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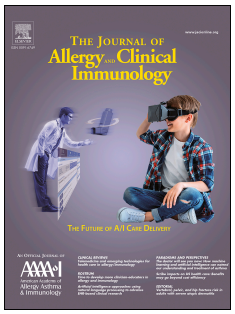

JAK Inhibitors in the Treatment of Atopic Dermatitis

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PII: S0091-6749(21)01298-7

DOI: https://doi.org/10.1016/j.jaci.2021.08.009

Reference: YMAI 15239

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 29 June 2021

Revised Date: 9 August 2021

Accepted Date: 18 August 2021

Please cite this article as: Chovatiya R, Paller AS, JAK Inhibitors in the Treatment of Atopic Dermatitis, *Journal of Allergy and Clinical Immunology* (2021), doi: https://doi.org/10.1016/j.jaci.2021.08.009.

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Title: JAK Inhibitors in the Treatment of Atopic Dermatitis

Short Title: JAK Inhibitors and Atopic Dermatitis

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Abstract word count: 200
Word count: 5,646
Figures: 1
Tables: 2
Supplemental Tables: 0

Key Words: atopic dermatitis; eczema; itch; therapy; JAK inhibitor

Abbreviations used: atopic dermatitis (AD); atopic dermatitis sleep scale (ADSS); adverse event (AE); antimicrobial peptide (AMP); twice-daily (BID; body surface area (BSA); creatine phosphokinase (CPK); deep vein thrombosis (DVT); dermatology life quality index (DLQI); eczema area and severity index (EASI); US food and drug administration (FDA); investigator's global assessment (IGA); interleukin (IL); janus kinase (JAK); long-term extension (LTE); numerical rating scale (NRS); open label (OL); patient oriented eczema measure (POEM); pruritus and symptoms assessment for AD (PSAAD); once-daily (QD); randomized double-blind vehicle- and active-controlled trial (RDBVACT); randomized double-blind vehicle-controlled trial (RDBVCT); randomized double-blind long-term extension (RDBLTE); randomized double-blind active-controlled trial (RDBACT); randomized double-blind placebo- and active-controlled trial (RDBPACT); randomized double-blind placebo-controlled trial (RDBPCT); scoring atopic dermatitis (SCORAD); spleen tyrosine kinase (SYK); topical corticosteroids (TCS); topical calcineurin inhibitors (TCI); tyrosine kinase (TYK); upper respiratory tract infection (URTI);

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Acquisition of Data: R Chovatiya, AS Paller
Analysis and interpretation of data: R Chovatiya, AS Paller
Drafting of the manuscript: R Chovatiya, AS Paller
Critical revision of the manuscript for important intellectual content: R Chovatiya, AS Paller
Statistical analysis: R Chovatiya, AS Paller
Obtained funding: none
Administrative technical or material support: none
Study supervision: none
Financial disclosures: none
Funding Support: none
Design and conduct of the study? n/a
Collection, management, analysis and interpretation of data? n/a
Preparation, review, or approval of the manuscript? n/a
Decision to submit the manuscript for publication? n/a
Conflicts of interest: Raj Chovatiya reports personal fees from Abbvie, Incyte, Regeneron, and Sanofi-Genzyme. Amy S. Paller reports personal fees from AbbVie, Arena, Bausch, Bristol Myer Squibb, Dermavant, Eli Lilly, Forte, Leo, Lifemax, Novartis, Pfizer, RAPT, Regeneron, and Sanofi. She is an investigator (funding to institution) for AbbVie, Anaptysbio, Eli Lilly, Incyte, Janssen, Regeneron, and UCB.

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Abstract

Atopic dermatitis is a chronic inflammatory skin disorder associated with heterogenous presentation and often immense patient burden. Safe, targeted treatment options are currently limited. We conducted a focused review of the published literature, including clinical trial results, case reports, and abstracts, as well as presentations from scientific meetings and data from industry press releases, to describe the use of topical and systemic janus kinase (JAK) inhibitors (JAKi) in the treatment AD. New topical JAKi include ruxolitinib (JAK1/2) and delgocitinib (pan-JAK). Ruxolitinib cream met all primary and secondary endpoints in phase 3 clinical trials for mild-to-moderate AD with minimal treatment-emergent adverse events (TEAEs). Delgocitinib ointment was recently approved in Japan for pediatric and adult AD. Oral JAKi include baricitinib (JAK1/2), abrocitinib (JAK1-selective), and upadacitinib (JAK1-selective). All three met primary and secondary endpoints across numerous trials for moderate-to-severe AD. TEAEs were mainly mild-to-moderate and included acne, nausea, headache, upper respiratory tract infection, and to a lesser degree, herpes infection and selected laboratory abnormalities. JAKi hold great promise as the next generation of targeted AD therapy. While their outstanding efficacy is balanced by a favorable safety profile in clinical trials, real-world data are needed to better understand long-term safety, durability, and treatment success.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that affects 7% of adults and 13% of children in the US.[1-4] AD is characterized by clinical signs of redness, swelling, excoriation, lichenification, xerosis and, especially in infants and with acute flares, oozing/weeping.[5] Pruritus (itch) is a cardinal symptom, often associated with skin-pain and sleep disturbance,[6, 7] and comorbid health conditions, including both atopic (e.g., asthma, allergic rhinoconjunctivitis, asthma) and non-atopic (e.g., anxiety/depression, cutaneous and non-cutaneous infections, cardio-metabolic disease) disorders,[8-10] are frequently observed. These factors contribute to physical and psychosocial patient-burden and impaired quality of life (QoL).[3, 11, 12] Variable disease course (e.g., chronic, intermittent, persistent) and severity further increase the complexity of AD and make it a challenging condition to manage. In this review we summarize pathogenesis, current treatments, and discuss the newest topical and oral JAK inhibitors as cutting-edge therapy for AD.

Pathogenesis

AD pathogenesis is multifactorial and driven by an interplay of epidermal barrier dysfunction and immune dysregulation in the context of host genetics and environmental factors.[13-15] In AD, the protein and lipid barrier of the outermost layers of the epidermis is impaired, primarily reflecting decreased expression of proteins of epidermal differentiation (e.g., filaggrin) and the tight junctions (the primary barrier against transepidermal water loss; e.g., claudins), as well as decreased concentration of very long-chain fatty acids and ceramides. The dysfunctional barrier results in increased susceptibility to external insults, such as microbes and pro-inflammatory allergens, toxins, and irritants.[14] In adults, reduced antimicrobial peptide

(AMP) production in response to triggers impairs the normal defense response to environmental pathogens, and the reduction in T helper type 1 (Th1) cytokines may blunt the antimicrobial response in affected children.[16-18]

Antigen-presenting cells take up immunogenic antigens for presentation to primarily CD4+ T cells, and keratinocytes directly release chemokines including CCL17 (TARC) and cytokines such as thymic stromal lymphoprotein (TSLP), interleukin-1β, IL-25, and IL-33. This inflammatory milieu results in an immune response predominantly skewed towards Th2 cells, leading to increased quantities of signature Th2 cytokines such as IL-4, IL-5, IL-13, and IL-31.[19, 20]. Th2 cytokines, especially IL-4 and IL-13, contribute to additional Th2 cell polarization, promote IgE class-switching and eosinophil recruitment (both of which have an unclear relationship to AD pathogenesis), and further impair epidermal barrier function by inhibiting epidermal differentiation, lipid production, and AMP expression. While Th2 skewing is universal among AD patients, activation of other T helper cell driven pathways (i.e., Th1 in adults, Th17 in children and Asians) is more heterogenous and may be related to other patient factors, including age and race.[21] Many of the same exogenous (e.g., allergens, irritants, pathogens) and endogenous (e.g., cytokines, neuropeptides, lipids) signals act as pruritogens and directly signal and/or modulate the sensation of itch by activating receptors on sensory neurons of the dorsal root ganglion. Activation of cytokine receptors (e.g., IL-4, IL-13, IL-31, IL-33, TSLP), G-protein coupled receptors, and transient receptor potential channels results in action potentials, which both propagate sensory information to central nervous system and stimulate local production of inflammatory mediators, such as calcitonin gene related peptide and substance P.[22]

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins binds to the intracellular portion of type I/II cytokine receptors that are responsible for

recognizing soluble inflammatory mediators such as interleukins and interferons.[23] Upon binding of an extracellular ligand to the cytokine receptor, JAK proteins become activated and phosphorylate STAT proteins, which in turn dimerize and translocate to the nucleus (**Figure 1**). There they activate downstream gene transcription. There are four members of the JAK family (JAK1, JAK2, JAK3, and TYK2) and an additional seven members of the STAT family that selectively associate with different cytokine receptors in various combinations.[24] The JAK-STAT signaling pathway is integral to mediating the effect of several key cytokines that bind to immune cells, keratinocytes, and peripheral sensory neurons to propagate inflammation and itch, including IL-4, IL-5, IL-13, IL-31, IL-22, and TSLP (**Figure 2**).[25]

Current Treatments

Current guidelines for AD treatment are based on a step-up approach to therapy, which emphasizes basic skin care (i.e., optimized bathing, moisturization, and itch-trigger avoidance) as the foundation of treatment.[26] For mild-to-moderate AD, prescription topical anti-inflammatory treatment with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) remains the mainstay of management.[27, 28] Crisaborole 2% ointment, a first-in-class topical phosphodiesterase 4 (PDE4) inhibitor, was approved in May 2016 for the treatment of mild-to-moderate AD in patents ≥2 years old with its indication extended to children as young as 3 months in March 2020.[29] However, safety concerns for TCS include theoretical risk of systemic absorption, especially for potent and ultrapotent agents, and thinning and atrophy at areas of sensitive skin. These issues are unusual, especially with appropriate use of TCS, but steroid phobia among patients and caregivers limits adherence. TCI are associated with a high rate of application site symptoms (i.e., stinging, burning),[30] have limited potency compared to TCS

stronger than medium strength, and have a Boxed Warning from the US Food and Drug Administration (FDA) for theoretical malignancy risk, despite long-term data to the contrary.[31] Despite a positive safety profile for crisaborole, limited efficacy[32, 33] and a high frequency of local application site reactions[34] have been problematic, and the need for additional targeted topical agents continues.

For patients with moderate-to-severe AD, which includes 40% of adults and 33% of children in the US,[2, 11] current guidelines recommend the initiation of advanced systemic therapy, which historically included phototherapy and oral immunosuppressants.[26, 35] Despite proven efficacy, phototherapy can be poorly tolerated, infeasible, or simply too cumbersome for routine use. Systemic corticosteroids are the only FDA-approved oral immunosuppressant for moderate-to-severe AD. While systemic corticosteroids may rarely be considered as transitional therapy for severe, acutely flaring AD, their routine use is discouraged, given risk of rebound flares, disease worsening upon discontinuation, and systemic side effects associated with chronic use.[35] Non-corticosteroid immunosuppressive agents, including cyclosporine, methotrexate, mycophenolate, and azathioprine, have been used off-label to treat AD for decades. However, variable efficacy, along with safety risks, systemic immunosuppression, and frequent laboratory monitoring, have limited their use.[35]

After years without safe, targeted systemic treatments for AD, newer, state-of-the-art agents are transforming AD therapy. Dupilumab, a first-in-class, fully humanized, monoclonal antibody biologic therapy that binds to IL-4 receptor alpha (IL-4Rα) and blocks IL-4 and IL-13 signaling, was approved by the FDA in March 2017 for moderate-to-severe AD in adults ≥18 years – the first non-corticosteroid to obtain this indication.[36] Dupilumab was subsequently FDA-approved for moderate-to-severe AD in adolescents ≥12 years old (March 2019) and

children ≥6 years old (May 2020), with additional indications for moderate-to-severe asthma and chronic rhinosinusitis with nasal polyposis. Dupilumab has shown excellent efficacy in multiple clinical trials and age groups, along with a favorable safety profile (consisting mainly of injection-site reactions and mild-to-moderate, reversible conjunctivitis), obviating the need for routine laboratory monitoring.[37-40] However, lesional clearance and itch reduction are neither uniform nor absolute across patients. Furthermore, subcutaneous injection may not be the preferred or most appropriate method for therapy in every patient. Additional systemic treatment options are needed for moderate-to-severe AD.

The therapeutic potential of JAK inhibition was first realized in studies of autoimmune and autoinflammatory diseases with JAK-STAT polymorphisms and/or heightened JAK-STAT signaling.[23, 24, 41]. More recently, JAK inhibition has been hypothesized as a novel treatment for AD, given the importance of JAK-STAT signaling (particularly JAK1) for Th2 cytokines, including IL-4, IL-13, and IL-31.[42] Experimental models have shown improved skin barrier function, suppression of pruritus, cutaneous nerve elongation, and impaired IL-4 and IL-13 dependent differentiation of Th2 cells in response to JAK inhibitors.[25, 43-45] While only four JAK inhibitors are currently FDA-approved (tofacitinib, ruxolitinib, baricitinib, upadacitinib), none are currently approved for AD. However, this therapeutic class is poised to expand both in number and indication following a recent revolution in the development of topical and oral JAK inhibitors. Herein, we discuss novel agents that are most advanced in development, with a summary of pivotal clinical trial data (**Table 1** and **Table 2)**.

Topical JAK Inhibitors

Tofacitinib

Tofacitinib (TOFA) is a first-generation, small molecule inhibitor of JAK1/3. It was first FDA-approved at 5 mg twice daily (BID) oral dosing in November 2012 for treating adults with moderate-to-severe rheumatoid arthritis (RA) inadequately responding or intolerant of methotrexate.[46] TOFA has since been approved for psoriatic arthritis, ulcerative colitis, and juvenile idiopathic arthritis. TOFA showed reasonable efficacy for moderate-to-severe AD, with improvements in clinician-assessed severity and patient-reported outcome (PRO) measures of itch and sleep and no adverse events (AEs) in a case series[47] and case reports.[48-50] However, data showing increased risk of serious AEs (SAEs), including venous thromboembolic events (VTEs), major adverse cardiac adverse events (MACEs), serious infections, malignancies, and death, in RA patients treated with TOFA has resulted in Boxed Warnings[46] and likely curtailed future clinical trials evaluating oral tofacitinib in AD patients.

Topical TOFA has since been evaluated for mild-to-moderate AD. In a 4-week, phase 2a randomized double-blinded vehicle-controlled trial (RDBVCT) in adults age 18-60, TOFA 2% ointment BID vs. vehicle met the primary endpoint of percentage change from baseline Eczema Area and Severity Index (%EASI) at week 4 (TOFA 2% ointment vs. vehicle: 81.7% vs. 29.9%).[51] TOFA 2% ointment also met several secondary endpoints including significant proportion of patients achieving Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement (IGA 0/1) and percentage change from baseline IGA (%IGA), body surface area (%BSA), and numerical rating scale of itch (%itch-NRS – detected as early as day 2). Infection, primarily nasopharyngitis and upper respiratory tract infection (URTI), was the most common treatment-emergent adverse event (TEAE) by system organ class and was

more prevalent with tofacitinib (17% vs. 9%). While topical tofacitinib is not advancing commercially, other topical JAK inhibitors are in various phases of development.

Ruxolitinib

Ruxolitinib (RUX), a first-generation small molecule inhibitor of JAK1/2, was initially FDA-approved in November 2011 for treating myelofibrosis and has since received additional indications for polycythemia vera and acute graft-versus-host disease.[52] While oral RUX is not being investigated for AD, a topical formulation has promise for mild-to-moderate AD. In a dose-ranging, randomized, 8-week, phase 2b, double-blind, vehicle- and active-controlled trial (RDBVACT), adults age ≥18 years treated with RUX 1.5% cream BID vs. vehicle achieved the primary endpoint of %EASI (RUX 1.5% cream vs. vehicle: 71.6% vs. 15.5%).[53] All other concentrations of RUX showed statistically significant %EASI at all timepoints, and RUX 1.5% cream BID showed numerically higher %EASI vs. triamcinolone 0.1% cream. RUX 1.5% cream BID achieved several key secondary endpoints at week 4 (percentage achieving ≥50%, ≥75%, and ≥90% improvement in baseline EASI [EASI-50, EASI-75, EASI-90, respectively], IGA 0/1, and %itch-NRS). Minimal clinically important difference in itch, defined as itch-NRS reduction ≥2 points from baseline (itch-NRS2), was seen by 36 hours (42.5% vs. 13.6%) and reached near-maximal level by week 4.[54] Improvement in itch was also associated with improved quality-of-life (QoL) at week 2. After the four-week treatment period, all patients were transitioned to four weeks of open label (OL) treatment with RUX 1.5% cream BID, and each group showed additional improvement in skin clearance. RUX was well tolerated and associated with a low frequency of TEAEs (most often nasopharyngitis, URTI, AD, and headache) comparable to vehicle in the double-blind period (24.0% vs. 32.7%).

In two parallel, 8-week, phase-3 RDBVCTs (TRuE-AD1, TRuE-AD2) comparing RUX 1.5% vs. 0.75% cream BID vs. vehicle in adolescents and adults age ≥12 years with mild-to-moderate AD, both formulations met the primary endpoint of IGA 0/1 (TRuE-AD1, RUX 1.5% vs. 0.75% cream vs. vehicle: 53.8% vs. 50.0% vs. 15.1%; TRuE-AD2: 51.3% vs. 39.0% vs. 7.6%), as well as key secondary endpoints of EASI-75 (62.1% vs. 56.0% vs. 24.6%; 61.8% vs. 51.5% vs. 14.4%) and clinically meaningful reduction in itch, defined as itch-NRS reduction ≥4 points (itch-NRS4) (52.2% vs. 40.4% vs. 15.4%; 50.7% vs. 42.7% vs. 16.3%) at week 8.[55] RUX treatment was associated with improvement in itch and skin-pain within 12 hours of application,[56] number of itch-free days,[56] Dermatology Life Quality Index (DLQI),[57] Patient-Reported Outcomes Measurement Information System (PROMIS) sleep measures,[58, 59] and daily activity and work productivity.[60] The overall frequency of TEAEs at either dose of RUX was comparable to vehicle across both trials (26.3% vs. 29.4% vs. 33.6%) with no SAEs reported. As in the phase 2b trial, application site reactions were infrequent and similar to vehicle. No AEs consistent with systemic activity of RUX were detected in short-term and 44-week safety analyses.[55] The New Drug Application (NDA) for topical RUX was accepted for Priority Review by the FDA in early 2021.

Delgocitinib

Delgocitinib (DELGO), a JAK1/2/3 and Tyk2 (i.e., pan-JAK) inhibitor, is the world's first approved topical JAK inhibitor. DELGO 0.5% ointment has been studied in Japan, where it was approved for treating AD in adults (January 2020) and children (March 2021, along with a 0.25% ointment).[61, 62] In a 4-week, dose-ranging, phase 2 RDBVACT, participants age ≥ 16 years with moderate-to-severe AD treated with DELGO ointment BID met the primary endpoint

of percentage change from baseline modified EASI (%mEASI) (DELGO 3% vs. 1% vs. 0.5% vs. 0.25% ointment vs. vehicle: 72.9% vs. 54.9% vs. 57.1% vs. 41.7% vs. 12.2%). Clinical improvement was similar to that seen with tacrolimus 0.1% ointment (62.0%).[63] DELGO 3%, 1% and 0.5% vs. vehicle met several secondary endpoints at week 4, including %IGA, %BSA, and %itch-NRS. Significant change in itch-NRS was seen by day 1. AEs among all patients treated with DELGO were similar to vehicle (19.2% vs. 16.0%), but overall lower than the tacrolimus group (43%). Among patients treated with DELGO, nasopharyngitis (3.4%) was the only TEAE with frequency ≥2%; furuncle, eczema herpeticum, and acne each occurred in 1.1% of the treatment group. In a 4-week, pediatric, phase 2 RDBVCT, children and adolescents ages 2-15 with AD treated with DELGO BID vs. vehicle also met the primary %mEASI endpoint (DELGO 0.5% vs. 0.25% ointment vs. vehicle: 61.8% vs. 54.2% vs. 4.8%), as well as secondary endpoints of lesional severity and itch.[64] The most common AEs in this group were nasopharyngitis, impetigo, and urticaria.

In a 4-week phase 3 RDBVCT, subjects age ≥16 years with moderate-to-severe AD treated with DELGO 0.5% ointment BID met the primary %mEASI endpoint (DELGO 0.5% ointment vs. vehicle: 44.3% vs. 1.7%), along with secondary mEASI-50 (51.9% vs. 11.5%) and mEASI-75 (26.4% vs. 5.8%) endpoints.[65] Both daytime and nighttime itch showed significant reduction after day 1 and steadily improved over 4 weeks (%itch-NRS: 28% vs. no improvement). After week 4, all patients received DELGO 0.5% for an additional 24 weeks in the second part of the phase 3 study and showed additional lesional improvement (%mEASI [56.3%], mEASI-50 [69.3%], mEASI-75 [35.8%]). The overall rate of TEAEs in the DELGO group was 15.4%, with only eczema herpeticum (1.9%) occurring in ≥1% of patients. In pooled safety data (including an additional 52-week phase 3 OL study), 15.4% of subjects had

treatment-related AEs,[66] most commonly folliculitis (2.4%) and acne (2.2%). Similar long-term efficacy and safety data were recently reported for pediatric patients.[67] Recent data from phase 2a and 2b RDBVCTs suggest that DELGO may be an option for treating chronic hand eczema.[68, 69]

Other Topical Therapies in Development

Brepocitinib (BREPO), a JAK1 / Tyk2 inhibitor, is under investigation for topical and oral therapy, including of AD. In a dose-ranging, 6-week phase 2b RDBVCT in adults and adolescents ages 12-75 with mild-to-moderate AD, BREPO 1% cream BID vs. vehicle met the primary endpoint of %EASI (75.0% vs. 47.6%), as did BREPO 3%, 1%, and 0.3% once daily (QD).[70] Key secondary endpoints met included EASI-75, IGA 0/1, and itch-NRS4. The rate of AEs was lower in BREPO treatment groups vs. vehicle.

ATI-502 Topical Solution, a JAK1/3 inhibitor, was well-tolerated in a 4-week, phase 2a OL study, with primary safety outcomes met. Improvements in EASI, IGA, and itch-NRS were also seen.[71]

Oral JAK Inhibitors

Baricitinib

Baricitinib (BARI), a first-generation oral JAK1/2 selective inhibitor, was FDA-approved in June 2018 at 2 mg QD for adult moderate-to-severe rheumatoid arthritis inadequately responsive to TNFα inhibitors.[72] Despite higher efficacy, 4mg QD dosing was not approved, given concern for severe AEs, including deep vein thrombosis (DVT) and pulmonary embolism

(PE). BARI was recently approved in Europe (October 2020) and Japan (December 2020) for moderate-to-severe AD in adults at both 4 and 2 mg QD.

In a 16-week phase 2b RDBPCT requiring 4 weeks of TCS prior to randomization and allowing for concurrent TCS use, significantly more adults age ≥18 years who received BARI 4 mg vs. placebo achieved EASI-50 (primary endpoint), with numerically higher EASI-50 at the 2 mg dose (BARI 4 vs. 2 mg vs. placebo: 61% vs. 57% vs. 37%).[73] EASI-50 was reached at week 4 at both BARI doses, and improvements in secondary endpoints of itch, sleep, and QoL were observed throughout the treatment period. TEAEs included increased blood CPK and nasopharyngitis.

In two parallel, non-U.S-based, 16-week phase 3 RDBPCTs (BREEZE-AD1, BREEZE-AD-2) comparing BARI monotherapy vs. placebo in adults age ≥18 years with moderate-to-severe AD, the primary endpoint of Validated Investigator's Global Assessment for AD (vIGA-AD)[74] score of 0 (clear) or 1 (almost clear) (vIGA-AD 0/1) was met by BARI 4 mg and 2 mg in both BREEZE-AD1 (BARI 4 vs. 2 vs. 1 mg vs. placebo: 16.8% vs. 11.4% vs. 11.8% vs. 4.8%) and BREEZE-AD2 (13.8% vs. 10.6% vs. 8.8% vs. 4.5%).[75] Across both trials, BARI 4 mg consistently met key secondary endpoints. While BARI 2 mg met most key secondary endpoints, response to BARI 1 mg was inconsistent. TEAE frequency was similar and did not show dose-dependence. Increased blood CPK and headache (mild, <1-day median duration) were most common, and neither nasopharyngitis nor URTI were increased in BARI vs. placebo. Herpes simplex was more frequent with BARI in BREEZE-AD1 (7.2% vs. 3.3% vs. 5.5% vs. 1.2%), but not BREEZE-AD2. There were no deaths, opportunistic infections, malignancies, VTEs or MACEs in any BARI group. After completing 16-week treatment, adults taking BARI 4 or 2 mg who were responders (vIGA-AD 0/1) or partial responders (vIGA-AD 2 [mild]) enrolled in an

ongoing phase 3 double-blind long-term extension (LTE) study evaluating efficacy and safety (BREEZE-AD3).[76] Patients maintained the same dose and could use TCS, and vIGA-AD 0/1 response was sustained at 68 weeks of treatment (BARI 4 mg: 45.7% vs. 40.0%; 2 mg: 46.3% vs. 50.0%) with no new safety findings.

In the North America-based, 16-week phase 3 RDBPCT (BREEZE-AD5) comparing BARI monotherapy vs. placebo in adults age ≥18 years with moderate-to-severe AD[77], the primary endpoint (EASI-75 at week 16) was achieved only with the 2 mg dose (BARI 2 vs. 1 mg vs. placebo: 29.5% vs. 12.9% vs. 8.2%). BARI 2 mg met nearly all secondary endpoints throughout the treatment period, including week 16 vIGA-AD 0/1 (24.0% vs. 12.9% vs. 5.4%) itch-NRS4 (25.2% vs. 12.9% vs. 5.7%), while the response to BARI 1 mg was more pronounced at earlier timepoints.[78] The most common TEAEs were URTI, nasopharyngitis, diarrhea, and nausea. Herpes simplex was infrequent but more common with BARI (1.4% vs. 2.0% vs. 0.7%).

The efficacy and safety of BARI with combination topical therapy was first examined in a 16-week, phase 3 RDBPCT (BREEZE-AD4) comparing BARI (4, 2, and 1 mg) + TCS vs. placebo in adults age ≥18 years with moderate-to-severe AD who failed treatment with or had a contraindication or intolerance to cyclosporine.[79] Only BARI 4 mg met the primary endpoint of EASI-75 at week 16 (BARI 4 vs. 2 vs. 1 mg vs. placebo: 31.5% vs. 27.6% vs. 22.6% vs. 17.2%), though all BARI groups met the secondary itch-NRS4 endpoint (38.2% vs. 22.9% vs. 23.1% vs. 8.2%).

BARI+TCS was assessed in another 16-week phase 3 RDBPCT (BREEZE-AD7) in adults ≥ 18 years with moderate-to-severe AD.[80] The primary endpoint of week 16 vIGA-AD 0/1 was again only achieved with BARI 4 mg (BARI 4 vs. 2 mg vs. placebo: 31% vs. 24% vs. 15%), as were key secondary endpoints EASI-75 and itch-NRS4. Both doses of BARI were associated

with improvement in PROs at multiple timepoints, including DLQI and PROMIS Itch Questionnaire.[81] More TEAEs were seen with BARI treatment, particularly related to infection (33% vs. 38% vs. 24%), and included nasopharyngitis, URTI, folliculitis, herpes infection, acne, back pain, diarrhea, and increased blood CPK. Pulmonary embolism occurred once with BARI 4 mg, but severe AEs were otherwise uncommon.

In a pooled safety analysis of eight BARI trials, including six RDBPCTs and two LTE studies, the overall rate of any TEAE in the placebo-controlled period was higher with BARI treatment.[82] Mild-to-moderate treatment-emergent infections were most common (primarily herpes simplex)[83], and decreased in incidence over the extended period. The adjusted incidence rate per 100 patient-years for serious infections was 3.0 and 1.5 for BARI 4 mg and 2 mg respectively, with eczema herpeticum, cellulitis, and pneumonia most commonly reported. One myocardial infarction (in a patient with pre-existing conditions) and one hemorrhagic stroke occurred in the BARI 2 mg group during the extended period. During the placebo-controlled period there was one reported VTE (BARI 4 mg: pulmonary embolism in a patient with smoking history and oral contraceptive use); in the extended period there was one VTE in each BARI group (4 mg: pulmonary embolism; 2 mg: below knee deep-vein thrombosis). Common laboratory abnormalities included increased blood CPK (grade 1) and elevated lipids (HDL>LD), minimal changes in hematologic, hepatic, and renal parameters. Malignancies were absent, and there was only one death (BARI 4 mg: gastrointestinal bleed, extended period). An additional extended pooled safety analysis of BARI 2 mg confirmed these findings.[84]

A supplemental NDA (sNDA) for BARI (4 or 2 mg QD) as treatment for adults with moderate-to-severe AD was submitted to the FDA in mid-2020.

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Upadacitinib

Upadacitinib (UPA) is a JAK1-selective inhibitor that was first FDA-approved in August 2019 for treatment of adult patients with moderate-to-severe rheumatoid arthritis (15 mg QD) with inadequate response to methotrexate. In a dose-ranging, 16-week phase 2b RDBPCT, all doses of UPA met the primary endpoint (EASI-75, 30 vs. 15 vs. 7.5 mg vs. placebo: 74% vs. 62% vs. 39% vs. 23%).[85] Key secondary endpoints met by all UPA groups included EASI-90, IGA 0/1, and itch-NRS4. Common AEs included URTI, acne, and worsening AD (≥10% in any group), followed by headache, increased blood CPK, nasopharyngitis, and nausea (≥5% in any group).

In two replicate, 16-week, phase 3 RDBPCTs (Measure Up 1, Measure Up 2) comparing UPA monotherapy vs. placebo in adolescents and adults ages 12-75 with moderate-to-severe AD, both UPA groups achieved the week 16 co-primary endpoints in both Measure Up 1 (UPA 30 vs. 15 mg vs. placebo; EASI-75: 79.9% vs. 69.6% vs. 16.3%; vIGA-AD 0/1: 62.0% vs. 48.1% vs. 8.4%) and Measure Up 2 (EASI-75: 72.9% vs. 60.1% vs. 13.3%; vIGA-AD 0/1:52.0% vs. 38.8% vs. 4.7%).[86] Both studies met all ranked secondary endpoints at week 16 with both UPA doses, including EASI-90 (65.8% vs. 53.1% vs. 8.1%; 58.5% vs. 42.4% vs. 5.4%) and worst itch-NRS4 (60.0% vs. 52.2% vs. 11.8%; 59.6% vs. 41.9% vs. 9.1%). The overall rate of TEAEs (73.3% vs. 62.6% vs. 59.1%; 61.3% vs. 60.1% vs. 52.5%) was similar across both trials, and the most common were acne (17.2% vs. 6.8% vs. 2.1%; 14.5% vs. 12.7% vs. 2.2%), URTI, nasopharyngitis, headache, and increased blood CPK. Low rates of herpes zoster (1-2%) were seen with UPA treatment. There were no opportunistic infections, VTEs, MACEs, or deaths.

A third, 16-week phase 3 RDBPCT (AD Up) examined the safety and efficacy of UPA+TCS among subjects ages 12-75 with moderate-to-severe AD. Both doses of UPA

achieved the co-primary endpoints of EASI-75 and vIGA-AD 0/1 at week 16 (UPA 30 vs. 15 mg vs. placebo; EASI-75: 77.1% vs. 64.6% vs. 26.4%; vIGA-AD 0/1: 58.6% vs. 39.6% vs. 10.9%).[87] Response rates across all key secondary endpoints were also significantly higher for both doses, including EASI-75/-90/-100 and worst itch-NRS4, The rapidity of response was notable, with significant differences observed at week 2 for skin clearance (EASI-75: 44.1% vs. 31.0% vs. 6.9%) and week 1 for itch (worst itch-NRS4: 19.2% vs. 12.2% vs. 3.1%). No new safety signals were seen. While rates of herpes zoster were similar across groups (1.7% vs. 1.0% vs. 1.0%), eczema herpeticum, although infrequent, only occurred with UPA treatment (1.3% vs. 1.0% vs. 0%).

More recently, in a 24-week phase 3b RDBACT (Heads Up) comparing UPA 30 mg once-daily oral monotherapy to dupilumab (DUPI) 300 mg subcutaneous injection (with 600 mg initial loading dose) in adults ages 18-75 with moderate-to-severe AD, UPA achieved head-to-head superiority over dupilumab.[88] A significantly higher proportion of UPA-treated patients achieved the week 16 EASI-75 primary endpoint (UPA 30 mg vs. DUPI: 71% vs. 61%) and all ranked secondary endpoints, including EASI-100 (28% vs. 8%) and worst itch-NRS4 at week 16, EASI-75 (44% vs. 18%) at week 2, and %worst itch-NRS at week 1 (31% vs. 9%). The safety profile of UPA was consistent with the previous phase 3 studies. One treatment-emergent death occurred in the UPA group (influenza-associated bronchopneumonia).

An adult phase 3b OL LTE (NCT04195698) and pediatric phase 1 pharmacokinetic and safety study (NCT03646604) are currently ongoing. A sNDA for UPA for adults (30 and 15 mg QD) and adolescents (15 mg QD) with moderate-to-severe AD was submitted to the FDA in late 2020.

Abrocitinib

Abrocitinib (ABRO) is an oral, once-daily JAK1-selective inhibitor. In a dose-ranging, 12-week, phase 2b RDBPCT, adults ages 18-75 with moderate-to-severe AD treated with ABRO 200 or 100 mg achieved the week 12 IGA 0/1 primary endpoint (ABRO 200 vs. 100 mg vs. placebo: 43.8% vs. 29.6% vs. 5.8%).[89] The key secondary endpoint (%EASI) plateaued between weeks 4-6 and was maintained through week 12 (82.6% vs. 59.0% vs. 35.2%). In the ABRO 200 and 100 mg groups, itch-NRS4 responses were achieved by day 2 and 5, respectively, reached maximal levels as early as week 2, and were maintained throughout the treatment course.[90] Significant improvement in several PRO measures was also achieved, including DLQI at week 1 and Pruritus and Symptoms Assessment for AD (PSAAD) at week 2. The most common AEs in any group were AD, URTI, headache, nausea, and diarrhea. In comparison across phase 2b trials, nausea was more commonly observed with ABRO (ABRO 200 mg vs. UPA 30 mg: 14.5% vs. 7.1%) while acne was only seen with UPA (not reported vs. 14.0%).[85] Two cases each of herpes zoster (ABRO 30 mg and 10 mg) and herpes simplex (100 mg and placebo) were reported, and only two patients experienced treatment-related severe AEs: pneumonia (200 mg) and eczema herpeticum (100 mg). Decreases in platelet count were noted during ABRO 200 and 100 mg treatment but values trended back towards baseline by week 12.

In two parallel, 12-week, monotherapy phase 3 RDBPCTs (JADE MONO-1, JADE MONO-2), in subjects ≥12 years with moderate-to-severe AD, both ABRO 200 mg and 100 mg met the co-primary endpoints at week 12: IGA 0/1 (JADE MONO-1, ABRO 200 vs. 100 mg vs. placebo: 44% vs. 24% vs. 8%; JADE MONO-2: 38% vs. 28% vs. 9%) and EASI-75 (63% vs. 40% vs. 12%; 61% vs. 45% vs. 10%).[91, 92] Both multiplicity-controlled key secondary endpoints were met (%PSAAD and proportion of patients achieving ≥4-point improvement from baseline

peak pruritus-NRS [PP-NRS4]).[93] PP-NRS4 increased from week 2 to maximal levels at week 12 (57% vs. 38% vs. 15% ;55% vs. 45% vs. 12%), and the PP-NRS score showed significant percentage reduction from baseline (%PP-NRS) within 24 hours of the first ABRO dose. ABRO-treated subjects also reported reduction in work time missed, impairment at work, and overall indirect annual costs.[94] The frequency of TEAEs (78% vs. 69% vs. 57%; 66% vs. 63% vs. 42%) was highest with ABRO 200 mg. In JADE MONO-1, the most commonly reported TEAEs were nausea (20% vs. 9% vs. 3%), nasopharyngitis, and headache. Low rates of conjunctivitis and herpes infections (primarily herpes simplex and oral herpes) were observed only with ABRO treatment. As in the phase 2b trial, dose-dependent decrease in platelet count peaked at four weeks and returned towards baseline over the treatment period. Similar findings were observed in JADE MONO-2, along with other dose-dependent TEAEs (acne, vomiting, upper abdominal pain) and mild laboratory abnormalities (elevated HDL, LDL, blood CPK). The frequency of acne in JADE MONO-2 at the highest dose of ABRO (5.8%) was lower than that seen with the highest doses of UPA monotherapy in Measure Up 1 and 2 (17.2% and 14.5%, respectively).[86] No VTEs or deaths occurred.

Patients completing 16 weeks of therapy in JADE MONO-1 or JADE MONO-2 were enrolled in an ongoing phase 3 randomized double-blind LTE (JADE EXTEND), consisting of 92 weeks of treatment (± topical medications) with ABRO 200 or 100 mg and then treatment with open-label ABRO (NCT03422822). Primary outcome measures included TEAEs, laboratory values, and other safety measures. In preliminary analysis at 48 weeks (12-weeks of preceding therapy + 36-week extension), patients who originally started and were maintained on ABRO 200 or 100 mg daily treatment without topical medications showed a similar rate of TEAEs (ABRO 200 vs. 100 mg: 86.1% vs. 80.7%).[95] Nearly all were mild-to-moderate. The

proportion of patients achieving IGA 0/1, EASI-75, and PP-NRS4 increased during the extension period, peaking between 24 to 36 weeks and remaining stable thereafter

In a 16-week, phase 3 randomized double-blind placebo- and active-controlled trial (RDBPACT) in adults ages ≥18 years with moderate-to-severe AD (JADE COMPARE) comparing ABRO vs. DUPI 300 mg subcutaneous injection every other week (with 600 mg loading dose) vs. placebo with concurrent use of topicals, both ABRO doses met the week 12 primary endpoint vs. placebo: IGA 0/1 (ABRO 200 vs. 100 mg vs. dupilumab vs. placebo: 48.4% vs. 36.6% vs. 36.5% vs. 14.0%) and EASI-75 (70.3% vs. 58.7% vs. 58.1% vs. 27.1%).[96] Key secondary endpoints included week 2 PP-NRS4 (49.1% vs. 31.8% vs. 26.4% vs. 13.8%), with significance met by ABRO vs. placebo and only ABRO 200 mg vs. DUPI, as well as week 16 IGA 0/1 and EASI-75, met only by ABRO vs. placebo. ABRO also improved EASI head-and-neck subscores faster and more efficaciously and either DUPI or placebo.[97] Six TEAEs were reported at a frequency ≥5% in any treatment group – nausea and acne (higher with ABRO), conjunctivitis (higher with DUPI), and nasopharyngitis, URTI, and headache (similar across groups). Laboratory abnormalities were consistent with the JADE MONO trials. Herpes zoster (1.8% vs. 0.8% vs. 0% vs. 0%) was only seen in the ABRO group, and 2 cases of eczema herpeticum occurred (ABRO 100 mg, placebo). Patients completing JADE COMPARE were also given the opportunity to enroll in the JADE EXTEND. Among those who achieved response (IGA 0/1, EASI-75, or PP-NRS4) with DUPI at the conclusion of JADE COMPARE, efficacy response was maintained in ≥90% at either ABRO dose at week 12 with no new safety signals.[98] Among DUPI non-responders from JADE COMPARE, a substantial proportion were able to obtain ABRO response with either dose by week 12.

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In a 12-week, phase 3 RDBPCT (JADE TEEN) comparing ABRO 200 or 100 mg vs. placebo with concurrent use of topicals in adolescents ≥12 years old, co-primary endpoints were met by both ABRO doses: IGA 0/1 (ABRO 200 vs. 100 mg vs. placebo: 46.2% vs. 41.6% vs. 24.5%) and EASI-75 (72.0% vs. 68.5% vs. 41.5%).[99] Significant improvement in PP-NRS was seen as early as day 2 with ABRO treatment, and PP-NRS4 was achieved by both doses. The most common AEs among any group were nausea, URTI, headache, nasopharyngitis, folliculitis, dizziness, acne, and vomiting.

Top-line data from a 52-week phase 3 RDBPCT (JADE REGIMEN) comparing ABRO 200 and 100 mg vs. placebo in individuals age ≥12 years with moderate-severe AD initially treated with open-label ABRO 200 mg for 12 weeks support long-term efficacy.[100] Responders from the initial 12-week induction period (i.e., those achieved both IGA 0/1 and EASI-75: 64.7% of all subjects) were randomized to ABRO or placebo groups and then followed for an additional 40 weeks. The primary endpoint (absence of "flare", i.e., loss of EASI-50 and IGA ≥2 [mild]) was achieved by both ABRO groups (ABRO 200 vs. 100 mg vs. placebo: 81.1% vs. 57.4% vs. 19.1%), with statistically superior results seen with ABRO 200 vs. 100 mg. These results suggest that once clearance is achieved on ABRO, continuous therapy is the optimal long-term strategy for flare prevention in most moderate-severe AD patients. Following randomization, the frequency of TEAEs was higher in those treated with ABRO (63.2% vs. 54% vs. 45.3%), as were SAEs (4.9% vs. 1.5% vs. 0.7%) and AE-related treatment discontinuation (6.0% vs. 1.9% vs. 1.5%).

A NDA for ABRO (200 or 100 mg QD) for adolescents and adults ≥12 years with moderate-to-severe AD was accepted for Priority Review by the FDA in late 2020 and is currently under review.

Other Oral Therapies in Development

Gusacitinib (GUSA) is an inhibitor of JAK and spleen tyrosine kinase (SYK) – a tyrosine kinase involved in signaling of pro-inflammatory, non-Th2 cytokines such as IL-1β and IL-17. An early phase 1b RDBPCT suggested that GUSA is safe and well tolerated.[101] The most common TEAEs were headache, nausea, and diarrhea, all of which were more frequently observed in the placebo group. Secondary endpoints of EASI-50 and improvement in baseline itch-NRS were met by only the highest doses of GUSA. A phase 2b study (NCT03531957) concluded in 2020 but data are currently unavailable. Based on encouraging efficacy and safety results from a separate phase 2b study (NCT03728504),[102] GUSA was granted Fast Track designation by the FDA in February 2021 for the treatment of moderate-to-severe chronic hand eczema.

Conclusion

During the past decade, our understanding of the pathophysiology and clinical burden of AD has rapidly evolved, leading to a revolution in safe and efficacious targeted AD therapy, including JAK inhibitors. While current data are highly promising, several questions still remain for this exciting new drug class. Supplemental clinical trials are needed to further characterize long-term safety and durability. Real-world data are required to better understand outcomes in a heterogenous, racially diverse population. Additional clinical and molecular phenotyping must be undertaken to identify subgroups that are best suited for this therapeutic class. Regardless, JAK inhibitors are no longer a potential treatment for AD – they are here, and the future is bright.

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Figure Legends

Figure 1. JAK-STAT signaling and advanced therapeutics in atopic dermatitis. (A) Cytokine binding induces receptor subunit dimerization which leads to intracellular phosphorylation by janus kinase (JAK) proteins. Signal transducer and activator of transcription (STAT) proteins are then recruited to the phosphorylated receptor and phosphorylated by JAK proteins. Phosphorylated STAT proteins dimerize and translocate to the nucleus to regulate gene transcription. (B) Cytokines bind to JAK-STAT dependent receptors to propagate inflammation and itch in atopic dermatitis (AD). IL-4 binds to a heterodimer consisting of the IL-4Rα and common gamma chain (γc) subunits and is dependent on JAK1/3. IL-13 binds to a heterodimer consisting of IL-4Rα and IL-13Rα1 (JAK1/2, TYK2), while IL-31, IL-22, and TSLP bind to IL-31Rα / OSM, IL-22Rα1 / IL-10Rβ2, and CRLF2 / IL-7Rα heterodimers, respectively (JAK1/2). IL-5, which has less clear functional significance in AD, binds to the IL-5Rα and cytokine receptor common subunit beta (βc) heterodimer (JAK1/2). Topical and oral JAK inhibitors reversibly inhibit JAK proteins with varying specificity: abrocitinib and upadacitinib (JAK1); ruxolitinib and baricitinib (JAK1/2); tofacitinib (JAK1/3); and delgocitinib (JAK1/2/3,TYK2). Biologic monoclonal antibody therapies inhibit upstream cytokine signaling. Dupilumab binds to the IL-4Rα receptor subunit shared by IL-4 and IL-13. Emerging biologic therapies for AD include lebrikizumab and tralokinumab (IL-13) and nemolizumab (IL-31Rα).

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Table 1. Topical JAK Inhibitors

JAK Inhibitor	Study Type	Trial Identifier	Number of Patients	Duration (weeks)	Dose (%)	Age (years)	Primary Endpoints Met	Key Secondary Endpoints Met	Notable Adverse Events
Tofacitinib (JAK1/3)	Phase 2a RDBVCT (monotherapy)	NCT02001181[51]	69	4	2% BID	18-60	%EASI	IGA 0/1 BSA %itch-NRS	Nasopharyngitis, URTI
Ruxolitinib (JAK1/2)	Phase 2b RDBVACT (monotherapy, vs. tac 0.1% BID)	NCT03011892[53, 54]	307	12 (8 + 4 [OL extension])	1.5% (BID, QD), 0.5% QD, 0.15% QD	18-70	%EASI (1.5% BID vs. vehicle)	%EASI -vs. vehicle (all) -vs. tac (n.s.) EASI-50/75/90 -vs. vehicle (only 1.5% BID) -vs. tac (n.s.) IGA 0/1 -vs. vehicle (all except 0.15%) -vs. tac (n.s.) %itch-NRS -vs. vehicle (all) -vs. tac (n.s.)	Nasopharyngitis, URTI, headache
	Phase 3 RDBVCT (monotherapy)	TRuE-AD1 (NCT03745638)[55, 58]	631	52 (8 + 44 [OL extension])	1.5% BID, 0.75% BID	≥12	IGA 0/1	EASI-75 Itch-NRS4	No new safety signals (consistent with phase 2b)
	Phase 3 RDBVCT (monotherapy)	TRuE-AD2 (NCT03745651)[55, 58]	618	52 (8 + 44 [OL extension])	1.5% BID, 0.75% BID	≥12	IGA 0/1	EASI-75 Itch-NRS4	No new safety signals (consistent with phase 2b)
Delgocitinib (JAK1/2/3 / TYK2)	Phase 2 RDBVACT	JapicCTI-152887[63]	327	4	3% BID, 1% BID, 0.5% BID, 0.25% BID	16-65	%mEASI	mEASI-50/75/90 IGA 0/1 (only 3%)	Nasopharyngitis, furuncle, acne, eczema herpeticum

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	(monotherapy, vs. tacrolimus 0.1% BID)							%IGA (all except 0.25%) %BSA (all except 0.25%) %itch-NRS (all except 0.25%)	
	Phase 2 RDBVCT (monotherapy)	JapicCTI-173553[64]	103	4	0.5% BID, 0.25% BID	2-15	%mEASI	mEASI-50/75 IGA 0/1 %itch-NRS	Nasopharyngitis, impetigo, urticaria
	Phase 3 RDBVCT (monotherapy)	JapicCTI-173554[65]	158	28 (4 + 24 [OL extension])	0.5% BID	≥16	%mEASI	mEASI-50/75 IGA 0/1 (face/neck only) %itch-NRS	Nasopharyngitis, eczema herpeticum, acne
	Phase 3 OL LTE (±TCS)	JapicCTI-173555[66]	352	52 [OL]	0.5% BID	≥16	Safety	%mEASI mEASI-50/75 IGA 0/1 %itch-NRS	Folliculitis, acne, eczema herpeticum
Brepocitinib (JAK1 / TYK2)	Phase 2b RDBVCT	NCT03903822[70]	240	6	3% (QD) 1% (BID, QD) 0.3% (BID, QD) 0.1% (QD)	12-75	%EASI (all except 0.1% and 0.3% BID)	EASI-75 (only 0.3% BID, 1% BID) IGA 0/1 (all except 1% QD, 0.3% QD, 0.1% QD) PP-NRS4 (all except 0.1%, 0.3%)	Nasopharyngitis, URTI, folliculitis, furuncle, herpes simplex, eczema herpeticum
ATI-502 (JAK1/3)	Phase 2a OL Study	NCT03585296[71]	22	4	Solution BID	≥18	Safety	%EASI IGA 0/1 %itch-NRS	None related to treatment

BID: twice-daily; BSA: body surface area; %BSA: percent improvement from baseline BSA; EASI: Eczema Area and Severity Index; %EASI: percent improvement from baseline EASI; EASI-50: proportion achieving Improvement ≥50% from baseline EASI; EASI-75: proportion achieving Improvement ≥75% from baseline EASI; EASI-90: proportion achieving

Improvement ≥90% from EASI; IGA: investigator's global assessment; IGA 0/1: proportion achieving IGA 0 or 1 (clear or almost clear) plus ≥2 grade improvement; itch-NRS: numerical rating scale of itch; %itch-NRS: percent improvement from baseline itch-NRS; itch-NRS4: proportion achieving itch-NRS reduction ≥4 points from baseline; JAK: janus kinase; LTE: long-term extension; mEASI: modified EASI; %mEASI: percent improvement from baseline mEASI; mEASI-50: proportion achieving Improvement ≥50% from baseline mEASI; mEASI-75: proportion achieving Improvement ≥75% from baseline mEASI; N.S.: not significant; OL: open label; PP-NRS: peak pruritus numerical rating scale; PP-NRS4: proportion achieving PP-NRS reduction ≥4 points from baseline; QD: once daily; RDBVACT: randomized double-blind vehicle- and active-controlled trial; RDBVCT: randomized double-blind vehicle-controlled trial; Tac: triamcinolone; TCS: topical corticosteroids; TYK: tyrosine kinase; URTI: upper respiratory tract infection.

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Table 2. Oral JAK Inhibitors

JAK Inhibitor	Study Type	Trial Identifier	Patients (N)	Duration (weeks)	Daily Dose (mg)	Age (years)	Primary Endpoints Met	Key Secondary Endpoints Met	Notable Adverse Events
Baricitinib (JAK1/2)	Phase 2B RDBPCT (+TCS)	NCT02576938[73]	124	16 (preceding 4 with TCS)	4, 2	≥18	EASI-50 (4 mg only)	%EASI %SCORAD (only 4 mg) Itch-NRS4 %DLQI	Headache, increased blood CPK, nasopharyngitis
	Phase 3 RDBPCT (monotherapy)	BREEZE-AD1 (NCT03334396)[75]	624	16	4, 2, 1	≥18	vIGA-AD 0/1 (only 4 and 2 mg)	vIGA-AD 0/1 (met by 1 mg) %EASI EASI-75 EASI-90 (only 4 and 2 mg) SCORAD-75 %skin-pain-NRS Itch-NRS4 (only 4 mg) %ADSS item-2 (only 4 mg)	Increased blood CPK and headache, herpes simplex
	Phase 3 RDBPCT (monotherapy)	BREEZE-AD2 (NCT033344)[75]	615	16	4, 2, 1	≥18	vIGA-AD 0/1 (only 4 and 2 mg)	vIGA-AD 0/1 (not met by 1 mg) %EASI EASI-75 (only 4 and 2 mg) EASI-90 (only 4 and 2 mg) SCORAD-75 %skin-pain-NRS Itch-NRS4 (only 4 and 2 mg) %item-2-ADSS	Increased blood CPK and headache
	Phase 3 RDBLTE (+TCS)	BREEZE-AD3 (NCT03334435)[76]	Enrolling	52 (+ prior originating study)	4, 2	≥18	Ongoing vIGA-AD 0/1 (week 16, 32, 52)	Ongoing IGA 0/1/2 IGA 0/1 (non-responders) EASI-75 Itch-NRS4 Skin-pain-NRS4	Ongoing Consistent safety profile with BREEZE-AD1 and BREEZE-AD2

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								Item-2-ADSS1.5	
	Phase 3 RDBPCT (+TCS)	BREEZE-AD4 (NCT03428100)[79]	463	16	4, 2, 1	≥18	EASI-75 (only 4 mg)	%EASI EASI-90 (none) vIGA 0/1 (only 4 mg) SCORAD-75 (only 2 mg) Itch-NRS4 %Skin-pain-NRS (only 4 and 2 mg) %Item-2-ADSS (only 4 and 1 mg)	Nasopharyngitis, headache, influenza
	Phase 3 RDBPCT (monotherapy)	BREEZE-AD5 (NCT03435081)[77]	440	16	2, 1	≥18	EASI-75 (only 2 mg)	EASI-90 (only 2 mg) vIGA 0/1 (only 2 mg) Itch-NRS4 (only 2 mg) %Skin-pain-NRS (only 2 mg) %Item-2-ADSS (only 2 mg) SCORAD-75 (only 2 mg)	URTI, nasopharyngitis, diarrhea, nausea, herpes simplex
	Phase 3 OL LTE (monotherapy)	BREEZE-AD6 (NCT03559270)[82, 84]	Enrolling	16 + variable	4,2	≥18	Ongoing EASI-75	Ongoing IGA 0/1 BSA ≤3% Itch-NRS4	Ongoing Only analyzed in pooled data
	Phase 3 RDBPCT (+TCS)	BREEZE-AD7 (NCT03733301)[80]	329	16	4, 2	≥18	vIGA-AD 0/1 (only 4 mg)	EASI-75 (only 4 mg) EASI-90 (none) %EASI (only 4 mg) SCORAD-75 (none) Itch-NRS4 (only 4 mg) %Skin-Pain-NRS (only 4 mg) %Item-2-ADSS (none)	Nasopharyngitis, URTI, folliculitis, oral herpes / herpes simplex virus, acne, back pain, diarrhea, increased blood CPK
Upadacitinib (JAK1)	Phase 2 RDBPCT (monotherapy)	NCT02925117[85]	167	16	30, 15, 7.5	18-75	EASI-75	EASI-50/90 EASI-100 (all except 7.5 mg) %EASI	URTI, acne, headache, increased blood CPK,

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								IGA 0/1 %Itch-NRS Itch-NRS4	nasopharyngitis, nausea
	Phase 3 RDBPCT (monotherapy)	Measure Up 1 (NCT03569293)[86]	847	16	30, 15	12-75	EASI-75 vIGA 0/1	EASI-90/100 Worst itch-NRS4 POEM4 DLQI4 / DLQI 0/1	Acne, URTI, nasopharyngitis, headache, increased blood CPK, herpes zoster
	Phase 3 RDBPCT (monotherapy)	Measure Up 2 (NCT03607422)[86]	836	16	30, 15	12-75	EASI-75 vIGA 0/1	EASI-90/100 Worst itch-NRS4 POEM4 DLQI4 / DLQI 0/1	Acne, headache, URTI, nasopharyngitis, increased blood CPK, herpes zoster
	Phase 3 RDBPCT (+TCS)	AD Up (NCT03568318)[87]	300	16	30, 15	12-75	EASI-75 vIGA 0.1	EASI-90 EASI-100 (only 30 mg) Worst itch-NRS4	Acne, nasopharyngitis, URTI, oral herpes, increased blood CPK, eczema herpeticum
	Phase 3b RDBACT (monotherapy, vs. DUPI)	Heads Up (NCT03738397)[88]	692	16	30	18-75	EASI-75	EASI-90 EASI-100 Worst itch-NRS4 %Worst itch-NRS	Acne
Abrocitinib (JAK1)	Phase 2b RDBPCT (monotherapy)	NCT02780167[89, 90]	267	12	200, 100, 30, 10	18-75	IGA 0/1 (only 200 and 100 mg)	%EASI	URTI, headache, nausea, diarrhea, decreased platelet count (transient)
	Phase 3 RDBPCT (monotherapy)	JADE MONO-1 (NCT03349060)[92]	387	12	200, 100	≥12	IGA 0/1 EASI-75	PP-NRS4 %PSAAD	Nausea, nasopharyngitis, headache, herpes infection, decreased platelet count (transient)
	Phase 3 RDBPCT (monotherapy)	JADE MONO-2 (NCT03575871)[91]	391	12	200, 100	≥12	IGA 0/1 EASI-75	PP-NRS4 %PSAAD	Nausea, nasopharyngitis, headache, acne vomiting, upper abdominal pain, herpes infection increased blood

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									CPK, decreased platelet count (transient)
	Phase 3 RDBPACT (+topical meds, vs. DUPI)	JADE COMPARE (NCT03720470)[96]	838	16	200, 100	≥18	IGA 0/1, week 12 -vs. placebo EASI-75, week 12 -vs. placebo	PP-NRS4 -vs. placebo (all) -vs. DUPI (only 200 mg) IGA 0/1 -vs. placebo (all) -vs. DUPI (none) EASI-75 -vs. placebo (all) -vs. DUPI (none)	Nausea, acne, nasopharyngitis, URTI, headache, herpes zoster
	Phase 3 RDBPCT (+topical meds)	JADE TEEN (NCT03796676)[99]	285	12	200, 100	12-17	IGA 0/1 EASI-75	PP-NRS4 (only 200 mg) %PSAAD (cannot be inferred)	Nausea, URTI, headache, nasopharyngitis, folliculitis, dizziness, acne, vomiting.
	Phase 3 RDBPCT (monotherapy, OL 12-week induction with ABRO 200 mg)	JADE REGIMEN (NCT03627767)[100]	1,233	52 (12 [induction] + 40)	200, 100	≥12	Flare [loss of EASI-50 and IGA ≥2]	IGA 0/1	No new safety signals observed
	Phase 3 RDBLTE (+topical meds)	JADE EXTEND (NCT03422822)[95]	Enrolling	92 + variable	200, 100	≥12	Ongoing Safety	Ongoing Numerous	Ongoing Nasopharyngitis, nausea, headache
Gusacitinib (JAK/SYK)	Phase 1b RDBPCT (monotherapy)	NCT03139981[101]	36	4	80, 40, 20	≥18	Safety	EASI-50 (all except 20 mg) Itch-NRS (only 80 mg)	Headache, nausea, and diarrhea

AD: atopic dermatitis; BID: twice-daily; BSA: body surface area; %BSA: percent improvement from baseline BSA; CPK: creatine phosphokinase; DLQI: dermatology life quality index; %DLQI: percent decrease in baseline DLQI; DLQI 0/1: proportion achieving DLQI score of 0/1; DUPI: dupilumab; EASI: Eczema Area and Severity Index; %EASI: percent improvement from baseline EASI; EASI-50: proportion achieving improvement ≥50% from baseline EASI; EASI-75: proportion achieving improvement ≥75% from baseline EASI; EASI-90: proportion achieving improvement ≥90% from baseline EASI; EASI-100: proportion achieving improvement ≥90% from baseline EASI; IGA: investigator's global assessment; IGA 0/1: proportion achieving IGA 0 or 1 (clear or almost clear) plus ≥2 grade improvement; Itch-NRS: numerical rating scale of itch; %Itch-NRS: percent improvement from baseline itch-NRS; Itch-NRS4: proportion achieving itch-NRS reduction ≥4 points from baseline; Item-2-ADSS: item 2 of the AD sleep scale; %Item-2-ADSS: percent improvement from baseline item-2-ADSS; Item-2-ADSS1.5: proportion achieving ≥1.5 point improvement in baseline item-2-ADSS; JAK: janus kinase; LTE: long-term extension; N.S.: not significant; OL: open label; POEM: patient-oriented eczema measure; POEM4: proportion achieving ≥4 point improvement from baseline POEM; PP-NRS: peak pruritus numerical rating scale; PP-NRS4: proportion achieving PP-NRS reduction ≥4 points from baseline; PSAAD: pruritus and symptoms assessment for AD; %PSAAD: percent improvement from baseline PSAAD; QD: once daily; RDBLTE; randomized

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double-blind long-term extension; RDBACT; randomized double-blind active-controlled trial; RDBPCT; randomized double-blind placebo-controlled trial; RDBPACT; randomized double-blind placebo- and active-controlled trial; SCORAD: SCORing AD; SCORAD-75: proportion achieving improvement ≥75% from baseline SCORAD; Skin-pain-NRS: numerical rating scale of skin-pain; %Skin-pain-NRS: percent improvement from baseline skin-pain-NRS; Skin-pain-NRS4: proportion achieving skin-pain-NRS reduction ≥4 points from baseline; SYK: spleen tyrosine kinase; TCS: topical corticosteroids; URTI: upper respiratory tract infection; vIGA-AD: validated investigator's global assessment for AD; vIGA-AD 0/1: proportion achieving vIGA-AD 0 or 1 (clear or almost clear) plus ≥2 grade improvement; Worst itch-NRS: numerical rating scale of worst itch; %Worst itch-NRS: percent improvement from baseline worst itch-NRS; Worst itch-NRS4: proportion achieving worst itch-NRS reduction ≥4 points from baseline;

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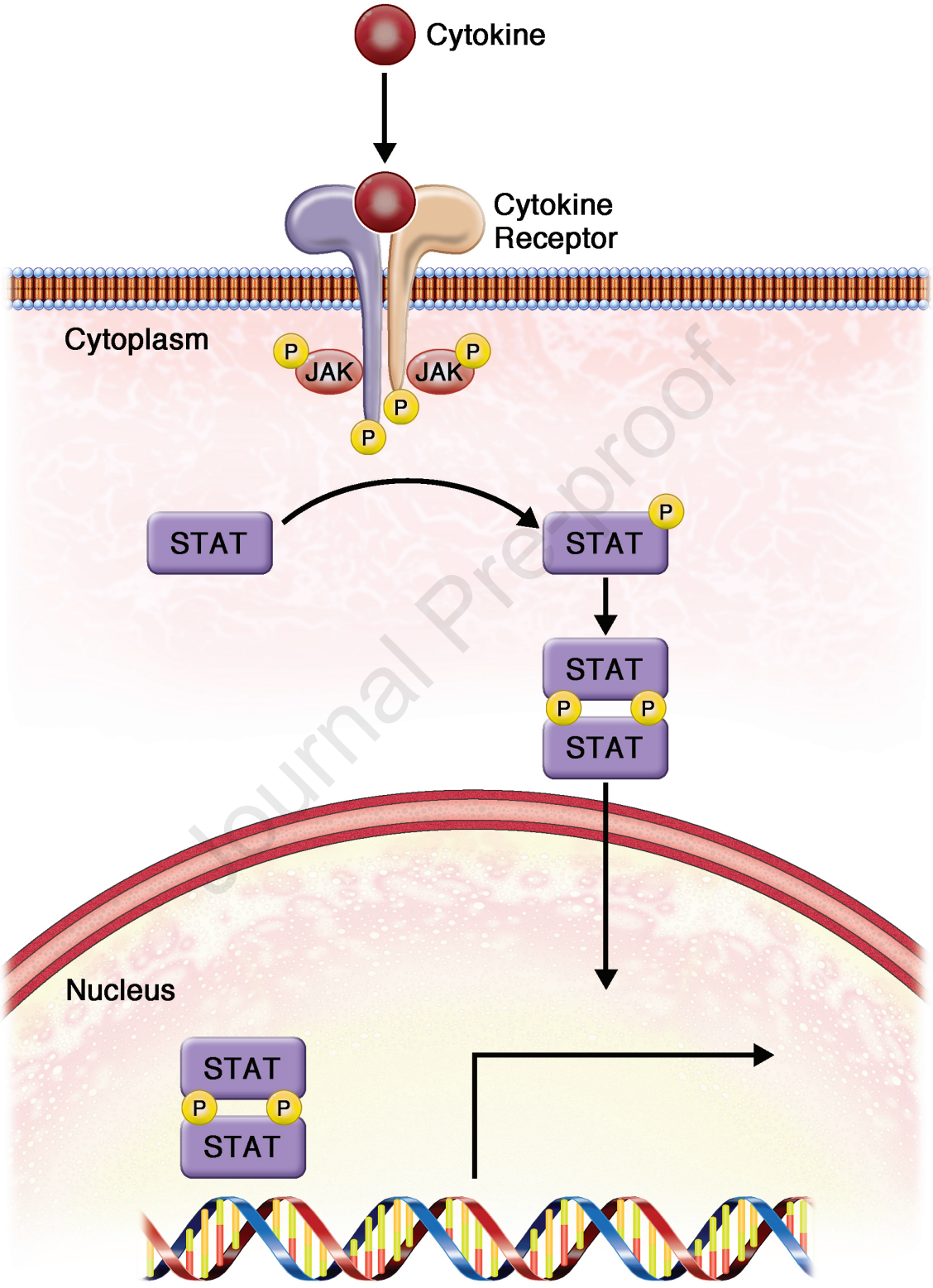

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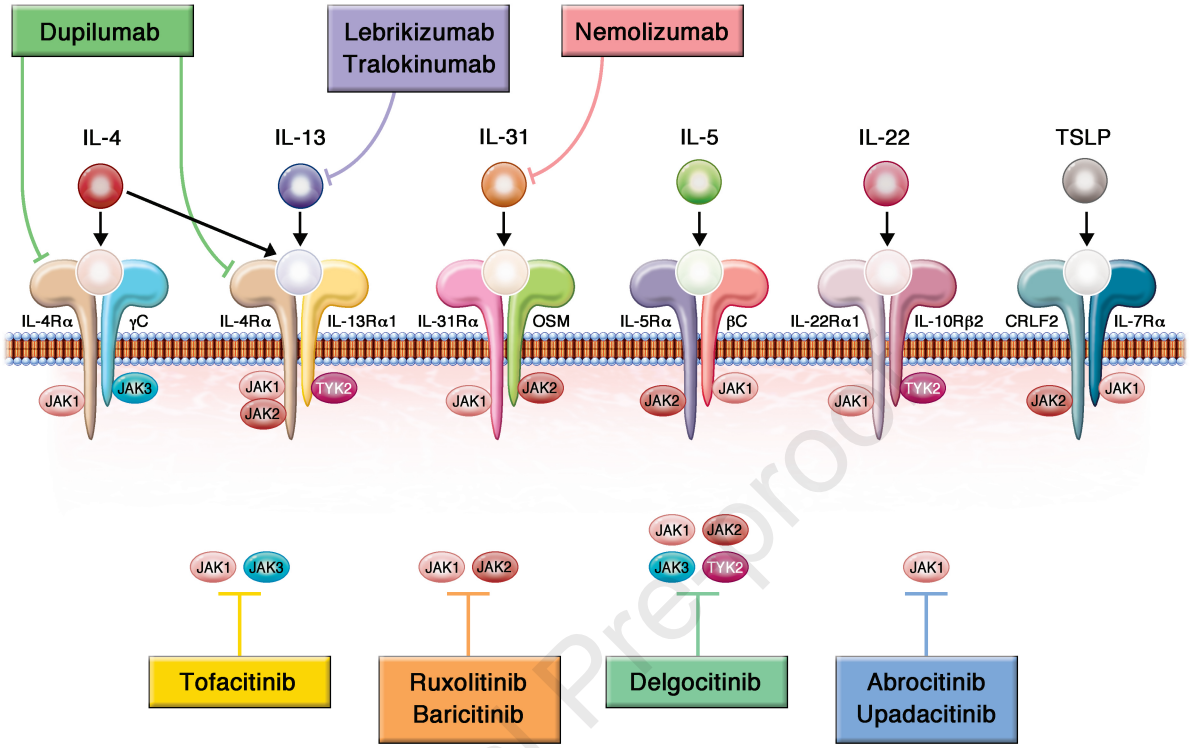

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