

Baricitinib: First Global Approval

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Abstract Baricitinib (OlumiantTM) is an orally-administered, small-molecule, janus-associated kinase (JAK) inhibitor developed by Eli Lilly and Incyte Corporation for the treatment of rheumatoid arthritis (RA), atopic dermatitis and systemic lupus erythematosus. JAKs transduce intracellular signals from cell surface receptors for various cytokines and growth factors involved in inflammation and immune function, suggesting JAK inhibitors may be of therapeutic benefit in inflammatory conditions. In February 2017, baricitinib was approved in the EU, as monotherapy or in combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Regulatory approval to market baricitinib as a treatment for RA has also been sought in the USA and Japan. This article summarizes the milestones in the development of baricitinib leading to this first global approval for the treatment for moderate to severe active RA in adult patients who have responded inadequately to, or are intolerant to one or more DMARDs.

1 Introduction

Eli Lilly and Incyte Corporation are developing baricitinib (OlumiantTM), an orally-administered, small-molecule, janus-associated kinase (JAK) inhibitor, for the treatment of rheumatoid arthritis (RA), atopic dermatitis and systemic lupus erythematosus. JAKs mediate the signalling of several important drivers of inflammatory disease; baricitinib selectively inhibits the JAK1 and JAK2 subtypes (with greater potency than the JAK3 and TyK2 subtypes), indicating that the drug may have therapeutic potential in a number of conditions. Baricitinib received its first global approval, in the EU, on 13 February 2017, as monotherapy or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) [1]. Applications for regulatory approval to market baricitinib as a treatment for RA have also been sought in the USA and Japan [2]. Baricitinib is also under investigation for the treatment of systemic lupus erythematosus and moderate to severe atopic dermatitis [2]. It was also being developed for the treatment of psoriasis and diabetic kidney disease; however, no additional studies in these indications are planned.

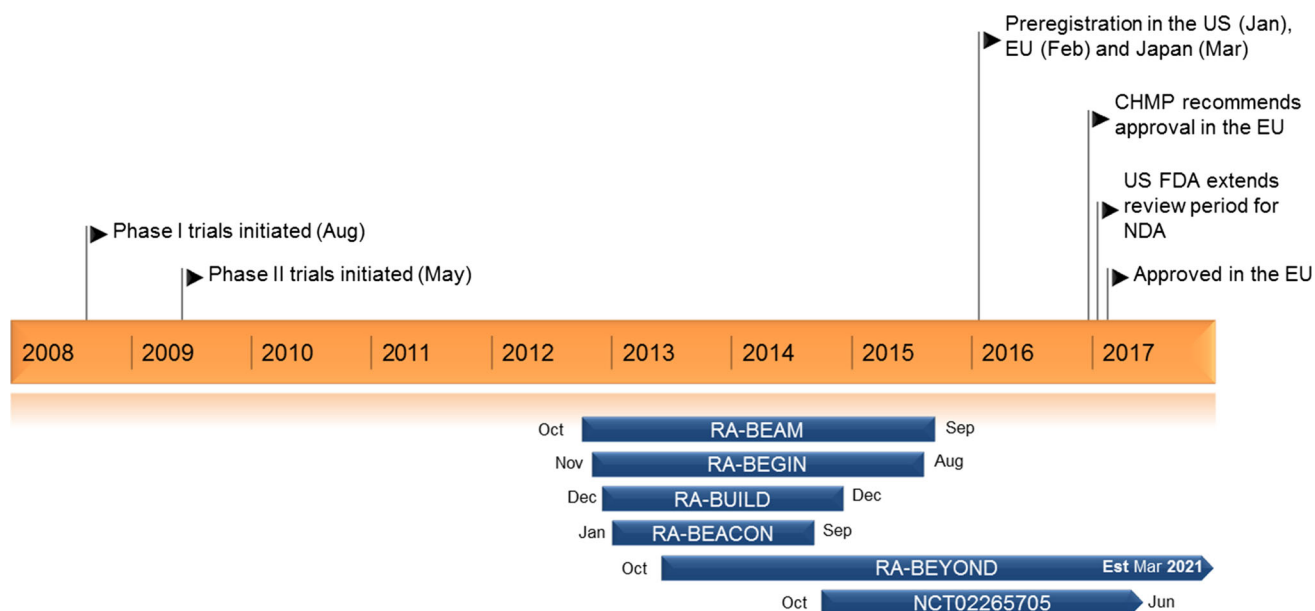
1.1 Company Agreements

In December 2009 Incyte entered into an exclusive worldwide license and collaboration agreement with Eli Lilly for the development and commercialisation of baricitinib and certain follow-on compounds. Eli Lilly was granted worldwide rights to develop and commercialise baricitinib as an oral treatment for all inflammatory conditions. In exchange for these rights, Incyte received an

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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Clinical development of baricitinib for the treatment of rheumatoid arthritis, focusing on phase III trials. CHMP Committee for Medicinal Products for Human Use, NDA New Drug Application

initial payment of \$US90 million and became eligible for up to \$US665 million upon achievement of additional development, regulatory and commercialisation milestones, as well as tiered royalty payments of up to 20% on future global sales. Incyte retained the option to co-develop its other JAK1/JAK2 inhibitors with Eli Lilly on a compound-by-compound and indication-by-indication basis, beginning at the phase IIb development stage. Additionally, Incyte has the option to co-promote products in the USA [3]. Incyte exercised its option to co-develop baricitinib with Eli Lilly during the third quarter of 2010. Incyte will be responsible for funding 30% of the associated global development costs through regulatory approval in RA, and the company's royalty rate will increase across all tiers.

1.2 Patent Information

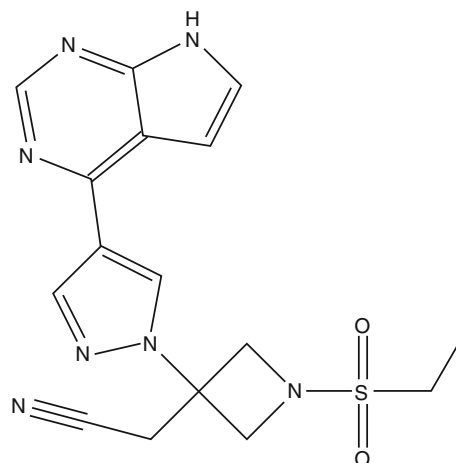
Incyte has issued and pending patents for baricitinib in the USA, EU and Japan. Granted and pending patents (if issued) will expire in 2029.

2 Scientific Summary

2.1 Pharmacodynamics

Baricitinib potently inhibits JAK1 and JAK2 (IC_{50} 5.9 and 5.7 nmol/L, respectively) but has lower potency against Tyk2 and JAK3 (IC_{50} of 53 and $\approx$ 560 nmol/L,

respectively) in vitro. In cell-based assays in human T-cells the drug potently (IC_{50} 20–50 nmol/L) inhibited phosphorylation of STAT3 and subsequent production of MCP-1, and IL-23 induced STAT3 phosphorylation and the subsequent production of IL-17 and IL-22. In an in vivo rat adjuvant arthritis study, 14 days' treatment with baricitinib 1, 3 or 10 mg/kg was associated with reductions in disease scores of 24 ($p < 0.05$), 57 ($p < 0.01$) and 81% ($p < 0.01$) compared with vehicle. The drug was also effective in several murine models of arthritis [4].



Chemical structure of baricitinib

2.2 Pharmacokinetics

The pharmacokinetic profile of oral baricitinib was dose-proportional over the dose range 1–20 mg in healthy volunteers in a single dose and a multiple dose study [5] and is linear over time [6]. Maximum plasma concentrations ($C_{\max}$) were reached in a median time ($t_{\max}$) of ≈ 1 h (range 0.5–3.0 h) [6]. Steady-state plasma concentrations were attained within 48 h after the first dose in the multiple dose study [5]. In patients with RA, steady-state $C_{\max}$ and area under the concentration-time curve (AUC) values are 1.4- and 2.0-fold higher than those in healthy subjects [6]. Baricitinib has an absolute bioavailability of $\approx 79\%$ and administration of the drug with a high-fat meal had no clinically relevant effect on exposure. Baricitinib is distributed into tissues, with a mean volume of distribution of 76 L after intravenous infusion and it is $\approx 50\%$ bound to plasma proteins [6].

Less than 10% of a dose of baricitinib undergoes biotransformation, mostly via CYP3A4. Baricitinib is excreted via renal elimination ($\approx 75\%$ of a dose) and in the faeces ($\approx 20\%$), mainly as the unchanged drug (84% of a dose; 6% is excreted as minor oxidative metabolites). In patients with RA, the mean apparent clearance was 9.42 L/h and the half-life was 12.5 h [6].

Baricitinib exposure is increased in patients with mild or moderate renal impairment compared with patients

with normal renal function (mean ratios of AUC 1.4 and 2.2, respectively; mean ratios of $C_{\max}$ 1.16 and 1.46). Dosage reduction is required in patients with creatinine clearance of 30–60 mL/min and baricitinib is not recommended for use in patients with creatinine clearance <30 mL/min [6].

In vitro, baricitinib is a substrate for CYP3A4, OAT3, P-gp, BCRP and MATE2-K and is an inhibitor of OAT1, OAT3, OCT1, OCT2, OATP1B3, BCRP, MATE1 and MATE2-K [6]. Co-administration with the potent OAT3 inhibitor probenecid was associated with a clinically relevant 2-fold increase in the AUC of baricitinib and a 69% decrease in renal clearance, but had no effect on $C_{\max}$ or $t_{\max}$. Coadministration of baricitinib with the lower potency OAT3 inhibitors ibuprofen and diclofenac, the potent CYP3A inhibitor ketoconazole, the CYP2C19/CYP2C9/CYP3A inhibitor fluconazole, the CYP3A inducer rifampicin and the P-gp inhibitor ciclosporin had no clinically meaningful effect on the pharmacokinetic profile of the drug. Baricitinib had no clinically meaningful effect on the pharmacokinetic profiles of digoxin (a P-gp substrate) or estradiol/levonorgestrel and simvastatin (CYP3A substrates). The pharmacokinetics of methotrexate and baricitinib are not significantly affected when the two drugs are given in combination to patients with RA [6, 7].

Features and properties of baricitinib

Alternative names	INCB-028050, INCB-28050, LY-3009104, Olumiant
Class	Acetonitriles, antipsoriatics, antirheumatics, azetidines, pyrazoles, pyrimidines, pyrroles, small molecules
Mechanism of action	Janus kinase (JAK)1 and 2 inhibitor
Route of administration	Oral
Pharmacodynamics	IC ₅₀ 5.9 nmol/L for JAK1 and 5.7 nmol/L for JAK2. Inhibits IL-6-induced STAT3 phosphorylation and activation
Pharmacokinetics	Median $t_{\max} \approx 1$ h, with steady state reached in 48 h; mean volume of distribution after IV infusion of 76 L; $t_{1/2}$ 12.5 h in patients with RA
Adverse events	
Most frequent	Increased LDL cholesterol, upper respiratory tract infections, nausea
Occasional	Infections (Herpes zoster, Herpes simplex, gastroenteritis, urinary tract infections), thrombocytosis, increased ALT levels
Rare	Neutropenia, increased triglycerides, increased AST levels, increased CPK levels
ATC codes	
WHO ATC code	A10X (other drugs used in diabetes), D05B (antipsoriatics for systemic use), D11A (other dermatological preparations), M01 (anti-inflammatory and antirheumatic products)
EphMRA ATC code	A10X (other drugs used in diabetes), D11 (other dermatological preparations), D5B (systemic antipsoriasis products), M1 (anti-inflammatory and antirheumatic products)
Chemical name	{1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}ethanenitrile

2.3 Therapeutic Trials

2.3.1 Rheumatoid Arthritis

2.3.1.1 Phase III The efficacy of baricitinib as a treatment for RA has been established in four pivotal phase III studies: RA-BEGIN (NCT01711359) in patients naïve to or with minimal prior exposure to methotrexate, a conventional disease-modifying anti-rheumatic drug (DMARD), and naïve to biologic DMARDs; RA-BUILD (NCT01721057) in patients with RA and an inadequate response or intolerance to conventional DMARDs; RA-BEAM in patients with RA who had not adequately responded to methotrexate, and RA-BEACON (NCT01721044) in patients with moderately to severely active RA who had not responded to tumour necrosis factor inhibitors and other biologic DMARDs or had unacceptable side effects. The primary endpoint in all four trials was the ACR20 response rate at 12 (RA-BUILD, RA-BEAM and RA-BEACON) or 24 (RA-BEGIN) weeks.

In RA-BEGIN, patients were randomised to 52 weeks' treatment with baricitinib 4 mg once daily as monotherapy ($n = 159$), methotrexate monotherapy (median dose 17.7 mg/week; $n = 210$) or combination therapy with baricitinib 4 mg once daily and methotrexate ($n = 215$). After 24 weeks' treatment, baricitinib monotherapy produced a significantly higher ACR20 response rate than methotrexate (77 vs. 62%; $p \leq 0.001$) and the response rate was similar for baricitinib monotherapy and baricitinib plus methotrexate combination therapy. The ACR20 response rate at week 52 was 73% in the baricitinib monotherapy and combination therapy groups compared with 56% in the methotrexate group. Significantly less radiographic disease progression [assessed using the van der Heijde modified Total Sharp Score (mTSS)] was seen after 24 (least squares mean (LSM) change from baseline 0.29 vs. 0.61; $p \leq 0.05$) and 52 (0.40 vs. 1.02; $p \leq 0.01$) weeks' treatment with baricitinib plus methotrexate versus methotrexate alone [8].

The RA-BUILD study compared 24 weeks' treatment with baricitinib 2 mg ($n = 229$) or 4 mg ($n = 227$) once daily to placebo ($n = 228$). ACR20 response at week 12 was achieved by 66 and 62% of patients given baricitinib 2 or 4 mg/day, respectively, compared with 39% of placebo recipients ($p \leq 0.001$ vs. baricitinib 4 mg/day). Similar results were observed at the 24-week endpoint (61 and 65% with baricitinib 2 and 4 mg/day, respectively, vs. 42% in the placebo group). Significantly less radiographic disease progression was seen at 24 weeks with baricitinib 2 mg (mTSS LSM change from baseline 0.33 vs. 0.70; $p \leq 0.05$) or 4 mg (0.15 vs.

0.70; $p \leq 0.01$) compared with placebo. In this study, patients who were receiving stable doses of up to two conventional DMARDs prior to study entry were permitted to continue this therapy as background treatment [9].

In RA-BEAM, patients were randomized to 52 weeks' treatment with oral baricitinib 4 mg once daily ($n = 487$), subcutaneous adalimumab 40 mg every other week ($n = 330$) or placebo ($n = 488$) in addition to stable background methotrexate therapy. After 24 weeks, placebo recipients were switched to baricitinib 4 mg once daily for the remaining 28 weeks; blinding was maintained throughout the 52-week treatment period [10]. ACR20 response rate at week 12 was significantly higher in baricitinib than placebo recipients (70 vs. 40%; $p < 0.001$). Similar results were observed at week 24 (74 vs. 37%; $p \leq 0.001$). At weeks 12 and 24, 61 and 66% of patients treated with adalimumab achieved ACR20 (both $p \leq 0.001$ vs. placebo). The ACR20 response rate at week 12 was significantly greater with baricitinib versus adalimumab ($p = 0.01$). Significantly less radiographic disease progression was seen with baricitinib (mTSS LSM change from baseline 0.41 vs. 0.90; $p < 0.001$) and adalimumab (0.33 vs. 0.90; $p < 0.001$) compared with placebo at 24 weeks. At 52 weeks, radiographic disease progression continued to be significantly less with baricitinib (0.71 vs. 1.80; $p < 0.001$) and adalimumab (0.60 vs. 1.80; $p < 0.001$) than with placebo [10].

In RA-BEACON, patients were randomised to 24 weeks' treatment with baricitinib 2 or 4 mg once daily ($n = 174$ and 177, respectively) or placebo ($n = 176$) in addition to stable background conventional DMARDs. ACR20 response rate at week 12 was 55% in the baricitinib 4 mg/day group compared with 27% in the placebo group ($p < 0.001$). This therapeutic benefit remained evident at 24 weeks (46 vs. 27%; $p < 0.001$). Baricitinib 2 mg/day produced ACR20 responses of 49 and 45% after 12 and 24 weeks (both $p < 0.001$ vs. placebo) [11].

Patients who completed their participation in the pivotal trials were eligible to enter the long-term extension study RA-BEYOND (NCT01885078). Those who had received treatment with baricitinib 4 mg/day for ≥ 15 months without rescue and who had achieved sustained low disease activity or remission were re-randomised in a double-blind manner to continue receiving baricitinib 4 mg/day ($n = 147$) or step down to 2 mg once daily ($n = 146$). At the 12-week assessment, the cohort stepped down from 4 to 2 mg/day had experienced small but statistically significant ($p \leq 0.05$) increases in disease activity across a number of measures, suggesting that baricitinib 4 mg once daily is the more effective dose [12].

2.3.1.2 Phase II Baricitinib 4 and 8 mg once daily were associated with a significantly greater proportion of patients achieving an ACR20 response than placebo in a global phase IIb study in patients with RA and an inadequate response to methotrexate (NCT01185353). Participants in this trial were randomised to baricitinib 1 (n = 49), 2 (n = 52), 4 (n = 52) or 8 mg (n = 50) once daily or placebo (n = 98) for 12 weeks. After 12 weeks, patients receiving baricitinib 2, 4 and 8 mg continued treatment at this dose for a further 12 weeks; patients in the placebo or baricitinib 1 mg/day cohorts received baricitinib 2 mg twice daily or 4 mg once daily during this period. The primary endpoint was the proportion of patients in the combined 4 and 8 mg groups achieving an ACR20 response versus placebo at week 12. 76% of patients treated with baricitinib 4 or 8 mg/day achieved an ACR20 response at week 12 compared with 41% of placebo recipients ($p < 0.001$). ACR20 response rates were maintained or improved through to 24 weeks in patients initially randomised to the baricitinib 2, 4 and 8 mg/day cohorts [13]. Clinical improvements seen at week 24 were maintained or improved through to week 128 in a long term, open-label extension study during which patients received baricitinib 4 mg once daily [14].

A similar phase IIb study (NCT01469013) in Japanese patients with RA and an inadequate response to methotrexate reported results consistent with the above trial, with 77% of baricitinib 4 or 8 mg once daily (n = 24 per cohort) recipients achieving ACR20 response compared to 31% in the placebo group (n = 49) at week 12 ($p \leq 0.001$) [15]. Efficacy was maintained during a single-blind 52-week extension of this study [16].

2.3.2 Psoriasis

2.3.2.1 Phase II Patients with moderate to severe chronic plaque psoriasis experienced significant improvements in Psoriasis Area and Severity Index (PASI) 75% (PASI-75) scores after 12 weeks' treatment with baricitinib in a placebo-controlled phase IIb trial (NCT01490632). The study initially enrolled patients in the USA and Canada, but was later expanded to include Japanese sites; however, the primary study objective, the proportion of patients achieving PASI-75 at week 12,

relied solely on data from North American sites. The study was conducted in 4 parts (A, B, C and D). Patients were initially randomised to placebo (n = 34) or baricitinib 2 (n = 32), 4 (n = 72), 8 (n = 64) or 10 (n = 69) mg once daily for 12 weeks (Part A). In part B, patients who responded to treatment during part A continued treatment at the same dose for a further 12 weeks. Patients classified as partial responders were re-randomised to remain on the same dose they received in part A, or (other than those who received the 10 mg dose in part A) to receive a higher dose. Non-responders were randomised to dose-escalation to 8 or 10 mg/day, with treatment discontinued in those who received 10 mg/day in part A. Part C was a 16-week washout to establish time to relapse; patients who responded in part B were randomised to a reduced baricitinib dose (n = 55) or placebo (n = 55). Part D was a retreatment period of up to 52 weeks in patients who had a relapse or flare. In part A, 42.9 and 54.1% of North American patients treated with baricitinib 8 or 10 mg/day achieved the primary objective (PASI-75 at week 12) compared with 16.7% of placebo recipients ($p < 0.05$ and $p < 0.001$). Change from baseline in mean PASI score at week 12 was significantly greater in patients treated with baricitinib ≥ 2 mg/day than in placebo recipients ($p < 0.05$). More than 81% of PASI-75 responders maintained their scores during part B [17]. In part C, patients randomised to a lower dose of baricitinib had lower relapse rates and longer time to relapse compared with placebo recipients. In part D, 37–67% of patients had achieved a PASI 75 response at week 12 [18]. No additional studies in this indication are planned.

2.3.3 Diabetic Kidney Disease

2.3.3.1 Phase II Treatment with baricitinib reduced 24-h urine albumin-to-creatinine ratio (UACR) compared with placebo in patients at high risk of diabetic kidney disease in a phase II study. 129 patients received standard care and were randomised to baricitinib 0.75 mg once daily, 0.75 mg twice daily 1.5 mg once daily, 4 mg once daily or placebo for 6 months. Significant reductions ($p < 0.05$) in UACR were observed after 3 months in the baricitinib 1.5 and 4 mg once daily groups, but only in the 1.5 mg once daily group after 6 months [19]. No additional studies in this indication are planned.

Key clinical trials of baricitinib (Eli Lilly and Incyte Corporation)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Baricitinib	Pharmacokinetic study in volunteers	I	Completed	UK	NCT02340104
Baricitinib, ciclosporin	Pharmacokinetic interaction study in volunteers	I	Completed	UK	NCT01968057
Baricitinib	Pharmacokinetic study in patients with liver disease	I	Completed	USA	NCT01870388
Baricitinib, omeprazole	Pharmacokinetic interaction study in volunteers	I	Completed	UK	NCT01925144
Baricitinib	Pharmacokinetic study in Japanese volunteers	I	Completed	Japan	NCT02263911
Baricitinib, ketoconazole, fluconazole	Pharmacokinetic interaction study in volunteers	I	Completed	UK	NCT01924299
Baricitinib, digoxin	Pharmacokinetic interaction study in volunteers	I	Completed	UK	NCT01859078
Baricitinib, ethinyl estradiol/levonorgestrel	Pharmacokinetic interaction study in volunteers	I	Completed	UK	NCT01896726
Baricitinib, placebo	Systemic lupus erythematosus	II	Recruiting	Multinational	NCT02708095
Baricitinib, probenecid	Pharmacokinetic interaction study in volunteers	I	Completed	UK	NCT01937026
Baricitinib	Chronic graft vs. host disease	I/II	Recruiting	USA	NCT02759731
Baricitinib, placebo	Rheumatoid arthritis	III	Ongoing	Argentina, Brazil, China	NCT02265705
Baricitinib, rifampicin	Pharmacokinetic interaction study in volunteers	I	Ongoing	UK	NCT01910311
Baricitinib, simvastatin	Pharmacokinetic interaction study in volunteers	I	Completed	UK	NCT01960140
Baricitinib, placebo, triamcinolone	Moderate-to-severe atopic dermatitis	II	Ongoing	USA, Japan	NCT02576938
Baricitinib, placebo	Rheumatoid arthritis (extension study)	III	Recruiting	Multinational	NCT01885078
Baricitinib, placebo	Diabetic kidney disease	II	Completed	Multinational	NCT01683409
Baricitinib, placebo	Moderately to severely active rheumatoid arthritis	III	Completed	Multinational	NCT01721044
Baricitinib, placebo	Moderately to severely active rheumatoid arthritis	III	Completed	Multinational	NCT01721057
Baricitinib, placebo	Moderate-to-severe plaque psoriasis	II	Completed	Multinational	NCT01490632
Baricitinib, adalimumab, placebo	Moderately to severely active rheumatoid arthritis	III	Completed	Multinational	NCT01710358
Baricitinib, methotrexate, folic acid, placebo	Moderate-to-severe rheumatoid arthritis	III	Completed	Multinational	NCT01711359
Baricitinib	Pharmacokinetic study in volunteers	I	Completed	USA	NCT01299285
Baricitinib, placebo	Pharmacokinetic study in Chinese volunteers	I	Completed	China	NCT02758613
Baricitinib, placebo	Active rheumatoid arthritis not adequately responding to DMARDs	II	Completed	USA, Czech Republic	NCT00902486
Baricitinib, moxifloxacin, placebo	Effect on the QT interval	I	Completed	USA	NCT01536951
Baricitinib, methotrexate, placebo	Rheumatoid arthritis	II	Completed	Multinational	NCT01185353
Baricitinib	Bioavailability in Volunteers	I	Completed	Singapore	NCT01398475
Baricitinib, methotrexate, placebo	Rheumatoid arthritis		Completed	Japan	NCT01469013
Baricitinib	Compassionate use in CANDLE, CANDLE-Related Conditions, SAVI and Severe Juvenile Dermatomyositis		Recruiting	USA, UK	NCT01724580

2.4 Adverse Events

The most frequent adverse events with baricitinib as monotherapy or in combination with conventional synthetic DMARDs in clinical trials were increases in low-density lipoprotein cholesterol (LDL-C) (33.6%), upper

respiratory tract infections (14.7%) and nausea (2.8%). Few patients receiving baricitinib or placebo in clinical trials had serious infections (1.1 vs. 1.2%); in baricitinib recipients, herpes zoster and cellulitis were the most common serious infections [6]. Increases in hepatic transaminase ($\leq 1.4\%$ of patients) and creatine

phosphokinase ($\leq 1.5\%$) levels with baricitinib or placebo were reported infrequently and most cases were transient [6].

A phase IIb study (NCT01469013) compared the effects of baricitinib 1, 2, 4 or 8 mg/day and placebo on the lipid profile of patients with RA ($n = 301$). Dose-dependent increases from baseline in total cholesterol, LDL-C, high-density lipoprotein cholesterol and triglyceride levels were seen in baricitinib recipients at 12 weeks [20]. Elevated LDL-C levels observed in controlled studies returned to pre-treatment levels after treatment with a statin [6].

Data from nine studies in patients with RA treated with baricitinib, including four phase III, three phase II, one phase Ib and one long term extension trial, have been assessed in an integrated analysis of safety. Of 3464 patients treated with baricitinib in these trials, 255 (6.1%) developed adverse events leading to study drug discontinuation, 143 (3.4%) developed Herpes zoster, 137 (3.2%) developed serious infections, 29 (0.7%) developed malignancies (excluding non-melanoma skin cancer), 16 (0.5%) developed major adverse cardiac events and 13 (0.3%) died. Among these adverse events, only Herpes zoster was observed at increased frequency in patients treated with baricitinib compared with placebo [21].

2.5 Ongoing Clinical Trials

Studies are ongoing evaluating the efficacy of baricitinib as treatment for systemic lupus erythematosus (NCT02708095), moderate-to-severe atopic dermatitis (NCT02576938) and chronic graft versus host disease (NCT02759731). A compassionate use program in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE), CANDLE-Related Conditions, stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy (SAVI) and Severe Juvenile Dermatomyositis is also in place (NCT01724580).

3 Current Status

Baricitinib received its first global approval on 13 February 2017 as monotherapy or in combination with methotrexate for the treatment for moderate to severe active RA in adult patients who have responded inadequately to, or are intolerant to one or more DMARDs, in the EU.

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