (0.8)	6 (1.1)
Neutropenia	3 (0.8)	2 (0.5)	6 (1.1)
Rash	3 (0.8)	0	6 (1.1)
Dizziness	3 (0.8)	4 (1.1)	5 (0.9)
Herpes zoster	2 (0.5)	5 (1.4)	5 (0.9)
Sinusitis	6 (1.6)	4 (1.1)	5 (0.9)
Weight increased	1 (0.3)	6 (1.6)	5 (0.9)
Abdominal pain	3 (0.8)	4 (1.1)	4 (0.7)
Dermatitis contact	4 (1.1)	7 (1.9)	4 (0.7)
Gastroenteritis	6 (1.6)	6 (1.6)	4 (0.7)
Gastrooesophageal reflux disease	4 (1.1)	4 (1.1)	4 (0.7)
Menstruation irregular	0	0	4 (1.2)
Pyrexia	2 (0.5)	4 (1.1)	4 (0.7)
Rhinorrhoea	0	5 (1.4)	4 (0.7)
Vulvovaginal candidiasis	0	6 (2.6)	4 (1.2)
Abdominal pain upper	2 (0.5)	5 (1.4)	2 (0.4)
Depression	6 (1.6)	5 (1.4)	2 (0.4)
Abdominal discomfort	2 (0.5)	4 (1.1)	0

In patients treated with any dose of baricitinib, adverse events that occurred in fewer than 1% of patients include myocardial infarction and B cell lymphoma.

Adverse events observed in the long-term extension of alopecia areata trials: venous thromboembolic events (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE), and malignancy.

In the long-term extension of alopecia areata clinical trials, in patients treated for at least 52 weeks, the safety profile of OLUMIANT 2 mg and OLUMIANT 4 mg was consistent with the long-term safety observations in rheumatoid arthritis and atopic dermatitis clinical trials and did not reveal a new safety signal.

Adverse Reactions

Adverse Drug Reactions (ADRs) from clinical studies are presented below by System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥10%); common (≥1% to <10%), uncommon (≥0.1% to <1%), rare (≥0.01% to <0.1%) or very rare (<0.01%).

Rheumatoid Arthritis

Table 6 Clinical Trial Adverse Reactions

Body system/adverse drug reaction terms	Very common ≥10%	Common ≥1% and <10%	Uncommon (Infrequent) ≥0.1% and <1%
Gastrointestinal disorders			
Nausea		x	
Abdominal pain[a]		x	
Infections and infestations			
Upper respiratory tract infections[b]	x		
Herpes simplex[c]		x	
Herpes zoster		x	
Urinary tract infection		x	
Investigations			
Weight increased			x
Nervous system disorders			
Headache		x	
Vascular disorders			
Deep Vein Thrombosis			x
Respiratory, thoracic, mediastinal disorders			
Pulmonary embolism			x
Skin and subcutaneous tissue disorders			
Acne[d]			x
Laboratory Parameters[e]			
Clinical Chemistry			
Creatine Phosphokinase >5 x ULN			x
LDL cholesterol ≥130 mg/dL (≥3.36 mmol/L)	x		
Triglycerides ≥500 mg/dL (≥5.65 mmol/L)			x
ALT ≥3 x ULN		x	
AST ≥3 x ULN			x
Hematology			
Neutropenia <1000 cells/mm^3			x
Thrombocytosis >600,000 cells/mm^3		x	

[a] Includes abdominal pain, abdominal pain lower, abdominal pain upper.

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

[c] Includes eczema herpeticum, herpes simplex, Kaposi's varicelliform eruption, genital herpes, genital herpes simplex, ophthalmic herpes simplex, oral herpes.

[d] Includes acne, acne varioliformis, dermatitis acneiform.

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

Atopic Dermatitis

In patients treated with OLUMIANT in the atopic dermatitis clinical trials, acne and creatine phosphokinase >5x ULN were common. The frequency of herpes zoster was very rare and the frequency of thrombocytosis >600 000 cells/mm^3, nausea and ALT ≥3 x ULN was uncommon.

Alopecia Areata

Table 7 Adverse Reactions for OLUMIANT 4 mg in Placebo-Controlled Trials: Up to 36 weeks

System Organ Class/ Preferred term	Very common ≥10%	Common ≥1% and <10%	Uncommon ≥0.1% and <1%
Gastrointestinal disorders			
Nausea		x	
Abdominal pain[a]			x
Infections			
Upper respiratory tract infections[b]	x		
Herpes simplex[c]		x	
Herpes zoster			x
Urinary tract infection		x	
Investigations			
Weight increased			x
Nervous system disorders			
Headache		x	
Respiratory, thoracic, mediastinal disorders			
Pulmonary embolism[d]			- [d]
Skin and subcutaneous tissue disorders			
Acne[e]		x	
Vascular disorders			
Deep vein thrombosis[d]			- [d]
Laboratory parameters[f]			
Clinical Chemistry			
Creatine Phosphokinase >5 x ULN		x	
LDL cholesterol ≥130 mg/dL (≥3.36 mmol/L)	x		
Triglycerides ≥500 mg/dL (≥5.65 mmol/L)			x
ALT ≥3 x ULN		x	
AST ≥3 x ULN		x	
Hematology			
Neutropenia <1000 cells/mm^3			x
Thrombocytosis >600,000 cells/mm^3			x

[a] Includes abdominal pain, abdominal pain lower, abdominal pain upper.

[b] Includes acute sinusitis, adenoiditis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection.

[c] Includes genital herpes, herpes simplex, oral herpes.

[d] not observed during 36 week placebo-controlled period; observed during long term extension of clinical trials

[e] Includes acne, dermatitis acneiform.

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

Description of selected adverse reactions – Rheumatoid Arthritis

Infections

Events related to upper respiratory tract infections, herpes simplex, and herpes zoster were commonly observed during controlled clinical trials. Most infections (as observed in 95% of patients reporting an infection) were mild to moderate in severity.

Serious infections occurred in 1.0% of patients treated with OLUMIANT 4 mg (6 study dataset), 1.3% with OLUMIANT 2 mg (4 study dataset) and 1.0% of patients treated with placebo (6 study dataset) during the initial 12 week period. In RA-BEGIN, the serious infection rate during the 24 week treatment period was 1.3% with OLUMIANT 4 mg monotherapy, 1.9% with OLUMIANT 4 mg plus methotrexate, and 1.4% with methotrexate monotherapy. The most common serious infections were herpes zoster and cellulitis.

Nausea

In treatment-naïve patients, through 52 weeks, the frequency of nausea was greater for the combination treatment of methotrexate and OLUMIANT (9.3%) compared to methotrexate alone (6.2%) or OLUMIANT alone (4.4%). Nausea was most frequent during the first 2 weeks of treatment.

Laboratory Parameters

Neutropenia

In controlled clinical trials, neutrophil counts below 1000 cells/mm^3 occurred in 0.3% of patients treated with OLUMIANT 4 mg, 0.6% of patients treated with OLUMIANT 2 mg, and 0% of patients treated with placebo during the initial 12 week treatment period. In RA-BEGIN, decreases in neutrophil counts below 1000 cells/mm^3 during the 24 week treatment period did not occur in any patient treated with OLUMIANT 4 mg monotherapy, with OLUMIANT 4 mg plus methotrexate, or with methotrexate monotherapy. In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with observations in the controlled periods of the studies.

No association was observed between decreases in neutrophil counts and the occurrence of serious infections. In clinical studies, treatment was interrupted in response to absolute neutrophil counts <1000 cells/mm^3 (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Thrombocytosis

In controlled clinical trials, increases in platelet counts above 600,000 cells/mm^3 occurred in 1.7% of patients treated with OLUMIANT 4 mg, 1.1% of patients treated with OLUMIANT 2 mg, and 0.9% of patients treated with placebo during the 12 week treatment period. In RA-BEGIN, increases in platelet counts above 600,000 cells/mm^3 during the 24 week treatment period occurred in 2.6% of patients treated with OLUMIANT 4 mg monotherapy, 1.9% of patients treated with OLUMIANT 4 mg plus methotrexate, and 2.4% of patients treated with methotrexate monotherapy.

In the all exposure population, the pattern and incidence of increases in platelet counts remained consistent with observations in the controlled periods of the studies.

Liver Enzyme Elevations

Events of increases in liver enzymes ≥3 x ULN were observed in patients treated with OLUMIANT.

ALT elevations ≥3 x ULN during the 12 week treatment period occurred in 1.3% of patients treated with OLUMIANT 4 mg, 1.5% with OLUMIANT 2 mg, and 1.0% with placebo.

AST elevations ≥3 x ULN during the 12 week treatment period occurred in 0.7% of patients treated with OLUMIANT 4 mg, 1.0% with OLUMIANT 2 mg, and 0.8% of patients receiving placebo.

In RA-BEGIN, ALT and AST elevations ≥3x ULN during the 24 week treatment period occurred in 1.9% and 1.3% of patients treated with OLUMIANT 4 mg monotherapy, 4.7% and 1.9% of patients treated with OLUMIANT 4 mg plus methotrexate, and 1.9% and 0% of patients treated with methotrexate monotherapy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Lipids

In controlled clinical trials, OLUMIANT treatment was associated with increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Elevations were observed at 12 weeks and remained stable thereafter. During 12 weeks of treatment, 33.7% of patients treated with OLUMIANT 4 mg, 20.3% of patients treated with OLUMIANT 2 mg and 11.3% of patients treated with placebo developed LDL-C ≥3.36 mmol/L.

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

While increases were observed in LDL and triglycerides, the mean LDL/HDL ratio remained stable. In the all-exposure population, the pattern and incidence of increases in LDL and triglycerides remained consistent with observations in the controlled periods of the studies (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Creatine Phosphokinase (CPK)

In controlled clinical trials, OLUMIANT treatment was associated with CPK elevations >5 x ULN in 0.7% of patients treated with OLUMIANT 4 mg, 0.2% of patients treated with OLUMIANT 2 mg, and 0.3% of patients treated with placebo during the 12 week treatment period. In RA-BEGIN, CPK elevations >5 x ULN during the 24 week treatment period occurred in 0.6% of patients treated with OLUMIANT 4 mg monotherapy, 4.3% of patients treated with OLUMIANT 4 mg plus methotrexate, and 0% of patients treated with methotrexate monotherapy.

In the all exposure population, there were no confirmed cases of rhabdomyolysis. The pattern and incidence of increases in CPK remained consistent with observations in the controlled periods of the studies.

<u>Description of selected adverse reactions – Atopic Dermatitis</u>

Infections

In controlled studies, for up to 16 weeks, the incidence rate of all infections (rate of patients with ≥ 1 event per 100 patient-years of exposure) was 134.5 with OLUMIANT 4 mg compared to 100.3 in the placebo group. Most infections were mild to moderate in severity. Infections were reported in 31.5%, 29.8% and 24.2% of patients up to 16 weeks in the 4 mg, 2 mg and placebo groups, respectively. The percentage of patients reporting infection-related ADRs for OLUMIANT 4 mg compared to placebo were: Upper respiratory tract infections (17.5% vs. 14.1%), herpes simplex (6.1% vs. 2.7%) and herpes zoster (0% vs. 0.3%). In atopic dermatitis clinical studies, the frequency of infections was generally similar to those observed in RA patients except for herpes zoster which was very rare. There were less skin infections requiring antibiotic treatment with OLUMIANT 4 mg (3.4%)

than with placebo (4.4%). The same percentage of patients with serious infections was observed with OLUMIANT 4 mg and placebo (0.6%). The overall incidence rate of serious infections with OLUMIANT in the atopic dermatitis clinical trial programme was 2.1 per 100 patient years.

Nausea

In atopic dermatitis clinical studies, the frequency of nausea was uncommon with OLUMIANT treatment (0.8%).

Neutropenia

In atopic dermatitis controlled studies, for up to 16 weeks, decreases in neutrophil counts below 1 x 10^9 cells/L occurred in 0.3% of patients treated with OLUMIANT compared to 0% of patients treated with placebo. There was no clear relationship between decreases in neutrophil counts and the occurrence of serious infections. However, in clinical studies, treatment was interrupted in response to ANC < 1 x 10^9 cells/L. The pattern and incidence of decreases in neutrophil counts remained stable at a lower value than baseline over time including in the long-term extension study.

Thrombocytosis

In atopic dermatitis controlled studies, for up to 16 weeks, increases in platelet counts above 600 x 10^9 cells/L occurred in 0.6% of patients treated with OLUMIANT 4 mg and 0% of patients treated with placebo. The frequency of thrombocytosis in AD studies was uncommon and lower than that observed in the RA patients.

No association was observed between increased platelet counts and adverse events of a thrombotic nature. The pattern and incidence of increases in platelet counts remained stable at a higher value than baseline over time including in the long term extension study.

Liver Enzyme Elevations

In controlled studies, for up to 16 weeks, ALT and AST elevations ≥ 3 x ULN were uncommonly observed in 0.2% and 0.5% of patients treated with OLUMIANT 4 mg, compared to 0.8% and 0.8% respectively of patients treated with placebo. Most cases of hepatic transaminase elevations were asymptomatic and transient. The pattern and incidence of elevation in ALT/AST remained stable over time including in the long-term extension study.

Lipids

In atopic dermatitis clinical trials, OLUMIANT treatment was associated with increases in lipid parameters including total cholesterol, LDL cholesterol, and HDL cholesterol. Elevations were observed at 12 weeks and mean total and LDL cholesterol increased through week 52. There was no increase in the LDL/HDL ratio. No dose-relationships were observed in controlled studies, for up to 16 weeks for total cholesterol, LDL cholesterol, or HDL cholesterol. There was no increase in triglycerides levels.

Creatine phosphokinase (CPK)

In atopic dermatitis controlled studies, for up to 16 weeks, increases in CPK values were common. Significant increases (> 5 x ULN) occurred in a dose-dependent manner in 3.3%, 2.5%, and 1.9% of patients treated with OLUMIANT 4 mg, 2 mg, and placebo, respectively. Most cases were transient and did not require treatment discontinuation.

For atopic dermatitis clinical trials, there were no confirmed cases of rhabdomyolysis. Elevations of CPK were observed at 4 weeks and remained stable at a higher value than baseline thereafter including in the long-term extension study.

Description of selected adverse reactions – Alopecia Areata

Infections

In the AA clinical program, a similar proportion of patients reported treatment-emergent infections in the OLUMIANT and placebo groups following 36 weeks of treatment. The majority of infections were of mild or moderate severity. Serious infections were reported in the 36-week placebo-controlled period. Overall, the IR of serious infections was small (0.6 in All BARI AA analysis set). Upper respiratory tract infections, herpes zoster (including multi-dermatomal cases), herpes simplex and urinary tract infections are recognised as adverse drug reactions for OLUMIANT based on data from the clinical trial population. No dose-relationship was observed for infections in both safety analysis sets comparing 2 mg and 4 mg with placebo following 36 weeks of treatment, and all patients with AA exposed to 2 mg and 4 mg from dose randomisation to dose or treatment change.

Nausea

In the AA clinical program, the frequency of nausea was common with OLUMIANT following 36 weeks of treatment (2 mg, 2.7%, 4 mg, 2.0% versus placebo, 1.6%).

Neutropenia

In AA controlled studies, neutrophil counts below 1 x 10^9 cells/L occurred in 0.6% and 0.9% of patients treated with OLUMIANT 2 mg, and 4 mg respectively, during the initial 36 weeks treatment period, compared to no patients treated with placebo.

Thrombocytosis

In AA controlled studies, increases in platelet counts above 600 x 10^9 cells/L occurred in 0.3% and 0.4% of patients treated with OLUMIANT 2 mg and 4 mg respectively, during the initial 36 weeks treatment period, compared to no patients treated with placebo.

Platelet count increases above 600 x 10^9/L were of low frequency and showed no clinically meaningful dose-related differences.

Liver Enzyme Elevations

In all AA safety analysis sets, there was no evidence of clinically relevant increases of hepatic transaminases. Increases of hepatic transaminases to ≥3 x ULN were seen less frequently with OLUMIANT than with placebo.

Lipids

In AA clinical trials, OLUMIANT treatment was associated with increases in mean LDL cholesterol, HDL cholesterol and total cholesterol in the first 12 weeks of treatment, and with increases in mean total and LDL cholesterol through to 52 weeks. During the placebo-controlled period and up to Week 52, the LDL/HDL ratio did not change over time in both OLUMIANT 2 mg and 4 mg treatment groups. No increases in mean triglycerides were observed.

Creatine phosphokinase (CPK)

In AA controlled studies, for up to 36 weeks, significant increases in CPK (> 5 x ULN) occurred in a dose-dependent manner in 5.1%, 2.2%, and 3.6% of patients treated with OLUMIANT 4 mg, 2 mg, and placebo, respectively.

For AA clinical trials, no rhabdomyolysis events were reported.

Postmarketing data

The following undesirable effect (adverse drug reaction) has been identified from postmarketing sources:

Gastrointestinal disorders:

Diverticulitis: uncommon (≥ 0.1%, < 1%)

Skin and subcutaneous tissue disorders:

Rash[a]: Common (≥1% and <10%)

[a] Includes rash, dermatitis, contact dermatitis, eczema, allergic dermatitis, macular and papular rash, pruritic rash, pustular rash, drug eruption, erythematous rash, macular rash.

Swelling of the Face: Uncommon (≥0.1% and <1%)

Urticaria: Uncommon (≥0.1% and <1%)

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems .

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-liming toxicity. 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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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. OLUMIANT contains baricitinib which modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2 and JAK3 with IC50 values of 5.9, 5.7, 53 and >400 nM, respectively.

Pharmacodynamics

OLUMIANT inhibition of IL-6 induced STAT3 phosphorylation

OLUMIANT administration 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. Similar levels of inhibition were observed using either IL-6 or TPO as the stimulus.

Immunoglobulins

Mean serum IgG, IgM, and IgA values decreased by 12 weeks after starting treatment with OLUMIANT, and remained stable through at least 52 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 with OLUMIANT, 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 (RA), decreases in serum C-reactive protein (CRP) were observed as early as 1 week after starting treatment with OLUMIANT and were maintained throughout dosing.

Creatinine

In atopic dermatitis, baricitinib induced a mean increase in serum creatinine levels (3.5 µmol/L) after 12 weeks of treatment, which remained stable thereafter during up to 68 weeks of treatment. 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 events. In alopecia areata, mean serum creatinine continued to increase over time. In atopic dermatitis and alopecia areata, baricitinib was associated with 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, OLUMIANT 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), OLUMIANT 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.

Clinical trials

Rheumatoid Arthritis

The efficacy and safety of OLUMIANT were assessed in four randomised, double-blind, multicentre studies in patients with active RA (Table 8). The patients were diagnosed according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria. Patients over 18 years of age were eligible if at least 6 tender and 6 swollen joints were present 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 8 Summary of Clinical Trials

Abbreviations: QD = Once daily; Q2W = Once every 2 weeks; SC = Subcutaneously;
[1] Patients who had received less than 3 doses of Methotrexate (MTX); naïve to other conventional or biologic DMARDs

Study name (duration)	**Population** (Number randomised)	**Treatment arms**	**Summary of key outcome measures**
RA-BEGIN (52 weeks)	MTX-naïve[1] (584)	• OLUMIANT 4 mg QD • OLUMIANT 4 mg QD + MTX • MTX	Primary endpoints: • ACR20 at week 24 Other endpoints: • Physical function (HAQ-DI) • Radiographic progression (mTSS) • Low disease activity and remission (SDAI, DAS28-hsCRP)
RA-BEAM (52 weeks)	MTX-IR[2] (1305)	• OLUMIANT 4 mg QD • Adalimumab 40 mg SC Q2W • Placebo All patients on background MTX	Primary endpoints: • ACR20 at week 12 Other endpoints: • Physical function (HAQ-DI) • Radiographic progression (mTSS) • Low disease activity and remission (SDAI, DAS28-hsCRP) • Morning joint stiffness (duration and severity) • Worst tiredness • Worst joint pain • Radiographic progression (mTSS) • ACR50 • ACR70
RA-BUILD (24 weeks)	cDMARD-IR[3] (684)	• OLUMIANT 4 mg QD • OLUMIANT 2 mg QD • Placebo On background cDMARDs if on stable cDMARD at study entry	Primary endpoints: • ACR20 at week 12 Other endpoints: • Physical function (HAQ-DI) • Radiographic progression (mTSS) • Low disease activity and remission (SDAI,DAS28-hsCRP) • Morning joint stiffness (duration and severity) • Worst tiredness • Worst joint pain
RA-BEACON (24 weeks)	TNF-IR[4] (527)	• OLUMIANT 4 mg QD • OLUMIANT 2 mg QD • Placebo On background cDMARDs	Primary endpoints: • ACR20 at week 12 Other endpoints: • Physical function (HAQ-DI) • Low disease activity and remission (SDAI,DAS28-hsCRP)
RA-BEYOND	Long Term Extension (2539 at 48 months)	• OLUMIANT 4 mg QD • OLUMIANT 2 mg QD	Primary endpoints: • Safety and tolerability assessments Other Endpoints • Durability of ACR20/50/70 response • Durability of low disease activity or remission (DAS28-hsCRP, DAS28-ESR, SDAI, and CDAI)

[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

Clinical Response

In all studies, patients treated with OLUMIANT 4 mg once daily had statistically significantly higher ACR20/50 responses at 12 weeks compared to placebo, methotrexate (MTX) and adalimumab. ACR70 responses in patients treated with OLUMIANT 4 mg once daily were statistically significantly higher at 12 weeks compared to placebo and MTX (see Table 9 and Table 10). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 1. Continued, durable response rates were observed, with ACR20/50/70 responses maintained for up to 6 years including the long-term extension study.

Treatment with OLUMIANT 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 OLUMIANT 4 mg resulted in improvements in patient and physician global assessments, HAQ-DI, pain assessment and CRP at weeks 12, 24, and 52 compared to adalimumab. The percentage of patients who achieved ACR20 response by visit within this study is shown in Figure 1.

In placebo-controlled trials in which MTX was not required, 501 subjects randomised to OLUMIANT 2 mg or 4 mg received MTX as background therapy, and 303 received cDMARDs other than MTX (approximately half with MTX and half without). The most common concomitant disease-modifying antirheumatic drugs (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 OLUMIANT.

Remission and Low Disease Activity

A statistically significantly greater proportion of patients treated with OLUMIANT 4 mg compared to placebo or MTX achieved remission, as defined by Simplified Disease Activity Index (SDAI) ≤3.3, at weeks 12 and 24 (see Tables 11 and 12). Similarly, when defined by Clinical Disease Activity Index (CDAI) ≤2.8, a greater proportion of patients treated with OLUMIANT 4 mg compared to placebo or MTX achieved remission at weeks 12 and 24.

In all 4 completed studies, a higher proportion of patients treated with OLUMIANT 4 mg compared to placebo or MTX achieved low disease activity or remission (Disease Activity Score 28-erythrocyte sedimentation rate [DAS28-ESR] or Disease Activity Score 28-high sensitivity C-reactive protein [DAS28-hsCRP] ≤3.2 and DAS28-ESR or DAS28-hsCRP <2.6) at weeks 12 and 24.

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 low disease activity/remission rates.

Table 9 ACR Response Rates – Active Comparator Trials

	Percent of Patients					
	DMARD-naïve			MTX-IR		
	Study RA-BEGIN			Study RA-BEAM		
	MTX	OLUMIANT 4 mg/day	OLUMIANT 4 mg/day + MTX	Placebo + MTX	OLUMIANT 4 mg/day + MTX	Adalimumab 40 mg Every Other Week + MTX
N	**210**	**159**	**215**	**488**	**487**	**330**
ACR 20						
Week 12	59 %	79 %***	77 %***	40 %	70 %***†	61 %***
Week 24	62 %	77 %**	78 %***	37 %	74 %***†	66 %***
Week 52	56 %	73 %***	73 %***		71 %††	62 %
ACR 50						
Week 12	33 %	55 %***	60 %***	17 %	45 %***††	35 %***
Week 24	43 %	60 %**	63 %***	19 %	51 %***	45 %***
Week 52	38 %	57 %***	62 %***		56 %†	47 %
ACR 70						
Week 12	16 %	31 %***	33 %***	5 %	19 %***†	13 %***
Week 24	21 %	42 %***	40 %***	8 %	30 %***†	22 %***
Week 52	25 %	42 %***	46 %***		37 %	31 %

Abbreviations: MTX = methotrexate
** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for RA-BEGIN)
† p ≤ 0.05; †† p ≤ 0.01;

Table 10 ACR Response Rates – Placebo Controlled Trials

	Percent of Patients					
	cDMARD-IR			TNFi-IR		
	Study RA-BUILD			Study RA-BEACON		
	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs
N	**228**	**229**	**227**	**176**	**174**	**177**
ACR 20						
Week 12	39 %	66 %***	62 %***	27 %	49 %***	55 %***
Week 24	42 %	61 %***	65 %***	27 %	45 %***	46 %***
ACR 50						
Week 12	13 %	34 %***	33 %***	8 %	20 %**	28 %***
Week 24	21 %	41 %***	44 %***	13 %	23 %*	29 %***
ACR 70						
Week 12	3 %	18 %***	18 %***	2 %	13 %***	11 %**
Week 24	8 %	25 %***	24 %***	3 %	13 %***	17 %***

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

Table 11 Low Disease Activity and Clinical Remission – Active Comparator Trials

	Percent of Patients					
	DMARD-naïve			MTX-IR		
	Study RA-BEGIN			Study RA-BEAM		
	MTX	OLUMIANT 4 mg/day	OLUMIANT 4 mg/day + MTX	Placebo + MTX	OLUMIANT 4 mg/day + MTX	Adalimumab 40 mg Every Other Week + MTX
N	**210**	**159**	**215**	**488**	**487**	**330**
SDAI ≤3.3[a]						
Week 12	6 %	14 %*	20 %***	2 %	8 %***	7 %***
Week 24	10 %	22 %**	23 %**	3 %	16 %***	14 %***
Week 52	13 %	25 %**	30 %***		23 %	18 %
CDAI ≤2.8[b]						
Week 12	7 %	14 %*	19 %***	2 %	8 %***	7 %**
Week 24	11 %	21 %**	22 %**	4 %	16 %***	12 %***
Week 52	16 %	25 %*	28 %**		22 %	18 %
DAS28-hsCRP ≤3.2[c]						
Week 12	30 %	47 %***	56 %***	14 %	44 %***††	35 %***
Week 24	38 %	57 %***	60 %***	19 %	52 %***	48 %***
Week 52	38 %	57 %***	63 %***		56 %†	48 %
DAS28-ESR ≤3.2[d]						
Week 12	15 %	21 %	34 %***	7 %	24 %***	21 %***
Week 24	23 %	36 %**	39 %***	10 %	32 %***	34 %***
Week 52	27 %	36 %	45 %***		39 %	36 %
HAQ-DI Minimum Clinically Important Difference (decrease in score of ≥0.30):[e]						
Week 12	60 %	81 %***	77 %***	46 %	68 %***	64 %***
Week 24	66 %	77 %*	74 %	37 %	67 %***†	60 %***
Week 52	53 %	65 %*	67 %**		61 %	55 %

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for RA-BEGIN)

† p ≤ 0.05; †† p ≤ 0.01; vs. adalimumab

[a] Simplified Disease Activity Index

[b] Clinical Disease Activity Index

[c] Disease Activity Score 28-high sensitivity C-reactive protein

[d] Disease Activity Score 28-erythrocyte sedimentation rate

[e] Health Assessment Questionnaire–Disability Index

Table 12 Low Disease Activity and Clinical Remission – Placebo Controlled Trials

	Percent of Patients					
	cDMARD-IR			TNFi-IR		
	Study RA-BUILD			Study RA-BEACON		
	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs
N	**228**	**229**	**227**	**176**	**174**	**177**
SDAI ≤3.3[a]						
Week 12	1 %	9 %***	9 %***	2 %	2 %	5 %
Week 24	4 %	17 %***	15 %***	2 %	5 %	9 %**
CDAI ≤2.8[b]						
Week 12	2 %	10 %***	9 %***	2 %	3 %	6 %
Week 24	4 %	15 %***	15 %***	3 %	5 %	9 %*
DAS28-hsCRP ≤3.2[c]						
Week 12	17 %	36 %***	39 %***	9 %	24 %***	32 %***
Week 24	24 %	46 %***	52 %***	11 %	20 %*	33 %***
DAS28-ESR ≤3.2[d]						
Week 12	7 %	21 %***	22 %***	4 %	13 %**	12 %**
Week 24	10 %	29 %***	32 %***	7 %	11 %	17 %**
HAQ-DI Minimum Clinically Important Difference (decrease in score of ≥0.30):[e]						
Week 12	44 %	60 %***	56 %**	35 %	48 %*	54 %***
Week 24	37 %	58 %***	55 %***	24 %	41 %***	44 %***

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ vs. placebo

[a] Simplified Disease Activity Index

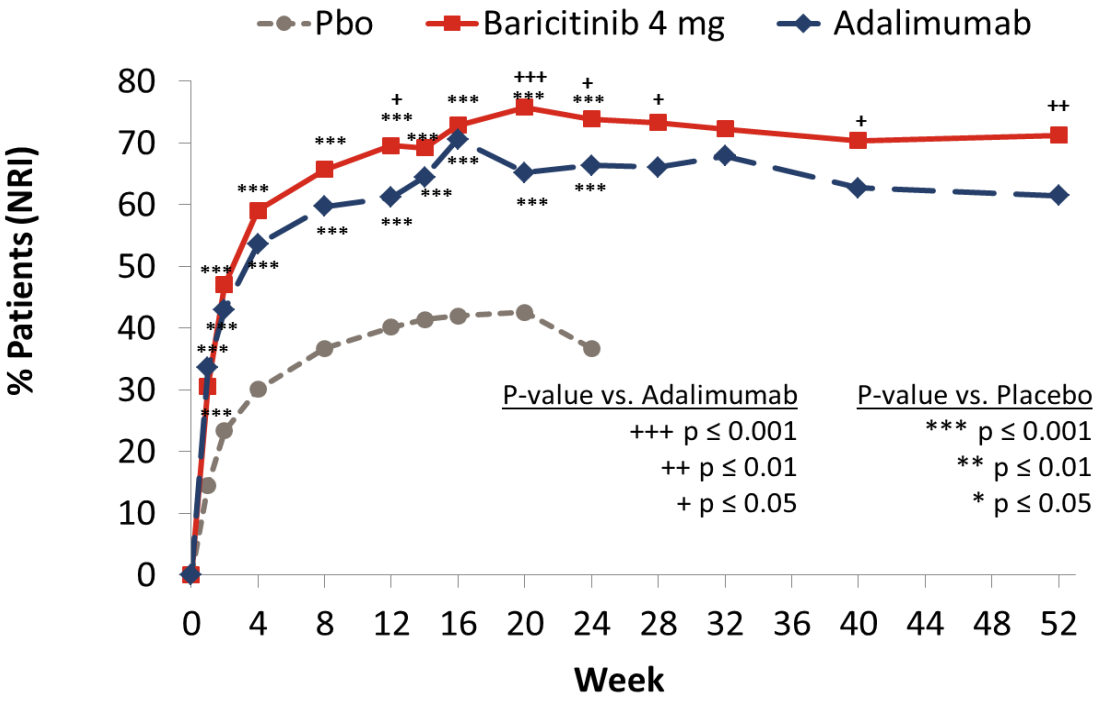
[b] Clinical Disease Activity Index

[c] Disease Activity Score 28-high sensitivity C-reactive protein

[d] Disease Activity Score 28-erythrocyte sedimentation rate

[e] Health Assessment Questionnaire–Disability Index

Figure 1 Percent of Patients Achieving ACR20 in RA-BEAM (mITT, using NRI)

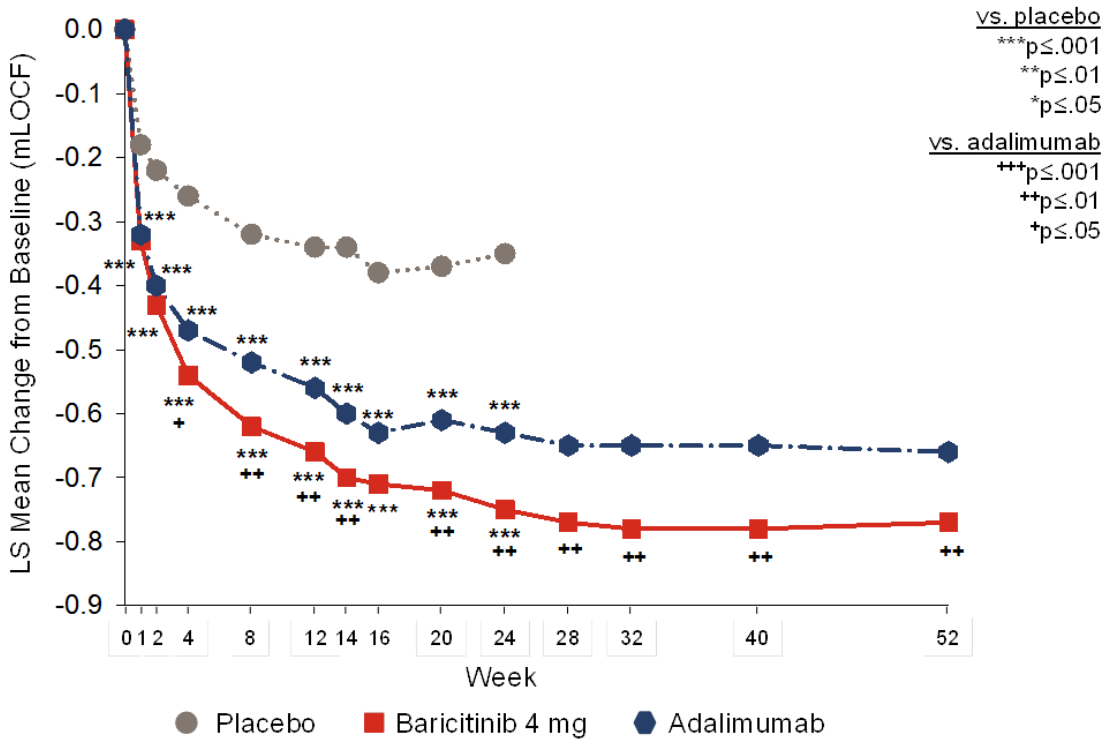


ACR20 ≥ 20% improvement in American College of Rheumatology criteria
N = number of modified intent-to-treat (mITT) patients
NRI = non-responder imputation.

Physical Function Response and Health-Related Outcomes

Treatment with OLUMIANT 4 mg, alone or in combination with cDMARDs, resulted in a statistically significant improvement in physical function compared to placebo and MTX as measured by HAQ-DI, at 12, 24 and 52 weeks. Improvements with OLUMIANT 4 mg treatment were also shown versus adalimumab at these time points. The proportion of patients achieving a clinically significant improvement (HAQ-DI improvement from baseline ≥0.30) was also higher with OLUMIANT compared to placebo or MTX at week 12 (Table 11 and 12). Improvements were seen as early as Week 1 and, in RA-BEGIN and RA-BEAM (see Figure 2), these were maintained for up to 52 weeks.

Figure 2 Change in HAQ-DI from Baseline to Week 52 in RA-BEAM (mITT, using mLOCF)



HAQ-DI = Health Assessment Questionnaire-Disability Index
N = number of modified intent-to-treat (mITT) patients
mLOCF = modified last observation carried forward

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

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

In all studies, OLUMIANT-treated patients reported improvements in patient-reported quality of life, as measured by the Short Form (36) Health Survey (SF36) Physical Component Score, fatigue, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) and work productivity, as measured by the Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI-RA)

Radiographic Response

The effect of OLUMIANT on progression of structural joint damage was evaluated radiographically in 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 OLUMIANT 4 mg resulted in a statistically significant inhibition of progression of structural joint damage (Table 13). 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 statistically significantly higher with OLUMIANT 4 mg compared to placebo at week 24.

Table 13 Radiographic Changes

Study	**RA-BEGIN** MTX-naïve patients			**RA-BEAM** MTX-IR patients			**RA-BUILD** cDMARD-IR patients		
Treatment group	MTX	OLU 4 mg	OLU 4 mg + MTX	PBO	OLU 4 mg	ADA 40 mg Q2W	PBO	OLU 2 mg	OLU 4 mg
N	210	159	215	488	487	330	228	229	227
Modified Total Sharp Score, mean change from baseline:									
Week 24	0.61	0.39	0.29*	0.90	0.41***	0.33***	0.70	0.33*	0.15**
Week 52	1.02	0.80	0.40**		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**		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		0.21	0.19			
Proportion of patients with no radiographic progression[a]:									
Week 24	68 %	76 %	81 %**	70 %	81 %***	83 %***	74 %	72 %*	80 %**
Week 52	66 %	69 %	80 %**		79 %	81 %			

Abbreviations: ADA = adalimumab; MTX = methotrexate; OLU = Olumiant; PBO = Placebo ; MTX-IR = methotrexate inadequate responders; cDMARD -IR = conventional disease-modifying antirheumatic drug inadequate responders.

[a] No progression defined as mTSS change ≤ 0.
* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for study RA-BEGIN)

OLUMIANT 4 mg vs. 2 mg

In clinical trials that included doses of 2 mg and 4 mg OLUMIANT once daily (RA-BUILD and RA-BEACON), efficacy on signs and symptoms was demonstrated with both doses. However, more consistent improvements in remission and low disease activity were seen with the 4 mg dose. The differences 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 OLUMIANT 4 mg compared to placebo at week 24 but not for OLUMIANT 2 mg compared to placebo. In addition, onset of efficacy was fastest and the effect size was generally largest for the 4 mg dose groups compared to 2 mg.

In a long-term extension study, patients from 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 OLUMIANT 4 mg once daily (N = 502) were re-randomised 1:1 in a double-blind manner to continue 4 mg once daily or reduce dose to 2 mg once daily. A down titration in the baricitinib dose was

associated with a significant reduction in efficacy. 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.

OLUMIANT Used as Monotherapy or in Combination with Methotrexate

In RA-BEGIN, OLUMIANT 4 mg monotherapy was statistically significantly superior to methotrexate monotherapy with respect to ACR20 response rates at 24 weeks (see Table 14). Combination of OLUMIANT 4 mg with methotrexate therapy was associated with larger improvements in inflammation related measures, including ESR; correspondingly, although most patients did not exhibit radiographic progression across the treatment groups, the lowest radiographic progression rates were seen in the combination group. OLUMIANT 2 mg was not studied in this trial.

In RA-BUILD, treatment effects compared to placebo were robust whether OLUMIANT was used as monotherapy, in combination with methotrexate, or in combination with cDMARDs other than methotrexate.

DMARD-Naïve RA Patients

RA-BEGIN, a 52-week study with the planned primary analysis at week 24, evaluated 584 DMARD-naïve adult patients with moderate to severe, active RA (mean disease duration was 1.3 years) and indicators of poor prognosis, such as elevated inflammatory markers (CRP) and the presence of rheumatoid factor or anti-cyclic citrullinated peptides. This study evaluated the efficacy of OLUMIANT 4 mg monotherapy, OLUMIANT 4 mg + MTX, and MTX alone in improving the signs and symptoms of RA, physical function, and rate of progression of joint damage. The primary endpoint was the proportion of patients achieving ACR20 at week 24.

A significantly higher proportion of patients in the OLUMIANT 4 mg and OLUMIANT 4 mg + MTX groups compared to MTX alone achieved an ACR20 response at week 24: 77% versus 62% ($p = 0.003$) for OLUMIANT 4 mg monotherapy and 78% versus 62% ($p \leq 0.001$) for OLUMIANT 4 mg + MTX. The OLUMIANT 4 mg monotherapy and OLUMIANT 4 mg + MTX groups also showed statistically significant improvement compared to MTX alone across the key secondary endpoints at week 24 and 52, including ACR20, SDAI remission, and change from baseline in DAS28-hsCRP and HAQ-DI. At 52 weeks, the OLUMIANT 4 mg + MTX group showed statistically significant improvement compared to MTX as measured by mTSS and a numerically greater response in the OLUMIANT 4 mg monotherapy group compared with MTX alone. The efficacy results from RA-BEGIN are shown in Table 14.

Table 14 Efficacy Results for RA-BEGIN in DMARD-naïve Patients

			OLUMIANT 4 mg/day N=159	OLUMIANT 4 mg/day + MTX N=215	MTX N=210
Primary Endpoint					
ACR20 (%)	Week 24		77**	NA	62
Key Secondary Endpoints					
ACR (%)	Week 24	ACR20	NA	78***	62
		ACR50	60**	63***	43
		ACR70	42***	40***	21
	Week 52	ACR20	73***	73***	56
		ACR50	57***	62***	38
		ACR70	42***	46***	25
HAQ-DI (mean change from baseline)					
	Week 24		-1.04***	-1.03***	-0.74
	Week 52		-0.99***	-1.06***	-0.71
DAS28-hsCRP <2.6 response (%)					
	Week 24		40***	40***	24
	Week 52		44***	49***	24
DAS28-hsCRP ≤3.2 response (%)					
	Week 24		57***	60***	38
	Week 52		57***	63***	38
SDAI remission ≤3.3 (%)					
	Week 24		22**	23***	10
	Week 52		25**	30***	13
Radiographic Endpoints (mean change from baseline)					
	Week 52	mTSS	0.80	0.40**	1.02
		Erosion Score	0.55	0.34**	0.81
		JSN	0.25	0.06	0.21
Radiographic non-progression (%) (change from baseline in mTSS ≤0)			69	80**	66

Abbreviations: NA = Not applicable; MTX = methotrexate; ACR20 = 20% improvement in American College of Rheumatology criteria; ACR50 = 50% improvement in American College of Rheumatology criteria; ACR70 = 70% improvement in American College of Rheumatology criteria; HAQ-DI = Health Assessment Questionnaire-Disability Index; DAS28-hsCRP = Disease Activity Score 28-high-sensitivity C-reactive protein; SDAI = Simplified Disease Activity Index; mTSS = modified Total Sharp Score

** $p \leq 0.01$; *** $p \leq 0.001$ vs. MTX.

Atopic Dermatitis

The efficacy and safety of OLUMIANT 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 outcomes of the primary and key secondary endpoints from these studies were adjusted for multiplicity.

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

Table 15 Summary of Clinical Trial

Study Name (Duration)	No. of Patients Treated (N)	Background Treatment[a]	Treatment arms (QD)	Outcome Measures
BREEZE AD-1 (16 weeks)	624	None	OLU 4 mg OLU 2 mg OLU 1 mg Placebo	**Primary endpoint** • IGA 0 or 1[b] at week 16 **Key secondary endpoint** • Improvement of ≥ 75% or 90% in Eczema Area and Severity Index from baseline (EASI 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 NRS **Other secondary endpoints** • EASI 50 • Itch Numerical Rating Scale (NRS) change from baseline • 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	OLU 4 mg OLU 2 mg Placebo	

OLU=OLUMIANT; QD = Once daily; TCI = Topical Calcineurin Inhibitor; TCS = Topical Corticosteroid
The primary and key secondary endpoints were adjusted for multiple comparisons. Other secondary endpoints were not adjusted for multiple comparisons.
[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 OLUMIANT 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 16).

A significantly greater proportion of patients randomised to OLUMIANT 4 mg achieved a rapid improvement in the Itch NRS compared to placebo (defined as ≥ 4-point improvement as early as Day 2; p ≤0.05). 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, up to week 16.

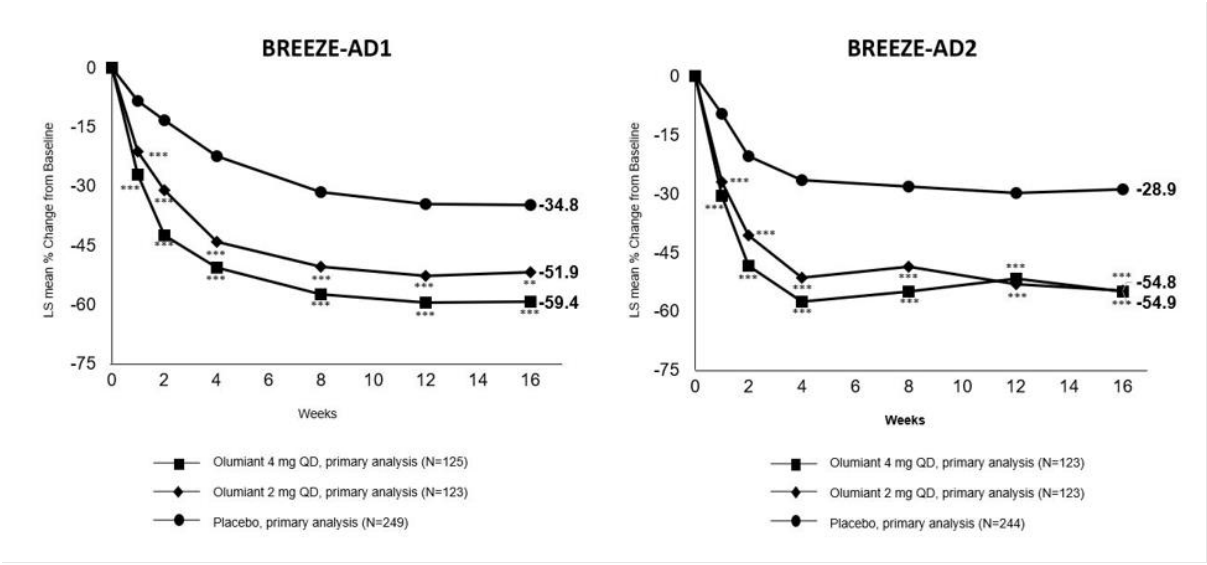
Treatment effects in subgroups (weight, age, gender, race, disease severity and previous treatment, including immunosuppressants) in BREEZE-AD1 and BREEZE-AD2 were consistent with the results in the overall study population.

Table 16 Efficacy of OLUMIANT monotherapy at week 16 (FAS[a])

Study	**BREEZE- AD1**			**BREEZE-AD2**		
Treatment Group	PBO	OLU 2 mg	OLU 4 mg	PBO	OLU 2 mg	OLU 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, g]	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 %*[f]	16.0 %***	2.5 %	8.9 %**	13.0 %***
SCORAD75, % responders[c]	1.2 %	7.3 %**[f]	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 change from baseline, LS mean (SE)[e, g]	-14.80 % (1.82)	-20.14 % (2.16)	-25.96 %*** (1.93)	-12.82 % (2.07)	-22.12 %** (2.37)	-23.98 %*** (2.17)

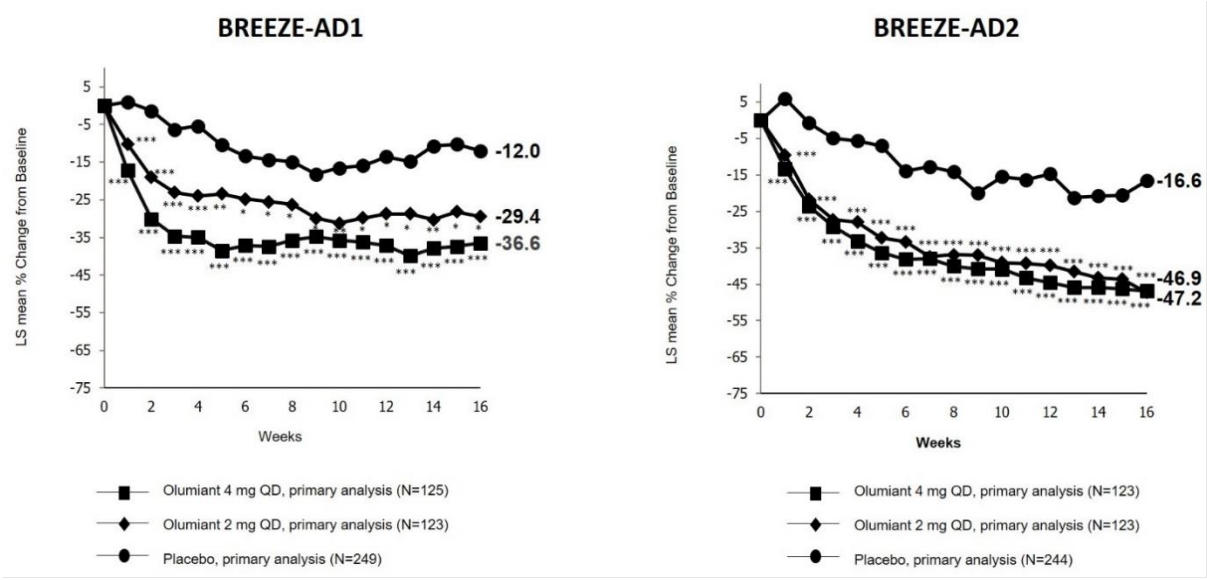
OLU = OLUMIANT; PBO = Placebo
*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo.
[a] Full analysis set (FAS) including all randomised patients.
[b] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on 0-4 IGA scale.
[c] Non-Responder Imputation: 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.
[f] Not statistically significant after adjustment for multiple comparisons.
[g] Endpoint was not adjusted for multiplicity.

Figure 3. Mean percent change from baseline in EASI in BREEZE-AD1 and BREEZE-AD2 (FAS)[a]



LS = Least squares; **p≤0.01, ***p≤0.001 versus 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 4. 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 OLUMIANT 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 17).

A significantly greater proportion of patients randomised to OLUMIANT 4 mg achieved a rapid improvement in the Itch NRS compared to placebo (defined as ≥ 4-point improvement as early as Week 2; p <0 .001). The improvement in Itch NRS occurred in conjunction with the improvement of objective skin signs of atopic dermatitis.

Figures 5 and 6 respectively show the mean percent change from baseline in EASI and in Itch NRS, 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 17 Efficacy of OLUMIANT in combination with TCS[a] at week 16 (FAS) [b]

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

OLU = Olumiant; 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.

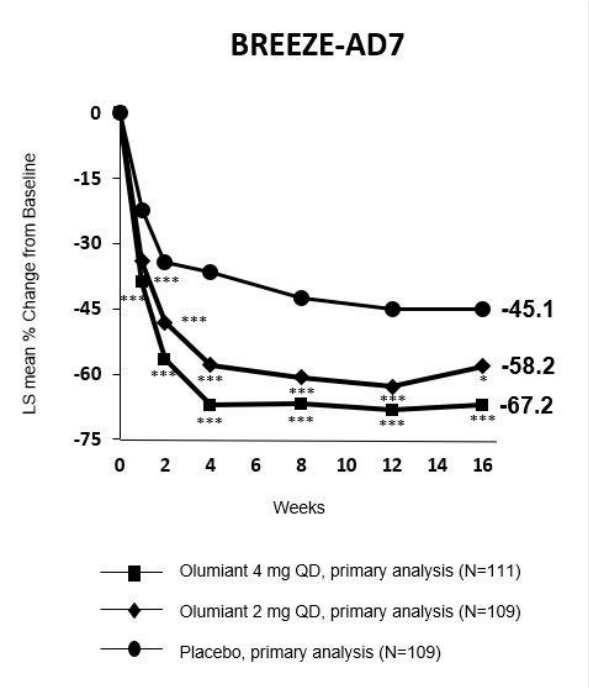
[e] Results shown in subset of patients eligible for assessment (patients with itch NRS ≥ 4 at baseline)

[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.

[g] Not statistically significant after adjustment for multiple comparisons.

[h] Endpoint was not adjusted for multiplicity.

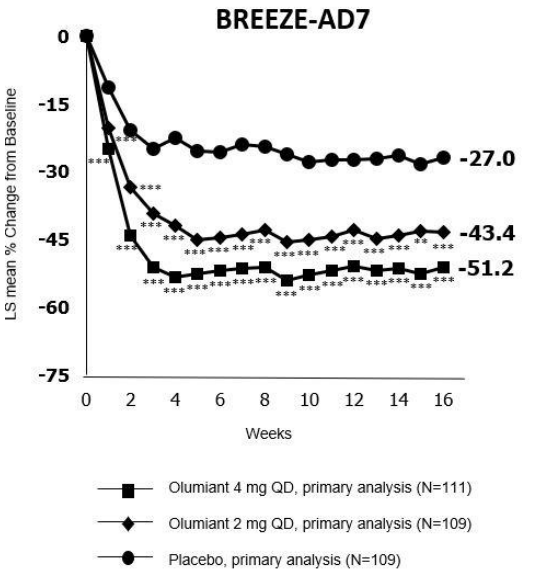
Figure 5. Mean percent change from baseline in EASI in BREEZE-AD7 (FAS)[a]



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 6. Mean percent change from baseline in itch NRS in BREEZE-AD7 (FAS)[a]



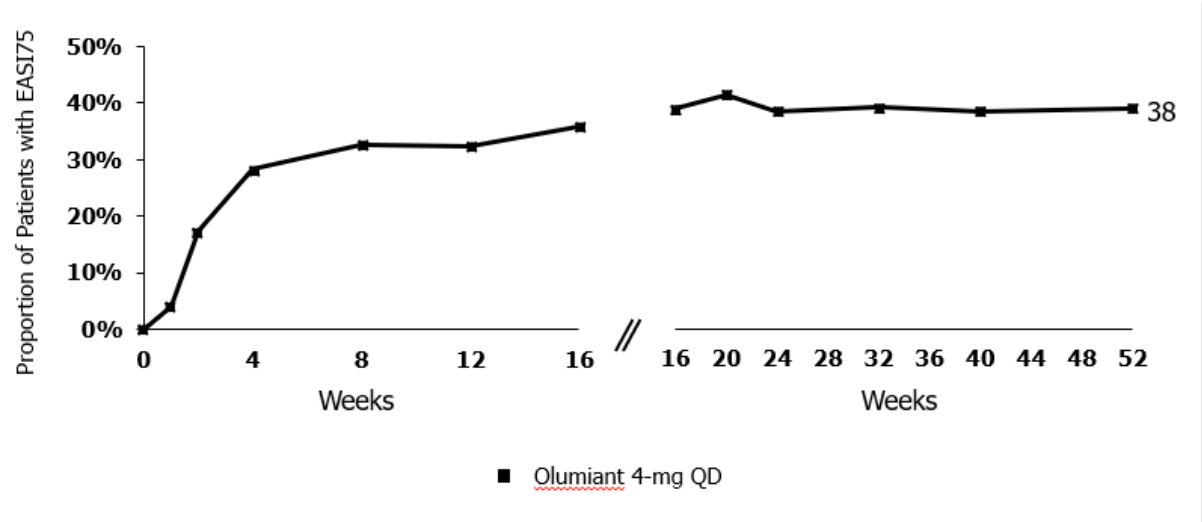
LS = Least squares; p≤0.05,**p≤0.01, ***p≤0.001 vs placebo

[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 and Durability of Response

To evaluate maintenance of response, subjects treated with OLUMIANT for 16 weeks in BREEZE-AD1 and BREEZE-AD2 were eligible to enrol in a long term extension study BREEZE-AD3 to an additional 36-weeks of treatment, for a cumulative 52-week study treatment. Continued, durable response was observed. Figure 7 shows the percentage of patients with EASI 75 from baseline in BREEZE-AD3 up to week 52.

Figure 7. EASI 75 Persistence over time for OLUMIANT 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), OLUMIANT 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 OLUMIANT groups compared to placebo at 16 weeks (See Table 18).

Table 18 Quality of Life/Patient-Reported Outcomes results of OLUMIANT monotherapy and OLUMIANT in combination with TCS at week 16 (FAS) [a]

	Monotherapy						TCS Combination		
Study	**BREEZE-AD1**			**BREEZE-AD2**			**BREEZE-AD7**		
Treatment group	PBO	OLU 2 mg	OLU 4 mg	PBO	OLU 2 mg	OLU 4 mg	PBO + TCS	OLU 2 mg + TCS	OLU 4 mg + TCS
N	249	123	125	244	123	123	109	109	111
ADSS Item 2 change from baseline, LS 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***[f] (0.15)	-1.42***[f] (0.15)
Skin Pain NRS change from baseline, LS 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 ***[f] (0.22)	-3.73***[f] (0.23)
POEM change from baseline, LS mean (SE)[b, g]	-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, g]	14.2%	29.3%***	42.4%***	9.2%	23.8%***	30.6%***	46.7	65.7**	70.6***
DLQI change from baseline, LS mean (SE)[b, g]	-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, g]	16.3%	26.8%*	47.4%***	13.4%	26.3%**	33.9%***	52.9	61.2	73.3***
HADS change from baseline, LS mean (SE)[b, g]	-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, % responders[d, e, g]	12.0	18.4	41.0***	11.4	20.0	25.6*	45.5	54.8	56.1
HADS Depression Score <8 % responders [d, e, g]	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 study drug 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.

[f] Not statistically significant after adjustment for multiple comparisons.

[g] Endpoint was not adjusted for multiplicity.

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). Both were randomised, double blind, placebo controlled, 36 weeks 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:

- ≥18 years of age and ≤60 years for male patients, and ≤70 years of age for female patients
- those with a current episode of severe or very severe alopecia areata defined respectively by Severity of Alopecia Tool (SALT) scores of 50 to 94 (that is 50% to 94% scalp hair loss) and 95 to 100 (95 to 100% scalp hair loss)
- those who had a duration of severe or very severe alopecia areata of at least 6 months and less than 8 years (unless episodes of regrowth had been observed on the affected areas of the scalp over the past 8 years)
- those who had no spontaneous improvement (that is, no more than 10-point spontaneous reduction in SALT) over the past 6 months.

From a clinical perspective, the only authorised concomitant AA therapies were finasteride (or other 5 alpha reductase inhibitors), oral or topical minoxidil and bimatoprost ophthalmic solution for eyelashes.

Both studies assessed as primary outcome the proportion of subjects who achieved a SALT score of ≤20 (at least 80% of scalp hair coverage) at week 36. Additionally, both studies evaluated patient assessment of scalp hair loss using a 5 point scale (Scalp Hair Assessment PRO™) and 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™).

Clinical Study Summary

Table 19 Summary of Clinical Trial

Study Name (duration)	**Phase**	**No. of Patients Randomised (N)**	**Treatment arms (QD)**	**Outcome measures**
BRAVE AA1 (200 weeks)	2[a]	110	• OLUMIANT 1 mg[b] • OLUMIANT 2 mg • OLUMIANT 4 mg • Placebo	**Primary endpoints:** • Proportion of patients achieving SALT ≤20 at Week 36 **Key Secondary endpoints:** • Proportion of patients achieving SALT ≤20 at Weeks 16 and 24 • Percent change from Baseline in SALT score at Week 36 • Proportion of patients achieving $SALT_{50}$ at Week 12 • Proportion of patients achieving $SALT_{90}$ at Week 36 • Proportion of patients achieving an absolute SALT ≤10 at Weeks 24 and 36 • Proportion of patients with PRO for Scalp Hair Assessment score of 0 or 1 with a ≥2-point improvement from Baseline at Week 36 among patients with a score of ≥3 at Baseline • Proportion of patients achieving ClinRO Measure for EB Hair Loss 0 or 1 with ≥2-point improvement from Baseline at Week 36 (among patients with ClinRO Measure for EB Hair Loss ≥2 at Baseline) • Proportion of patients achieving ClinRO Measure for EL Hair Loss 0 or 1 with ≥2-point improvement from Baseline at Week 36 (among patients with ClinRO Measure for EL Hair Loss ≥2 at Baseline)
	3	654	• OLUMIANT 2 mg • OLUMIANT 4 mg • Placebo	
BRAVE AA2 (200 weeks)	3	546		

Abbreviations: AA = alopecia areata; ClinRO = clinician-reported outcome; EB = eyebrow; EL = eyelash; PRO = patient-reported outcome; QD = Once daily; SALT = Severity of Alopecia Tool; $SALT_{50}$ = at least 50% improvement from Baseline in SALT score; $SALT_{90}$ = at least 90% improvement from Baseline in SALT score.

[a] The purpose of the Phase 2 BRAVE AA1 study was to identify up to two doses for the Phase 3 studies among baricitinib 1-mg, 2-mg, and 4-mg; data from this portion of the study was not included in the integrated efficacy analysis, however, these data are part of the integrated safety analysis.

[b] Patients in the baricitinib 1-mg group were switched to baricitinib 4 mg after the Decision Point, which was based upon an interim analysis of the Phase 2 data at Week 12

Baseline Characteristics

The Phase III portion of BRAVE AA1 study and the Phase III BRAVE AA2 study included 1200 adult patients. Across all treatment groups, the mean age was 37.5 years, 61% of patients were female. The mean duration of AA 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, and approximately 44% of patients were reported as AA 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 AA at some point before entering the studies, and 50% at least one systemic immunosuppressant. The use of authorised concomitant AA 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 2 mg or 4 mg once daily achieved a SALT ≤20 at week 36 compared to placebo, with significance starting at week 8 in Study BRAVE AA1 and week 12 in Study BRAVE AA2 for baricitinib 4 mg. For baricitinib 2 mg, a significant improvement as measured by SALT≤20 was achieved by week 24 in Study BRAVE AA1 and by week 16 in Study BRAVE AA2. Consistent efficacy was seen across some of the most important secondary endpoints (Table 20). Figure 8 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 AA episode duration) were consistent with the results in the overall study population at week 36.

Table 20. Efficacy of baricitinib through week 36 (FAS[a])

	BRAVE-AA1			**BRAVE-AA2**		
	PBO N=189	**BARI 2 mg N=184**	**BARI 4 mg N=281**	**PBO N=156**	**BARI 2 mg N=156**	**BARI 4 mg N=234**
Primary Endpoint						
Proportion of patients achieving SALT ≤20 at week 36	5.3%	**21.7**%***	**35.2**%***	2.6%	**17.3**%***	**32.5**%***
Key Secondary Endpoints						
Proportion of patients achieving SALT ≤20 at week 24	4.8%	**11.4**%*	**26.7**%***	1.3%	10.9%**	**28.2**%***
Percentage of patients achieving an absolute SALT ≤10 at: week 24 week 36	 2.6% 3.7%	 **7.6**%* **12.5**%**	 **18.1**%*** **26.0**%***	 0.6% 0.6%	 7.7%** 10.9%**	 18.8%*** **23.5**%***
Percent change from baseline in SALT score at week 36	-8.13%	**-31.23**%***	**-45.79**%***	-2.96%	-28.21%***	**-47.45**%***
PRO for Scalp Hair Assessment						
Scalp Hair Assessment PRO 0 or 1 at week 36 with a ≥2 point improvement from baseline[b]	5.0%	**16.0**%***	**33.1**%***	4.0%	**16.1**%**	**34.4**%***
ClinRO Measures for Eyebrow and Eyelash Hair Loss						

ClinRO Measure for Eyebrow Hair Loss of 0 or 1 at week 36 with a ≥2 point improvement from baseline[c]	3.2%	**19.1**%***	**31.4**%***	4.5%	11.5%	**34.8**%***
ClinRO Measure for Eyelash Hair Loss of 0 or 1 at week 36 with a ≥2 point improvement from baseline[d]	3.1%	13.5%*	**33.5**%***	5.6%	10.1%	**34.3**%***

BARI = Baricitinib; PBO = Placebo; ClinRO = clinician-reported outcome; PRO = patient-reported outcome; SALT = Severity of Alopecia Tool

*p-value for baricitinib versus placebo ≤0.05.

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

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

Note: Results in **bold** were statistically significant after adjustment for multiplicity. Other results designated with asterisks had p≤0.05 but were not significant after adjustment for multiplicity.

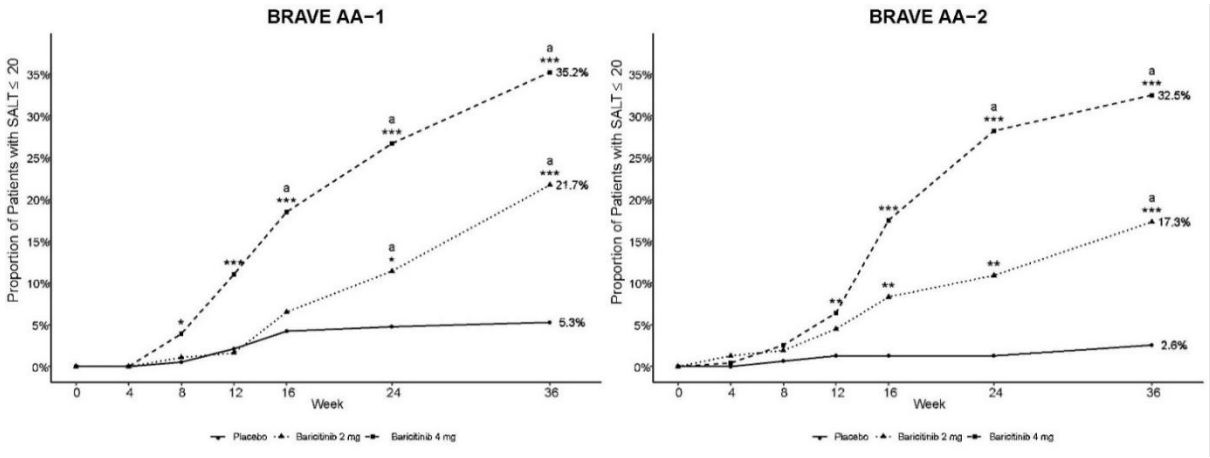
[a] Full analysis set (FAS) including all randomised patients.

[b] 0 = No missing hair, 1 = A limited area (1% to 20%) of scalp hair loss. In patients with Scalp Hair PRO score of ≥3 at baseline (n=181, 175 and 275, respectively, for BRAVE -AA1 and n=151, 149 and 215, respectively, for BRAVE -AA2)

[c] 0 = Eyebrows have full coverage and no areas of hair loss, 1 = There are minimal gaps in eyebrow hair and distribution is even. In patients with ClinRO Measure for Eyebrow Hair loss score of ≥2 at baseline (n=124, 136 and 188, respectively, for BRAVE- AA1 and n= 112, 104 and 161, respectively, for BRAVE- AA2)

[d] 0 = Eyelashes form a continuous line along the eyelids on both eyes, 1 = There are minimal gaps and the eyelashes are evenly spaced along the eyelids on both eyes. In patients with ClinRO Measure for Eyelash Hair loss score of ≥2 at baseline (n= 96, 111 and 167, respectively, for BRAVE AA1 and n= 90, 89 and 140, respectively, for BRAVE- AA2)

Figure 8: Proportion of Patients with SALT ≤20



a Statistically significant after adjustment for multiplicity.

* p value for baricitinib versus placebo ≤0.05; **p value for baricitinib versus placebo ≤0.01;

***p value for baricitinib versus placebo ≤0.001.

Efficacy at week 52

Continued response was observed in those patients being treated with baricitinib up to week 52, with 40.5% of patients on baricitinib 4 mg and 21.9% of patients on baricitinib 2 mg achieving SALT ≤20 (74% of patients have been included in this analysis). The results for the baseline disease severity and episode duration subpopulations at week 52 were consistent with those observed at week 36.

Dose tapering substudy

In the study BRAVE-AA2, patients who had received baricitinib 4 mg once daily since the initial randomisation 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

Absorption

Following oral administration, baricitinib is rapidly absorbed with a median t_{max} of approximately 1 hour and an absolute bioavailability of approximately 80%. 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. Baricitinib is a substrate of the Pgp, BCRP, OAT3 and MATE2-K transporters, which play roles in drug distribution.

Metabolism

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

Excretion

Renal elimination is the principal mechanism for baricitinib 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 hours (CV = 27.4%), respectively. C_{max} and AUC at steady state were 1.4- and 2.0 fold higher, respectively, in patients with RA 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.

Other Intrinsic Factors

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

Renal Impairment

Renal function was found to significantly affect baricitinib exposure. Subjects with moderate, Stage 3 renal impairment (GFR 30 - ≤60 mL/min/1.73m$^{2)}$ and severe, Stage 4 & 5 renal impairment (GFR <30 mL/min/1.73m^2) have approximately 2-fold and 4-fold increases, respectively, in baricitinib AUC values compared to subjects with normal renal function.

The recommended dose of OLUMIANT in patients with estimated GFR of 30 - ≤60 mL/min/1.73 m^2 is 2 mg once daily. OLUMIANT is not recommended for use in patients with estimated GFR of <30 mL/min/1.73 m^2.

Hepatic Impairment

There was no clinically relevant effect on the PK of baricitinib in patients with mild or moderate hepatic impairment. No dose adjustment is necessary in these patients. The use of OLUMIANT has not been studied in patients with severe hepatic impairment and is therefore not recommended.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Baricitinib was not genotoxic in bacterial reverse mutagenicity assays (Ames assay), in the *in vitro* human peripheral blood lymphocyte chromosomal aberration assay, or in the *in vivo* micronucleus assay in the rat. All assays were validated by the use of appropriate controls. The overall risk of genotoxicity is considered to be low.

Carcinogenicity

Baricitinib did not produce neoplastic changes in two year rat and six month transgenic mouse carcinogenicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

croscarmellose sodium
magnesium stearate
mannitol
microcrystalline cellulose
iron oxide red
lecithin
macrogol 3350
polyvinyl alcohol

purified talc
titanium dioxide

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Stored below 30°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

OLUMIANT is available as debossed, film-coated, immediate-release tablets in PVC/PE/PCTFE (Aclar)/Al or PA/Al/PVC/Al blister packs of 7 and 28.

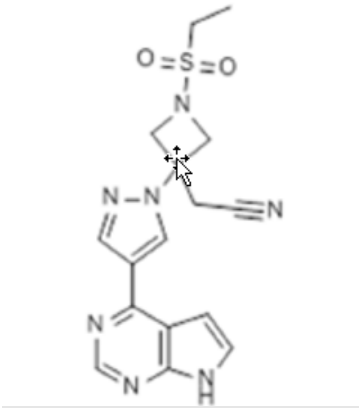
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active ingredient in OLUMIANT® tablets is baricitinib. OLUMIANT is a Janus Kinase (JAK) inhibitor with the chemical name {1-(ethylsulfonyl)-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl} acetonitrile. The empirical formula is $C_{16}H_{17}N_7O_2S$ which corresponds to a molecular weight of 371.42 daltons. The chemical structure is:



CAS number

The CAS number for baricitinib is 1187594-09-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 January 2018

10 DATE OF REVISION

11 November 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
5.1	Additional text on RA-BEYOND