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Baricitinib: therapeutic potential for moderate to severe atopic dermatitis

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ABSTRACT

Introduction. Atopic dermatitis (AD) is a chronic inflammatory skin disease mediated by multiple signals including janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. Current therapeutic armamentarium consists of a limited number of drugs which may result in the insufficient management of AD. Preclinical evidence regarding inhibition of JAK/STAT led to the development of a promising class of therapeutics, namely, JAK inhibitors. Baricitinib, a novel JAK1/JAK2 inhibitor is currently under investigation in AD clinical trials. **Areas covered.** This review offers an overview of Baricitinib and examines clinical efficacy and safety data in patients with moderate-to-severe AD. **Expert opinion.** Baricitinib showed promising preliminary data in terms of efficacy in phase II and III trials, with a very rapid onset of response and great improvements of itch and sleep disturbances. These aforementioned aspects combined with the advantage of an oral formulation have reduced drug production costs compared to biologic agents and could lead to consideration of baricitinib as a first line systemic treatment. Also, in some countries, it could be a therapeutic option in the case of contraindication or failure of conventional systemic drugs prior to biologic therapies. Data related to long-term safety and efficacy will be important to refine the place-in-therapy of this drug.

Keywords: atopic dermatitis, baricitinib, JAK, JAK inhibitors, small molecules

Article Highlights:

- Current conventional drugs for atopic dermatitis (AD) do not always provide therapeutic control of the disease
- Thorough understanding the immune landscape in AD will shed light on emerging disease-specific therapeutic options.
- JAK/STAT inhibitors represent a new promising drug class for AD treatment.
- Baricitinib, a selective JAK1/2 inhibitor, was recently investigated in phase 3 AD clinical trials with encouraging results.
- Additional data concerning baricitinib long term efficacy and safety profile are needed.

1. Introduction

Atopic dermatitis (AD) is an immune-mediated skin disease with a chronic-relapsing course and a multifactorial pathogenesis. AD is the most common inflammatory skin disorder with a worldwide prevalence ranging from 5 to 10% in children and 1-3% in adults [1,2]. Clinical manifestations are usually associated with intense itching and typically consist of symmetric, erythematous and scaly papules or plaques, with secondary features of lichenification and excoriation, and high-risk of superimposed infections [3]. The recurrent eczematous lesions are predominantly localized on extensor areas, face, scalp, and diaper area in childhood AD [4], whereas flexural areas, face, neck and distal extremities are commonly affected in adolescent and adult AD patients [5]. However, different AD phenotypes have been recently described and some of them have been characterized as the result of distinct endotypes according to age, ethnicity, body localization, disease stage, IgE levels, immune pathway activation, and *filaggrin* mutation [6]. This novel distinction of AD in different subgroups will pave the way for the introduction of a personalized therapeutic approach replacing the traditional “one-size-fits-all” strategy.

No longer considered as an only-cutaneous disease, AD often precedes other atopic manifestations priming the so-called “atopic march”. Moreover, AD may be associated with a significant increased risk of comorbidities, including cardiovascular, neuropsychiatric and malignant disorders [7]. Nevertheless, atopic dermatitis might be associated with a profound negative impact on the quality of life (QoL), due to constant itch and sleep disturbances. Both

social and emotional functioning can be detrimentally affected, leading to work impairment and social isolation [8].

1.1. AD pathogenesis

AD pathogenesis consists of a complex mechanism involving genetic and environmental factors, leading to skin barrier dysfunction and immunological impairment. The immune system dysregulation involves both innate and adaptive immunity. Although AD has been conventionally considered mediated by a Th2-skewed adaptive immune response, associated with eosinophil recruitment, mast cell activation, and IgE production from activated B cells, the immune map of the disease is expanded to T cytotoxic 2 cells (Tc2), type 2 innate lymphoid cells (ILC2s), and to multiple inflammatory pathways, namely Tc22/Th22, Th17, Th9, and Th1 (Fig. 1)[9].

In the acute phase of AD, type 2 (Th2-, ILC2-, Tc2-derived) and Th22-derived cytokines (i.e., IL-22) are mostly involved, contributing to skin inflammation, epidermal barrier dysfunction and itch, while in the chronic stage, the intensification of Th2 and Th22 cytokines axes occurs, with an important contribution of both Th1 and Th17 pathways in sustaining inflammation [10]. Pruritus is mainly induced by IL-31 [10].

1.2 Role of JAK/STAT signaling pathway in AD

The Janus kinases (JAK)/signal transducer and activator of **transcription (STAT)** pathway is a paradigm of receptor-mediated signal transduction, which is essential for both immune and hematopoietic function.

The JAK family belongs to the group of cytoplasmic tyrosine kinases and includes four isoforms: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) [11]. Once activated, JAKs phosphorylate the intracellular domain of the cytokine receptor creating a docking site for STATs [12]. The ultimate effect of the activation of JAK/STAT pathway is strongly influenced by the isoforms recruited and their complex interaction. Type 2 cytokines (namely IL-4 and IL-13) which are central to AD pathogenesis, act through JAK1/JAK3 and STAT3, STAT5, and STAT6 [13], mediating different steps of AD pathogenesis. Binding the type I IL-4 receptor, IL-4 and IL-13 activate JAK/STAT pathway, (i) altering the keratinocyte differentiation process leading to skin barrier impairment; (ii) *regulating keratinocyte-derived chemokine and antimicrobial peptide production*; and (iii) inducing sensory neuronal stimulation [14-20]. The overall result of JAK-STAT activation is the contribution to both AD skin inflammation and chronic itch [20]. However, the pathogenic role of JAK-STAT signaling is not only related to IL-4 and IL-13 as other key-pathogenic mediators. For instance, IL-31 and thymic stromal lymphopoietin (TSLP) transduce their pruritogenic *stimuli* through JAK-STATs pathways [21,22]. Collectively, these lines of evidence suggested the central role of JAK/STAT in AD pathogenesis and the therapeutic development of JAK inhibitors in treating human AD (Fig. 2).

2. Material and methods

Search of the English-language literature regarding the pathogenic role of JAK/STAT pathway dysregulation in AD was carried out, in addition to clinical data on baricitinib therapy. Multiple databases, namely PubMed, Embase, Google Scholar and Scopus, have been consulted using the following terms: baricitinib, INCB028050, olumiant, atopic dermatitis, JAK/STAT pathway, JAK inhibitors. Ongoing clinical trials and preliminary results concerning investigational use of

baricitinib in AD were searched on Clinicaltrial.gov. Data from recent international meetings were also taken into account.

3. Overview of the market

The choice of AD treatment widely varies depending on various factors. Topical approach is usually the first line treatment for mild disease, while phototherapy and systemic agents are recommended for moderate-to-severe patients. Apart from cyclosporine that is approved for treatment of AD, the remaining immunosuppressive drugs have been used as alternative, off-label therapies. In 2017, the Food and Drug Administration (FDA) has approved dupilumab, a fully human monoclonal antibody blocking the shared IL-4 receptor α (IL4R α) subunit binding to both IL-13 and IL-4, for the treatment of moderate-to-severe AD in both adults and adolescence [23].

3.1 Emerging therapies for AD

Several novel therapeutic agents, including biologic agents, topical and oral small molecules, are currently being investigated for AD treatment [24]. Currently, some of these agents are in advanced stage of development: nemolizumab, an anti-IL-31 monoclonal antibody (mAb) met the primary endpoint in a phase II trial [25,26]; lebrikizumab and tralokinumab, both targeting IL-13, are currently under investigation in phase III studies [27]. Tezepelumab, mAb targeting TSLP [26], and ustekinumab, an anti-IL-12/23mAb, demonstrated controversial results in phase II trials [29], whereas fezakizumab, an anti-IL-22 mAb, has proven to be effective particularly in patients with severe AD (SCORAD > 50) and with high IL-22 serum levels at the baseline [30].

An oral inhibitor of phosphodiesterase 4 (PDE4), apremilast, was investigated in one phase II clinical trial for AD, but showed inconsistent results [31]. Conversely, upadacitinib, a selective JAK1 inhibitor, successfully passed phase II, and is now being tested in multiple phase III clinical trials,

including a phase IIIb *versus* dupilumab. Abrocitinib, another specific JAK1 inhibitor, is currently investigated in a phase III trial (NCT03422822). Another class of drugs, which appeared on the landscape of AD pipeline, comprises oral H₄R antihistamines such as ZPL-3893787, tested on phase II [32].

3.2 JAK inhibitors: a new promising class of therapeutics

Alterations of JAK/STAT pathway and their relation to the pathophysiology of many chronic immune-mediated disorders were thoroughly investigated and JAK inhibitors shed light on their therapeutic potentiality in treating various inflammatory skin disorders [33-35]. Blocking one or more members of the JAK family, JAK inhibitors exert anti-inflammatory, immunosuppressive and antiproliferative properties [36]. Nowadays, two generations of JAK inhibitors exist: the first generation, including tofacitinib, ruxolitinib and baricitinib, blocks multiple JAKs, while the second generation is more selective, blocking one single JAK, narrowing the inhibitory range of cytokines [37].

4. Introduction to the compound

Baricitinib (LY3009104, previously known as INCB028050) is an orally administered small molecule, already approved for the treatment of moderate to severe rheumatoid arthritis (RA) [38]. Noteworthy, a black-box warning has been included because of the occurrence of serious infections, such as herpes zoster and tuberculosis reactivation, malignancies, arterial and venous thromboses, observed during analysis of phase II and III trials on patients affected by moderate-to-severe RA. However, given its emerging therapeutic potential, baricitinib is currently under

investigation for the treatment of other chronic immune-mediated diseases such as moderate-to-severe psoriasis, systemic lupus erythematosus, chronic graft versus host disease and atopic dermatitis.

4.1 Chemistry

The chemical name of baricitinib is {1-(ethylsulfonyl)-3-[4-(7Hpyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile. The empirical formula of baricitinib is C₁₆H₁₇N₇O₂S and the molecular weight is 371.42 g/mol [39].

4.2 Pharmacodynamics

Baricitinib is capable to selectively inhibit both JAK1 and JAK2 tyrosine kinases, with half-maximum inhibitory concentrations (IC₅₀) of 5.9 and 5.7 nmol/L, respectively. To a lesser extent, it also inhibits the other two members of Janus kinases, TYK2 and JAK3 (IC₅₀ of 53 and ≈560 nmol/L, respectively). In human T-cells assays, strong inhibition of STAT3 phosphorylation resulted in suppression of IL-6 and IL-23 signaling, and a subsequent decreased production of MCP-1, IL-17 and IL-22 [40].

4.3 Pharmacokinetics and metabolism

Drug plasma concentration, following oral administration, typically peaks after 1.5 hours [41,42]. Additionally, baricitinib demonstrated dose-proportional dependent PK, with minimal systemic accumulation after repeated doses [42]. Absolute drug bioavailability consists of about 79%, which is reduced (up-to-14%) by the co-administration of high-fat and high-calorie meal, without significant impact on clinical effect. Up to 50% of baricitinib binds to plasma proteins and less than 10% of the drug's plasma dose undergoes transformation through CYP3A4 cytochrome.

A phase I trial (NCT01870388) evaluated baricitinib PK in patients with liver disease. In detail, 8 subjects with hepatic impairment classified as Child-Pugh score A or B (mild or moderate impairment, respectively) and 8 healthy controls underwent treatment with 4-mg baricitinib daily for one week. No serious adverse event (AE) or deaths occurred in any arm, while nausea and neutrophil count decrease (classified as non-serious AE), were slightly more frequent in patients with moderate liver impairment (1/8, 12.50% *versus* 0% in healthy controls).

The drug is mainly excreted unchanged through renal and gastrointestinal elimination (75% and \approx 20% of the dose, respectively). Co-administration with the potent OAT3 inhibitor probenecid is associated with a clinically relevant increase in baricitinib serum levels and with 69% decrease in renal clearance. Patients with mild or moderate renal impairment (creatinine clearance of 30–60 mL/min) have reduced baricitinib renal clearance compared with healthy individuals, thus, dose reduction is required, whereas baricitinib administration is not recommended in patients with stage 4 or 5 chronic kidney disease (creatinine clearance <30 mL/min).

4.4 Clinical efficacy

4.4.1 Phase II trial program

A phase II, randomized, double-blind, placebo-controlled trial (NCT02576938) evaluated safety and efficacy of baricitinib in patients with moderate-to-severe AD [43]. One hundred twenty-four patients were enrolled and randomized in a 4:3:3 ratio to once-daily placebo (49 patients), 2-mg or 4-mg baricitinib tablets (37 and 38 patients, respectively) for 16 weeks, eventually associated to mid-potency topical corticosteroid (triamcinolone 0.1% cream).

The primary endpoint was the proportion of participants achieving 50% or greater improvement in the baseline Eczema Area Severity Index (EASI) score at week 16 (EASI₅₀ at week 16). EASI₅₀ was achieved by 37% of patients in placebo group, 57% in 2-mg baricitinib group, and 61% in 4-mg

baricitinib group at week 16. Comparison between the 4-mg baricitinib group and the placebo group showed a significant difference (p : 0.027), whereas the EASI50 response induced by 2-mg baricitinib did not result significantly higher than placebo (p : 0.065). Since active arms applied almost 30%-less quantity of topical corticosteroids compared to the placebo group, clinical outcomes have been likely influenced by the diverse usage of topical corticosteroids among different groups, increasing efficacy rates in the placebo group. Measures reflecting the Health-related Quality of Life (HRQoL) showed significant improvements in both active groups compared to placebo, at various time points. Furthermore, percent reduction from baseline in SCORAD-derived pruritus and sleeplessness scores was statistically significant in the 4-mg group compared to placebo as early as week 1, enhancing its superiority at week 4 (p : 0,001; Table 1). Similarly, reduction of mean baseline in itch-NRS was observed as early as week 1 (Table 1).

4.4.2 Phase III trial program

Eight phase III trials have been conducted to explore the efficacy and safety of baricitinib as monotherapy or in combination with topical corticosteroids in adults, adolescents, and children affected by moderate-to-severe AD (Table 2). Among these, two multicenter, double-blind, placebo-controlled studies were recently concluded: BREEZE-AD1 (NCT03334396) and BREEZE-AD2 (NCT03334422) [44] (Table 3). Six hundred twenty-four patients in BREEZE-AD1 and 615 in BREEZE-AD2 were randomized with a 2:1:1:1 ratio to receive once-daily placebo, baricitinib 1 mg, 2 mg, or 4 mg (Table 3).

In both trials, the primary endpoint (IGA 0-1) was achieved by a significantly higher proportion of patients in the 2-mg and 4-mg groups, compared to placebo. EASI75, EASI90 and SCORAD75 at week 16 were detected in a significantly higher proportion of participants in the 2-mg and, more markedly, in the 4-mg groups ($p=0.001$).

Along with pruritus, skin pain and sleep loss due to AD symptoms started to improve by week 1 in the treatment groups. Overall, in both trials, outcome measures in the 1-mg group compared to placebo did not achieve consistent significance.

Another phase III trial (BREEZE-AD7, NCT03733301) was recently completed [45]. Adult patients with moderate-to-severe AD (n=329) were randomized in a 1:1:1 ratio to 4-mg baricitinib, 2-mg or placebo (Table 4). IGA 0-1, with at least 2-point IGA improvement, was obtained by 30.6% and 23.9% of participants in the 4-mg and 2-mg group, respectively, with a significant superiority of the 4-mg arm over placebo (14.7%, $p=0.01$). Higher proportion of patients achieved EASI75 by week 16 in the 4-mg group (47.7%, $p=0.01$) and 2-mg (43.1%, $p=0.001$) than placebo (22.9%). A ≥ 4 point improvement in Itch-NRS from baseline was marked as early as week 4 in both baricitinib arms, with a nearly progressive reduction of patients who reached this endpoint by week 16 (44% in the 4 mg group at week 16, $p=0.01$). Amelioration of sleep quality revealed satisfying results in the baricitinib groups compared to placebo ($p=0.001$ at week 16). As expected, more TCSs-free days were reported in the 4-mg (32.9%, $p=0.001$) than in the 2-mg baricitinib group (25.3%, $p=0.005$) and placebo (17.4%).

The phase III program encompasses other ongoing studies, including 2 trials (NCT03334435, BREEZE-AD3; NCT03559270, BREEZE-AD6) evaluating long-term safety and efficacy of baricitinib, while one trial will be conducted on children and adolescents (NCT03952559, BREEZE-AD-PEDS, Table 1).

4.5 Safety and tolerability

In the phase II trial no deaths were reported in any arm and a low percentage of patients discontinued treatment because of AE (3% in the 2-mg, 13% in the 4-mg, and 10% in the placebo

group). Serious Treatment-Emergent Adverse Events (TEAE) were observed in 3 baricitinib-treated patients. The overall number of non-serious TEAEs (either mild or moderate AEs) was higher in the 4-mg group (19 patients out of 38) and commonly consisted of headache, increase of creatine phosphokinase (CPK) serum level and nasopharyngitis.

In BREEZE-AD1 and AD2 trials, no deaths, nor gastrointestinal perforations, major cardiovascular events (MACE), malignancies or venous thromboembolic events occurred in any participant. The most frequently observed TEAEs were in line with the phase II trial. The overall number of infectious AEs and SAEs was not superior in the baricitinib arms compared to placebo. The rate of herpes simplex infections was greater in the 4-mg baricitinib group only in BREEZE AD1; no herpes zoster infections were reported in any treatment group in both trials.

In BREEZE-AD7, the overall percentage of TEAEs was higher in the 4-mg (57.7%) and in the 2-mg baricitinib (56%) groups than placebo (38%). No deaths, MACE, malignancies (including NMSC), deep vein thrombosis or gastrointestinal perforations were observed in any arm, and the percentages of patients who experienced SAEs in the 4-mg baricitinib group were similar to those seen in the placebo group.

4.6 Regulatory affairs

On February 2017 European Medicines Agency (EMA) approved baricitinib as monotherapy or in combination with methotrexate for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). On June 2018, FDA approval was obtained for 2-mg baricitinib tablet for the treatment of moderate-to-severe RA, refractory to one or more TNF inhibitors [46-48].

5.0 Conclusions

AD comprises a variety of clinical phenotypes, which correspond to an even more heterogeneous immunological background. Based on the better understanding of the complex AD pathogenesis, the use of new promising therapeutic agents has been encouraged, similarly to what occurred in psoriasis in the past two decades. Baricitinib, inhibiting multiple inflammatory pathways involved in AD pathogenesis, showed rapid onset of clinical response and early improvement of patients' reported symptoms are the main features of baricitinib efficacy in phase II and III trials.

6. Expert opinion

Baricitinib showed promising preliminary data in both phase II and phase III trials. The efficacy seen in clinical trials was similar to dupilumab, with a very rapid onset of response (by week 1) and great improvements of itch and sleep disturbances, since the first days of administration. Other favorable aspects related to baricitinib use are: *(i)* the oral formulation that could be preferred over subcutaneous injections, *(ii)* the lower costs in producing a small-molecule drug, as compared to a biologic agent, and *(iii)* possibility of therapy modulation (eg. withdrawal and retreatment) as no immunogenicity or anti-drug antibody formation can be expected. The combination of these advantages owned by baricitinib, compared to biologic agents, could presumably hypothesize its use as first line systemic treatment. Because in some countries, drug prescription is strictly regulated by national or regional authorities placing conventional systemic agents as the first line treatment, baricitinib could be considered in case of contraindication or failure to traditional systemic drugs, prior to biologic agent prescription. Challenges include serious AEs reported in RA trials (malignancies, thrombosis, and serious infections), which have raised important safety concerns regarding the use of baricitinib (and other JAK inhibitors). A causal link with baricitinib

mode-of-action cannot be ruled out, but, because these AEs have been described in RA population and not in AD patients, they could be attributed to the disease-specific pathogenic aspects or to patient comorbidities. However, a close laboratory monitoring in treated patients may be necessary, representing a disadvantage in drug management if compared to dupilumab.

Data from the multiple ongoing phase III trials, their extension phases and especially from real-life experience, will provide insight into the baricitinib long term safety profile in AD population.

An innovative aspect of the baricitinib investigational program is the identification of biomarkers for assessment of the therapeutic response that might be difficult to evaluate through clinical tools. Attempts to detect biomarkers correlating with baricitinib efficacy have been performed in RA and AD patient populations. Phase III trials testing baricitinib in RA patients (NCT01721044; NCT01721057) revealed a progressive decrease in serum C reactive protein levels associated with drug efficacy [49,50]. Notably, a phase II trial including 124 AD patients, detected a gradual lowering in IL-19 serum levels, a keratinocyte pro-proliferative marker, throughout baricitinib treatment, which was tightly related to EASI improvement [51]. Preclinical evidence also suggested the reduction of IL-6, IL-23, and other cytokines deriving from both Th1 and Th17 cells as potential biomarkers of baricitinib response, which did not found confirmation in treated AD patients [52].

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Declaration of Interest

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Figure legends

Figure 1. Pathogenic steps inhibited by JAK-1/2 blockade.

Pathogenic mechanism involves multiple immune cells that predominantly contribute to type 2 inflammation (i.e., ILC2, Th2, Eosinophils, and IgE-producing B cells). Additional pathways including Th1-, Th17-, and Th22-mediated signals, characterize both acute and chronic stages of the eczematous lesion formation. Baricitinib is able to suppress the activation of multiple signals mediated by different cytokines. Abbreviations: AMP: antimicrobial peptide; DC: dendritic cells; IL-: interleukin; Eos: eosinophils; ILC2: Innate Lymphoid Cells 2; KC: keratinocyte; Th: T helper; TSLP

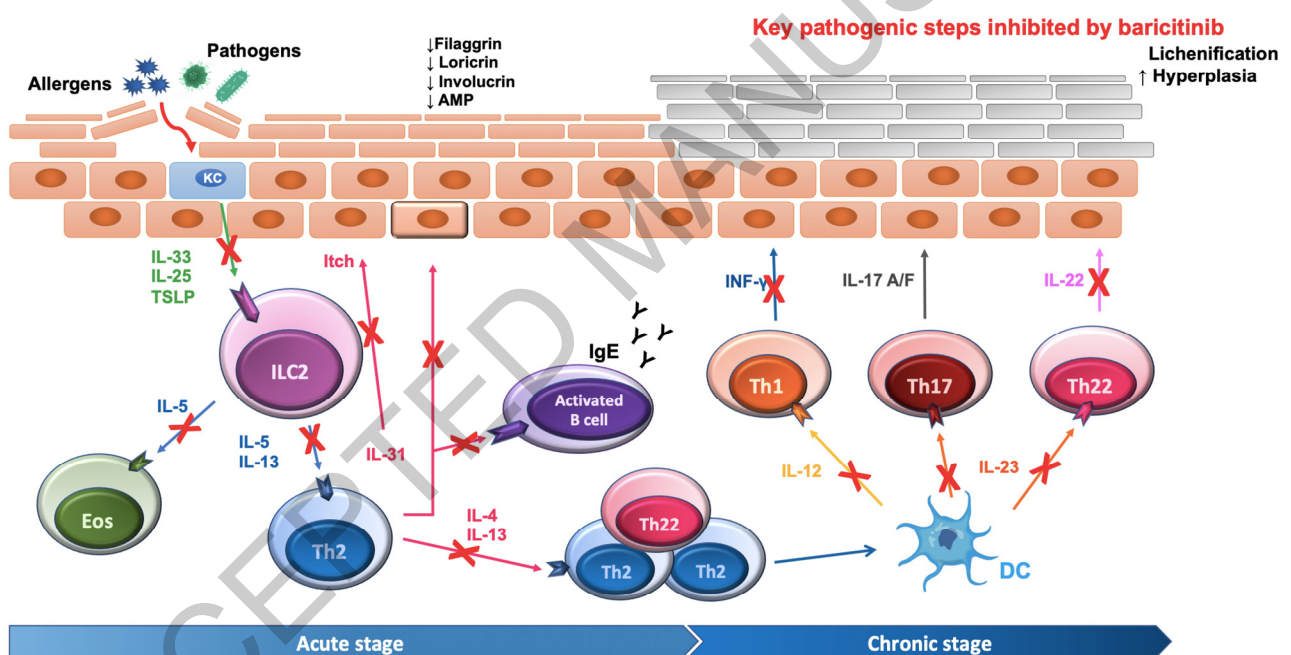


Figure 2. Cell types involved in atopic dermatitis pathogenesis and targeted by baricitinib.

Inhibiting both JAK1 and JAK2, baricitinib suppresses cell activation induced by key pathogenic cytokines such as IL-4 and IL-13. Multiple cells participating to AD pathogenesis, such as including Th2 cells, ILC2, DC, and KC, are affected by the inhibitory activity of baricitinib. Abbreviations: AMP: antimicrobial peptide; DC: dendritic cells; IL-: interleukin; Eos: eosinophils; ILC2: Innate Lymphoid Cells 2; KC: keratinocyte; JAK: Janus kinase; Th: T helper; TSLP

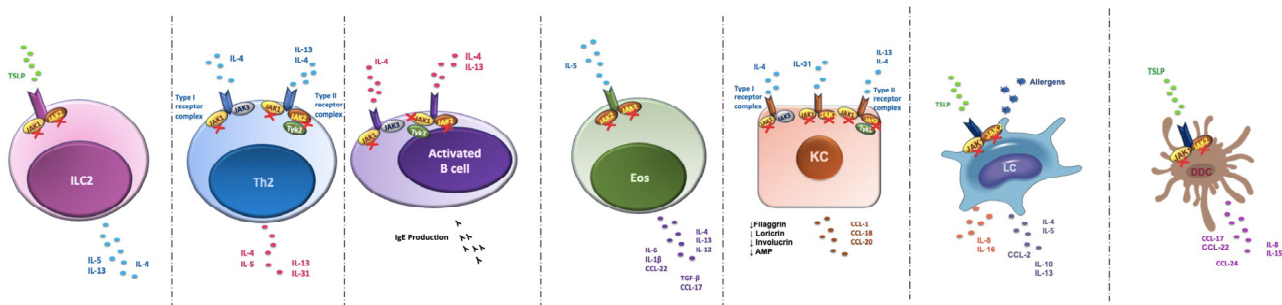


Table 1. Main outcomes of phase II trial. Summary of primary and key secondary endpoints at Week 4 and Week 16 (LY3009104).

| | Placebo (n =49) | | Baricitinib 2 mg (n =30) | |
|--|-----------------|--------|--------------------------|--------|
| | Week4 | Week16 | Week4 | Week16 |
| Primary outcome | | | | |
| EASI50 | 16% | 37% | 62%*** | 57% |
| Secondary outcomes | | | | |
| EASI75 | 6% | 20% | 24%* | 30% |
| EASI90 | 2% | 6% | 5% | 19% |
| vIGA-AD 0-1(≥2-point improvement from baseline) | 2% | 8% | 5% | 22% |
| Mean change from baseline in Itch NRS | --- | -1.72 | --- | -2.61 |
| Percentage change in SCORAD total | --- | -21% | --- | - 41%* |

PBO, placebo; Bari, baricitinib; ADSS, Atopic Dermatitis Sleep Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; n, number of subjects in the specified category; NRS, Numeric Rating Scale; SCORAD, SCORing Atopic dermatitis; vIGA-AD, Validated Investigator's Global Assessment of atopic dermatitis. *p: 0.05 **p: 0.01 ***p:0.001

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Table 2. Clinical trial program investigating baricitinib efficacy and safety.

Abbreviations: AD: Atopic Dermatitis; BARI: Baricitinib

| Study/Sponsor | ClinicalTrials.gov identifier(s) | Phase | Status | Main features |
|--|----------------------------------|-------------|-------------------------|---|
| LY3009104 (Eli Lilly and Company) | NCT02576938; I4V-MC-JAHG | II, per os | Completed | A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Baricitinib in Adult Patients With Moderate-to-Severe AD |
| BREEZE-AD1 (Eli Lilly and Company) | NCT0334396; I4V-MC-JAHL | III, per os | Completed | A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients With Moderate to Severe AD |
| BREEZE-AD2 (Eli Lilly and Company) | NCT03334422; I4V-MC-JAHM | III, per os | Completed | A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients With Moderate to Severe AD |
| BREEZE-AD3 (Eli Lilly and Company) | NCT03334435; I4V-MC-JAHN | III, per os | Active, not recruiting | A Phase 3 Multicenter, Double-Blind Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Adult Patients With Moderate to Severe AD |
| BREEZE-AD4 (Eli Lilly and Company) | NCT03428100; I4V-MC-JAIN | III, per os | Active, not recruiting | A Long-term Study of Baricitinib With Topical Corticosteroids in Adults With Moderate to Severe AD That Cannot Be Treated With Cyclosporine or for Those Who Cannot Tolerate Cyclosporine Because it is Not Medically Advisable |
| BREEZE-AD5 (Eli Lilly and Company) | NCT03435081; I4V-MC-JAIW | III, per os | Active, not recruiting | A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients With Moderate to Severe Atopic Dermatitis |
| BREEZE-AD6 (Eli Lilly and Company) | NCT03559270; I4V-MC-JAIX | III, per os | Enrolling by invitation | A Multicenter, Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients With Moderate to Severe AD |
| BREEZE-AD7 (Eli Lilly and Company) | NCT0373301; I4V-MC-JAIY | III, per os | Completed | A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Combination With Topical Corticosteroids in Adult Patients With Moderate to Severe AD |
| BREEZE-AD PEDS (Eli Lilly and Company) | NCT03952559; I4V-MC-JAIP | III, per os | Recruiting | A Phase 3, Multicenter, Randomized, controlled, Parallel-group, Outpatient Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Baricitinib in Pediatric Patients With Moderate to Severe AD |

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Table 3. Main outcomes of phase III trials. Summary of primary and key secondary endpoints at Week 16 (BREEZE-AD1, BREEZE-AD2).

| Study | BREEZE-AD1 | | | | | |
|---|------------------------|-------------------------|-------------------------|-------------------------|----------------|-------------------------|
| Duration | Dose ranging, 16 weeks | | | | | |
| Participants | PBO (n=249) | Bari 1 mg QD (n=127) | Bari 2 mg QD (n=123) | Bari 4 mg QD (n=125) | PBO (n=244) | Bari 1 mg QD (n=122) |
| Primary outcome (w16): | | | | | | |
| vIGA-AD 0-1 (with ≥2-point improvement from baseline) | 4.8% (12) | 11.8% (15)* | 11.4% (14)* | 16.8% (21)*** | 4.5% (11) | 8.8% (12) |
| Secondary outcomes (w16): | | | | | | |
| EASI75 | 8.8% (22) | 17.3% (22)* | 18.7% (23)** | 24.8% (31)*** | 6.1% (15) | 12.8% (16) |
| EASI90 | 4.8% (12) | 8.7% (11) | 10.6% (13)* | 16% (20)*** | 2.5% (6) | 6.4% (8) |
| EASI percentage change from baseline | -34.8 | -48.2* | -51.9** | -59.4*** | -28.9 | -41.5 |
| SCORAD75 | 1.2% (3) | 5.5% (7)* | 7.3% (9)** | 10.4% (13)*** | 1.6% (4) | 4.8% (6) |
| ≥4-point improvement in Itch NRS from baseline | 7.2% (16) | 10.5% (11) | 12% (12) | 21.5% (23)*** | 4.7% (10) | 6% (7) |
| Change from baseline in Skin pain NRS | -0.84 | -1.92** | -1.58 | -1.93** | -0.86 | -1.0 |
| Change from baseline in ADSS Item 2 | -0.84 | -1.21 | -1.04 | -1.42** | -0.50 | -0.7 |

ADSS, Atopic Dermatitis Sleep Scale; Bari: baricitinib; DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; n, number of subjects in the specified category; NRS, Numeric Rating Scale; PBO: placebo; SCORAD: SCORing Atopic dermatitis; vIGA-AD, Validated Investigator's Global Assessment of atopic dermatitis. *p: 0.05 **p: 0.01 ***p:0.001

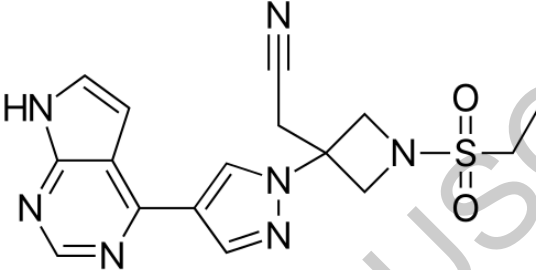
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Table 4. Summary of primary and key secondary endpoints at Week 16 (BREEZE-AD7).

| Study | BREEZE-AD7 | | |
|--|------------------------|-----------------|-----------------|
| Duration | Dose ranging, 16 weeks | | |
| | PBO + TCS | Bari 2 mg + TCS | Bari 4 mg + TCS |
| Participants | (n=109) | (n=109) | (n=111) |
| Proportion of TCS-free days | 17.4% | 25.3%* | 32.9%** |
| Primary outcome (w16) | | | |
| vIGA-AD 0-1 (with ≥ 2 -point improvement from baseline) | 14.7% | 23.9% | 30.6%** |
| Secondary outcomes (w16) | | | |
| EASI percentage change from baseline | -45.1 | -58.2* | -67.2 ** |
| EASI75 | 22.9% | 43.1%** | 47.7%** |
| Itch NRS percentage change from baseline | -27 | -43.4** | -51.2 ** |
| Itch NRS ≥ 4 -point improvement from baseline | 20.2% | 38.1%** | 44%** |
| Change from baseline in ADSS Item 2 | -0.51 | -1.33** | -1.42** |
| Skin pain change from baseline | -2.06 | -3.22 ** | -3.73** |
| Skin pain NRS ≥ 4 -point improvement from baseline | 25.5% | 45.2%** | 48.8%** |
| DLQI (0,1) response | 7.3% | 16.5%* | 23.4%** |
| POEM ≥ 4 -point improvement from baseline | 46.7% | 65.7%** | 70.6%** |

ADSS: Atopic Dermatitis Sleep Scale; Bari: baricitinib; DLQI, Dermatology Life Quality Index; EASI: Eczema Area Severity Index; n: number of subjects in the specified category; NRS: Numeric Rating Scale; PBO: placebo; SCORAD: SCORing Atopic dermatitis; TCS: Topical Corticosteroids; vIGA-AD, Validated Investigator's Global Assessment of atopic dermatitis. *p: 0.05 **p: 0.01 ***p:0.001

| Drug Summary Box | |
|--|--|
| Drug name | Baricitinib |
| Phase | Phase III |
| Indication | Moderate-to-severe atopic dermatitis |
| Pharmacology description/ Mechanism of action | Selective inhibitor of JAK1/JAK2 and subsequent blockade of JAK/STAT pathway |
| Route of administration | Oral tablet |
| Chemical structure | |
|  | |
| Pivotal trials | LY3009104; BREEZE-AD1; BREEZE-AD2; BREEZE-AD7 |