Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Approved and Emerging Non-steroidal Agents for the Treatment of Atopic Dermatitis

Abrocitinib (Cibinqo)

Baricitinib (Olumiant)*

Upadacitinib (Rinvoq)

Ruxolitinib (Opzelura)

Tralokinumab (Adbry)

Dupilumab (Dupixent)

Crisaborole (Eucrisa)

Tacrolimus (Protopic)

Pimecrolimus (Elidel)

*The “emerging” medication is not yet FDA-approved for treatment of atopic dermatitis

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Abbreviations

The following contains a list of abbreviations used throughout the main text of this report:

AAAAI	American Academy of Allergy, Asthma & Immunology
AAD	American Academy of Dermatology
ACAAI	American College of Allergy, Asthma & Immunology
AD	atopic dermatitis
ADA	anti-drug antibodies
AEs	adverse events
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
DDI	drug-drug interactions
DLQI	Dermatology Life Quality Index
DVT	deep vein thrombosis
EADV	European Academy of Dermatology and Venerology
EASI	Eczema Area Severity Index
EDF	European Dermatology Forum
ETFAD	European Task Force on Atopic Dermatitis
EU	European Union
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HR	hazard ratio
ICER	Institute for Clinical and Economic Review
IGA	Investigator's Global Assessment
IGADA	Investigator's Global Atopic Dermatitis Assessment (IGADA)
IL	interleukins
IL-4	interleukin-4
IL-13	Interleukin-13
ISGA	Investigator's Static Global Assessment
JAK	Janus kinase inhibitor
kg	kilogram
LD	loading dose
MACE	major adverse cardiovascular events
mg	milligram
MI	myocardial infarction
mL	milliliter
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMSC	non-melanoma skin cancer (NMSC)
PDE-4	phosphodiesterase 4 (PDE-4) inhibitor
PDL	Preferred Drug List
PE	pulmonary embolism
PK	pharmacokinetic
POEM	Patient Oriented Eczema Measure

PP-NRS	Peak Pruritus Numerical Rating Scale
PsA	psoriatic arthritis
PSAAD	Pruritus and Symptoms Assessment for Atopic Dermatitis
P&T	pharmacy & therapeutics
QoL	quality of life
RA	rheumatoid arthritis
RCTs	randomized controlled trials
RR	relative risk
SASSAD	Six Area, Six Sign Atopic Dermatitis
SCORAD	Scoring Atopic Dermatitis Index
SQ	subcutaneous
SRs	systematic reviews
SRMAs	systematic reviews and meta-analysis
STAT	Signal Transducer and Activator of Transcription
Tb	tuberculosis
TCIs	topical calcineurin inhibitors
TCSs	topical corticosteroids
TNF	tumor necrosis factor
TPIs	topical phosphodiesterase inhibitors
UK	United Kingdom
URTI	upper respiratory tract infection
US	United States
UTI	urinary tract infection
UV	ultraviolet
vIGA-AD	validated Investigator's Global Assessment for Atopic Dermatitis
VTE	venous thromboembolism

Executive Summary

Background:

Disease Introduction: Atopic dermatitis (AD), also referred to as atopic eczema, is a chronic, relapsing, inflammatory skin condition that predominately affects children ≤ 5 years of age, but may occur at any age.[1-5] Treatment consists of topical and systemic therapies. For mild-to-moderate disease, topical treatment as monotherapy is usually sufficient, whereas systemic treatment is reserved for more severe cases.[3,5-7] This report will review non-steroidal agents that are either under United States (US) Food and Drug Administration (FDA) review (ie, "emerging" therapies) or approved therapies to treat AD.

Agents included in this report: 6 recently-approved agents are included in this report:

i. 2 oral Janus kinase (JAK) inhibitors, abrocitinib (Cinbinqo) and upadacitinib (Rinvoq);
ii. 2 subcutaneous products, dupilumab (Dupixent), an antibody that antagonizes interleukin-4 (IL-4) receptor alpha, and tralokinumab (Adbry), a selective IL-13 targeting antibody; and
iii. 2 topical products, ruxolitinib (Opzelura), a JAK inhibitor, and crisaborole (Eucrisa), a phosphodiesterase 4 (PDE-4) inhibitor.

One other new systemic JAK inhibitor included is baricitinib, which is not yet FDA-approved but is currently under review for the treatment of moderate-to-severe AD. Baricitinib has already been approved in other countries for this use.[8] According to a press release, the FDA decision date for baricitinib has been extended due to safety concerns for major adverse cardiovascular events (MACE) and malignancies based on the post-marketing safety study [Oral Surveillance] of another oral JAK inhibitor, tofacitinib.[9,10] In December 2021, the FDA required revisions to the black box warning for tofacitinib, upadacitinib, and baricitinib to reflect the increased risk of MACE, mortality, and malignancies compared to TNF blockers in rheumatoid arthritis [RA] patients.[10,11]

Older agents include topical calcineurin inhibitors (TCIs), pimecrolimus (Elidel) and tacrolimus (Protopic).

Indications of included agents: The products reviewed in this report have AD indications that differ (or are likely to differ) in several respects, including age of approved use, AD severity, and route/frequency of administration. They are similar in that they are all approved (or expected to be approved) for use in the adult population; 6 of the 9 products are also approved for the pediatric population (except for abrocitinib, baricitinib, and tralokinumab). Among those with pediatric indications, crisaborole is approved for use at the youngest age (≥ 3 months); other agents have ages for pediatric uses that range from 2+ years (the TCIs, tacrolimus and pimecrolimus), 6+ years (dupilumab), and 12+ years (ruxolitinib and upadacitinib). Most topical products are approved for mild-to-moderate AD except for tacrolimus, which is approved for moderate-to-severe disease. The non-topical treatments tralokinumab and dupilumab are also approved for moderate-to-severe disease that is not controlled by topical treatments, or for when topical treatments cannot be used.[12,13] Upadacitinib and abrocitinib are approved for moderate-to-severe AD, that is not adequately controlled with other systemic agents, including biologics, or when the use of those therapies is not advised.[14,15] In Europe, baricitinib is approved for the treatment of moderate-to-severe AD in adults requiring systemic treatment for adequate control.[8]

Some of the products are approved for additional non-AD uses. Dupilumab is also approved as add-on treatment for certain types of moderate to severe asthma (ages 6+ years) and as add-on treatment for rhinosinusitis with nasal polyposis in adults.[13] Upadacitinib and baricitinib are approved for the treatment of adults with moderate-to-severe RA with a previous failure or intolerance to one or more tumor necrosis factor (TNF) antagonists,[15,16] and upadacitinib is also approved for psoriatic arthritis (PsA) in adults with an intolerance or an inadequate response to one or more TNF antagonists.[15]

Guideline Recommendations:

Goals of pharmacologic treatment for AD include reducing skin inflammation and pruritus, restoring skin barrier properties, and improving patient quality-of-life (QoL).[2,5,6,17]

Pimecrolimus and tacrolimus: The most recent US guidelines from American Academy of Dermatology (AAD) [2014] and American Academy of Allergy, Asthma & Immunology (AAAAI)/ American College of Allergy, Asthma & Immunology (ACAAI) [2012] recommend pimecrolimus and tacrolimus as second-line anti-inflammatory agents for acute and non-continuous chronic treatment in adults and children (ages 2+ years) who have failed to respond to other topical prescription treatments, or who have intolerance to those treatments;[5,6,17-19] however, only the lower concentration of tacrolimus, which is available in 0.03% and 0.1% formulations, is recommended for children ages 2 to 15 years.[19] During pregnancy, the European Task Force on Atopic Dermatitis (ETFAD) favors the use of topical tacrolimus over topical pimecrolimus due to the greater amount of data with systemic use during pregnancy.[20] (Nonetheless, prescribing information for both products recommend caution and careful risk/benefit analysis in pregnancy.[18,19]) These agents may be preferred to topical corticosteroids (TCSs) in particular situations, such as steroid resistance or induced atrophy, involvement of sensitive areas, and long-term continuous use of TCSs.[6]

Newer agents: The US guidelines predate FDA approval for crisaborole, topical ruxolitinib, abrocitinib, upadacitinib, dupilumab, and tralokinumab. However, some European organizations have provided recommendations about the use of systemic agents not addressed by US guidelines. For example, the National Institute for Health and Care Excellence (NICE) recommends dupilumab or baricitinib as alternative options for adults with moderate-to-severe AD, unresponsive or intolerant/contraindicated to at least one other systemic immunosuppressant agent (eg, cyclosporin, methotrexate, azathioprine, or mycophenolate mofetil).[21,22] The 2018 consensus-based European guideline recommends the use of dupilumab exclusively for moderate-to-severe AD in adults, in which disease control is not achieved with topical treatment or a contraindication exists; and it is not suitable to use other systemic treatments (similar to those NICE mentions).[17,23] The 2020 European Task Force on Atopic Dermatitis of the European Academy of Dermatology and Venerology (ETFAD/EADV) position paper recommends dupilumab for individuals (≥ 12 years of age) with moderate-to-severe AD, requiring systemic therapy.[24]

Objective:

The aim of this report is to compile and synthesize experimental evidence from systematic reviews (SRs) and/or randomized controlled trials (RCTs) for any head-to-head safety and efficacy comparisons of the non-steroidal AD agents and any placebo comparisons for non-FDA approved non-steroidal treatments for AD.

Methods:

A systematic search in Ovid MEDLINE and Epistemonikos (SRs only) was conducted from January 2018 to December 2021 for direct head-to-head (for all agents) and placebo-controlled (for non-FDA approved agents) comparisons. Ovid-Medline was searched for RCTs, to supplement the SR search, with a date restriction based on the latest search date of an included robust SR's search strategy, adjusted for the findings for each particular agent. We additionally searched the drug sponsor's website for any preliminary information about drugs that were not approved by the FDA. As some non-FDA-approved medications have been approved in other countries, product information for these agents was searched on the regulatory site of other countries.

Utilization Data: Pharmacy claims were extracted among the Utah Medicaid fee-for-service population from January 1, 2019 to December 31, 2021. Data included unique patients counts and claims for each product. Utilization was stratified by age groups (≥ 18 years of age, < 18 years of age), including additional categorization among pediatric ages (ie, 12-17, 6-11, and <6).

Literature search results:

Comparative Efficacy Evidence: 11 SRs and 12 RCTs were identified that met eligibility criteria, including several head-to-head comparisons of tacrolimus versus pimecrolimus, a small number head-to-head comparisons with dupilumab (versus upadacitinib or abrocitinib), and placebo comparisons of baricitinib. No head-to-head studies were found for the remaining approved agents (crisaborole, ruxolitinib, or tralokinumab).

Tacrolimus vs. pimecrolimus: The majority of the evidence suggests that tacrolimus is more effective at treating AD compared to pimecrolimus among children and adults with varying disease severity levels ranging from mild to severe.[25-27] In adults with moderate to very severe AD, study withdrawal due to a lack of efficacy occurred more frequently with pimecrolimus compared to tacrolimus.[25,26] In addition, tacrolimus produced a more rapid relief of symptoms compared to pimecrolimus. Numerically, more events of local application-site reactions (eg, burning, pruritus, pain, warmth, erythema) occurred in the tacrolimus-treated patients compared to patients treated with pimecrolimus; however, the differences were not statistically significant.[25,26]

Dupilumab vs. upadacitinib or abrocitinib: A head-to-head trial suggests that the higher dose of upadacitinib (30 mg daily) is more effective than dupilumab (300 mg every other week after 600 mg loading dose [LD]) at improving moderate-to-severe AD in patients ages 12 years and older at 16 weeks.[28] In addition, a quicker onset of action and greater improvements in skin clearance was observed with upadacitinib compared to dupilumab. Rates of acne, serious infection, eczema herpeticum, and herpes zoster were reported more frequently in patients treated with upadacitinib, whereas rates of conjunctivitis (mild or moderate) and injection site reactions were higher among patients that received dupilumab.[28]

A direct head-to-head trial in adults only, showed comparable efficacy at week 16 for abrocitinib (100 mg or 200 mg daily) versus dupilumab; however the higher end dose of abrocitinib (200 mg) was better at reducing itch response by week 2, suggesting an earlier onset of action compared to dupilumab.[29]

Conjunctivitis occurred most frequently in the dupilumab arm (6.2%). However, the safety profile may favor dupilumab over abrocitinib in terms of overall adverse events, particularly for acne and nausea.[29]

Baricitinib vs placebo: No head-to-head comparisons were identified for baricitinib versus other non-steroidal agents for the treatment of AD. In placebo-controlled trials in adults with AD uncontrolled by TCS therapy, baricitinib (4 mg, 2 mg, or 1 mg daily) demonstrated improvement in signs and symptoms of moderate-to-severe AD compared to placebo, with higher doses showing a larger magnitude of effect.[30-32] A significantly faster onset of action was observed with baricitinib 4 mg and 2 mg compared to placebo, whereas baricitinib 1 mg made modest improvements compared to placebo. The most common adverse events across clinical trials were URTIs, herpes simplex infection, and nasopharyngitis.[30-32]

Safety warnings and precautions:

TCIs carry a black box warning regarding a possible increased risk of malignancy and recommend avoiding *continuous* long-term use due to the lack of established long-term safety data.[18,19] Other considerations with TCIs include the possibility of an elevated risk of immunosuppression and lymphadenopathy, a recommendation to avoid sun exposure or application of TCIs when experiencing pre-malignant lesions, bacterial/viral infections, or conditions associated with insufficient skin barriers leading to increased systemic absorption.[18,19] TCIs should be avoided in the immunocompromised or those with a developing immune system (children under 2 years of age). Unlike pimecrolimus, tacrolimus carries a warning for renal insufficiency due to post-market reports of acute renal failure during its use.[19]

Crisaborole is well-tolerated and carries only a warning about a risk of hypersensitivity reactions (eg, severe itching, swelling, and erythema).[33]

The systemic monoclonal antibodies dupilumab and tralokinumab carry warnings for hypersensitivity reactions, development of ocular side effects (eg, conjunctivitis and keratitis), and the need to treat parasitic helminth infections prior to initiating treatment.[12,13] Dupilumab carries additional warnings related to use in patients with asthma, and recommends that patients avoid abruptly stopping corticosteroids (topical or systemic) when starting dupilumab.[13] In patients with asthma and chronic sinusitis with nasal polyps treated with dupilumab, serious systemic eosinophilic conditions have been reported.

Similar to the systemic monoclonal antibodies, the administration of live vaccinations should be avoid during treatment with systemic JAK inhibitors.[15,16,34] The JAK inhibitors each also carry risks for pharmacokinetic drug-drug interactions, which vary by product.[14-16,35] They also carry warnings about risks for hematologic cytopenias (types vary by product).[14-16] Product labeling for JAK inhibitors include black box warnings about serious infections (eg, tuberculosis and viral hepatitis), which necessitates screening before initiation, as well as increased risks of serious thrombotic events, all-cause mortality, malignancy, and major cardiovascular events.[14-16] Warnings unique to baricitinib and upadacitinib include risks of gastrointestinal perforation and liver enzyme elevations.[15,16] In addition, baricitinib may cause hypersensitivity reactions.[16] Upadacitinib is associated with an increased risk for embryo-fetal toxicity.[15] *Note that warnings for baricitinib were extrapolated from labeling based on FDA approval for its indication for RA; this may or may not change if this product is approved for AD in the US.*

Summary:

No direct evidence was found comparing 4 of the non-steroidal AD treatments (topical ruxolitinib, tralokinumab, crisaborole, and baricitinib) to any other. There was 1 study each comparing oral JAK inhibitors (abrocitinib and upadacitinib) to dupilumab for the treatment of moderate-to-severe AD.[28,29] These studies suggest higher doses of upadacitinib (30 mg daily) are more effective than dupilumab (300 mg every other week), and both upadacitinib and abrocitinib had a faster onset of action compared to dupilumab at skin clearance and relieving itch, respectively. Rates of acne, serious infection, and serious adverse events were numerically higher with either JAK inhibitor (at the higher dose), whereas rates of conjunctivitis (mild or moderate) were higher among patients that received dupilumab. [28,29] Relative to other systemic therapies, dupilumab has the advantage of having FDA approval for other atopic conditions (asthma and chronic rhinosinusitis),[13] which are common comorbidities among patients with AD.[36] For TCIs, the head-to-head experimental evidence suggests that tacrolimus is more effective for AD than pimecrolimus in children and adults with varying disease severity levels, but it may have a higher incidence of local application site reactions.[25-27]

The safety profile of the products varies based on the formulation (topical versus systemic) and generally by class of the non-steroidal therapy.

US guidelines that predate regulatory approval of most non-steroidal agents do not prefer one TCI over another; however, TCIs are preferred in certain situations (eg, sensitive areas, steroid-induced skin atrophy) to TCSs.[5,6] Non-steroidal systemic agents are typically reserved for patients with moderate-to-severe AD who have not adequately responded to conventional topical therapy. The two oral JAK inhibitors that have been approved for moderate-to-severe AD by the FDA (abrocitinib and upadacitinib), are approved for refractory AD or for AD that cannot be advisably treated by other systemic therapies including biologics.[14,15] The oral JAK inhibitor (baricitinib) remains under FDA review for moderate-to-severe AD in patients that require systemic treatment for adequate control.

Utah Medicaid utilization findings:

Products preferred by Utah Medicaid, according to the Preferred Drug List (PDL) published January 1, 2022, include topical pimecrolimus (generic), topical tacrolimus (brand Protopic), and dupilumab (brand Dupixent). Non-preferred drugs include crisaborole (brand Eucrisa), upadacitinib (brand Rinvoq), baricitinib (brand, Olumiant), generic tacrolimus, and pimecrolimus (brand Elidel). The recently-approved products, topical ruxolitinib, tralokinumab, and abrocitinib, are not included on the PDL.

Among Medicaid fee-for-service (FFS) pharmacy claims data, over a 3-year period from January 2019 through December 2021, 150 unique patients filled a prescription for a preferred agent; of these, 62 (41%) were under 18 years of age. In the overall population in 2021, the most highly utilized agents in order of frequency during this period were dupilumab (40% of claims), generic pimecrolimus cream (29% of claims), and tacrolimus (28% of claims). Among those under 18 years, the most highly-utilized agents were generic pimecrolimus cream, followed by tacrolimus ointment. Utilization was lowest for crisaborole; though notably, majority of crisaborole claims were among pediatric patients. We found no fills for the recently-approved agents, tralokinumab or ruxolitinib. Claims for abrocitinib and upadacitinib were excluded because they were not FDA-approved for the indication of AD at the time of data extraction.

Regarding preference of the 9 reviewed non-steroidal treatments for AD in the Utah Medicaid PDL, the Utah Medicaid P&T Committee may consider the following recommendations:

A. Consider including as preferred at least one non-steroidal topical product that is FDA-approved for pediatric AD.
    - AD affects up to 20-25% of the pediatric population and approximately 1-3% of adults.[3,5] Among the pediatric population, approximately 80% of AD is mild. Consequently, it is appropriate to treat patients in a stepwise manner, starting with topical pharmacologic therapy after failure of non-pharmacologic options like moisturizers. Guidelines do not prefer a particular TCI (ie, pimecrolimus or tacrolimus), but they do prefer TCIs to TCSs in key situations (ie, steroid resistance, involvement of sensitive areas, steroid-associated skin atrophy).[6]
    - The place in therapy for crisaborole and topical ruxolitinib is not established by guidelines; the indication for ruxolitinib per FDA labeling is for short-term use in non-immunocompromised patients ages 12+ years with AD that cannot be treated with other topical therapies.[35] Crisaborole is an option as continuous therapy for mild-to-moderate AD in children as young as 3 months old.[33]
B. Consider including as preferred at least one systemic biologic agent that is FDA-approved for moderate-to-severe AD.
    - Depending on the location and severity of lesions and the percentage of body surface area (BSA) affected, systemic therapy may be more appropriate than topicals for moderate-to-severe AD.[37]
    - According to the FDA-approved label, oral JAK inhibitors (abrocitinib and upadacitinib) should be used when other systemic agents cannot be used, including biologics such as dupilumab or tralokinumab.[14,15] Patients requiring these therapies could access them with prior authorization.

Introduction

Atopic dermatitis (AD), also referred to as atopic eczema, is a chronic, relapsing, inflammatory skin condition that predominately affects children ≤ 5 years of age, but may occur at any age.[1-5] AD affects up to 20-25% of the pediatric population and approximately 1-3% of adults.[3,5] Clinical manifestations consist of pruritus, pain, and persistent or relapsing inflammatory eczematous lesions due to skin barrier dysfunction and immune dysregulation.[3,5] Pharmacologic treatment consists of topical therapies typically for mild-to-moderate disease, whereas systemic therapy is reserved for more severe cases.[3,5-7]

The scope of this review consists of 9 agents for the treatment of AD. Recently-approved agents include 2 oral Janus kinase (JAK) inhibitors, abrocitinib (Cinbinqo) and upadacitinib (Rinvoq); dupilumab (Dupixent), a subcutaneous an interleukin-4 (IL-4) receptor alpha antagonist that blocks IL-4 and IL-13 transmission; tralokinumab (Adbry), a subcutaneously administered monoclonal antibody that is selective for IL-13; the topical Janus kinase (JAK) inhibitor, ruxolitinib (Opzelura); and crisaborole (Eucrisa), a topical phosphodiesterase 4 (PDE-4) inhibitor. Older agents include topical calcineurin inhibitors (TCIs), pimecrolimus (Elidel) and tacrolimus (Protopic). An emerging therapy that is currently under United States (US) Food and Drug Administration (FDA) review for the treatment of AD is the oral JAK inhibitor, baricitinib (Olumiant).

Crisaborole was approved in 2016 for mild-to-moderate AD, initially for patients 2 years of age and older. Based on the phase IV trial CrisADe CARE 1, crisaborole is now approved in patients as young as 3 months of age.[38] TCIs (pimecrolimus and tacrolimus) are labeled for use in patients 2 years of age and older with tacrolimus approved for the treatment of moderate-to-severe AD, whereas pimecrolimus is indicated for mild-to-moderate AD.[18,19] Tacrolimus is available in two different concentrations, 0.03% and 0.1%, with only the lower concentration recommended for children 2 to 15 years of age.[19] Topical ruxolitinib was approved in 2021 for mild-to-moderate AD in patients 12 years of age and older.[35] The subcutaneously-administered monoclonal antibody, tralokinumab, was approved in December 2021 for the treatment of moderate-to-severe AD in adults with an inadequate response to topical prescription therapies or when these therapies are not recommended.[12] The systemic JAK inhibitor, abrocitinib, was approved in January 2022 for the treatment of refractory, moderate-to-severe AD in adults, uncontrolled with other systemic agents, including biologics.[14] These medications (pimecrolimus, tacrolimus, ruxolitinib, abrocitinib, and tralokinumab) have no other FDA approved indications.[12,14,18,19,33,35] Another systemic JAK inhibitor, upadacitinib was approved January 2022 for refractory, moderate-to-severe AD in patients 12 years of age and older, in which disease is not controlled with other systemic agents, including biologics.[15] Dupilumab was approved in 2017 for moderate-to-severe AD in adults, uncontrolled by topical prescription treatments (or when these should not be used);[13] in 2020, the indication was extended to children aged 6 years and older.[39] Although not yet approved for AD in the US, baricitinib is approved for the treatment of moderate-to-severe AD in adults requiring systemic treatment for adequate control in Europe.[8] No dupilumab or tralokinumab biosimilars are available.[40] Generic products are available for the TCIs, but not for any of the remaining non-biologic therapies.

According to a press release, the FDA decision date for baricitinib has been extended due to safety concerns for major adverse cardiovascular events (MACE) and malignancies based on the post-

marketing safety study [Oral Surveillance] of another oral JAK inhibitor, tofacitinib.[9,10] The Oral Surveillance study revealed safety concerns for major adverse cardiovascular events (MACE) and malignancies for tofacitinib compared to an alternative treatment (tumor necrosis factor [TNF] blockers) among older rheumatoid arthritis (RA) patients.[9,10] In December 2021, the FDA required revisions to the black box warning for tofacitinib, upadacitinib, and baricitinib to reflect the increased risk of MACE, mortality, and malignancies compared to TNF blockers in RA patients.[10,11]

Some of the products have other FDA-approved indications. Upadacitinib and baricitinib are FDA-approved for the treatment of adults with moderate to severe RA with a previous failure or intolerance to one or more TNF antagonists.[15,16] In addition, upadacitinib is approved for psoriatic arthritis (PsA) in adults with an intolerance or an inadequate response to one or more TNF antagonists.[15] Dupilumab is indicated as add-on maintenance treatment for moderate-to-severe asthma (eosinophilic phenotype or oral corticosteroid dependent) in patients 6 years of age and older.[13] In adult patients, it is approved as add-on maintenance treatment for chronic rhinosinusitis with nasal polyposis.[13]

Regarding frequency of administration, all of the topical therapies are applied twice daily. The oral JAK inhibitors, abrocitinib and upadacitinib, are given once daily.[14,15] The long-acting monoclonal antibodies, dupilumab and tralokinumab are given the least frequently, once every 2 weeks. They can be patient-or caregiver-administered (depending on site), with appropriate training.

The research objective of this report is to determine whether there are significant efficacy and safety differences for AD treatment between the 9 agents of interest summarized in **Table 1** and **Table 2**. Products preferred by Utah Medicaid, according to the Preferred Drug List (PDL) published January 1, 2022, include topical pimecrolimus (generic), topical tacrolimus (brand Protopic), and dupilumab (brand Dupixent). Non-preferred drugs include crisaborole (brand Eucrisa), upadacitinib (brand Rinvoq), baricitinib (brand, Olumiant), generic tacrolimus, and pimecrolimus (brand Elidel). The recently-approved products, topical ruxolitinib, tralokinumab, and abrocitinib, are not included on the PDL.

Regarding the Medicaid fee-for-service (FFS) pharmacy prescription fills for January 2019 through December 2021, 150 unique patients filled a prescription for a preferred agent; of these, 62 (41%) were under 18 years of age. In the overall population in 2021, the most highly utilized agents in order of frequency during this period were dupilumab (40% of claims), generic pimecrolimus cream (29% of claims), and tacrolimus (28% of claims). Among those under 18 years, the most highly-utilized agents were generic pimecrolimus cream, followed by tacrolimus ointment. Utilization was lowest for crisaborole; though notably, majority of crisaborole claims were among pediatric patients. We found no fills for the recently-approved agents, tralokinumab or ruxolitinib. Claims for abrocitinib and upadacitinib were excluded because they were not FDA-approved for the indication of AD at the time of data extraction.

Table 1 provides an overview of approved indications and prescribing information for FDA-approved non-steroidal AD agents. **Table 2** includes *proposed* AD indications and dosing for baricitinib, the agent currently seeking FDA approval for AD.

Table 1. FDA -Approved Agents for the Treatment of Atopic Dermatitis

Generic Name **Brand** and Preparation (approval year)	**Labeled Indication**	**Dosing Recommendation**	**Other FDA-approved Indications**
	Topical Phosphodiesterase 4 Inhibitor[a]		
Crisaborole **Eucrisa** • 2% ointment (60g, 100g tube) (2016)	**Mild-to-moderate AD**, continuous use **Age**: ≥ 3 **months** old	**Adults and children:** thin layer topically to affected skin BID	None
	Topical Calcineurin Inhibitor(s)[a]		
Pimecrolimus **Elidel** Generic available • 1% cream (30g, 60g, 100g tube) (2001)	**Mild-to-moderate AD** in non-immunocompromised patients, as a second-line therapy after failure (or inadvisable use) of other topical prescription options for short-term, non-continuous chronic use[b] **Age:** ≥ 2 years • Not for children under 2 years • Do not use with occlusive dressing	**Adults and children:** thin layer topically to affected skin BID	None
Tacrolimus **Protopic** Generic available • 0.03% ointment (30g, 60g, 100g tube) • 0.1% ointment (30g, 60g, 100g tube) (2000)	**Moderate-to-severe AD** in non-immunocompromised patients, as a second-line therapy after failure (or inadvisable use) of other topical prescription options for short-term, non-continuous chronic use[b] **Age:** ≥ 2 years • Not for children under 2 years • Do not use with occlusive dressing	**Adults and children:** thin layer topically to affected skin BID • 0.03%: for age 2 to 15 years • 0.03% or 0.1%: for age ≥ 16	None
	Topical Janus Kinase Inhibitor[a]		
Ruxolitinib **Opzelura**	**Mild-to-moderate AD** in non-immunocompromised patients, after failure (or inadvisable use) of other topical prescription options for short-term, non-continuous chronic use[c]	**Adults and children:** thin layer topically to affected skin BID • No more than 20% of BSA per application	None

Table 1. FDA -Approved Agents for the Treatment of Atopic Dermatitis

• 1.5% cream (60g tube) (2021)	**Age**: ≥ 12 years Limitation: not recommended for use in combination with strong immunosuppressants (ie, therapeutic biologics, other JAK inhibitors, or others like azathioprine or cyclosporine)	• No more than 60 grams per week	
Systemic Interleukin-4 Receptor Alpha Antagonist			
Dupilumab **Dupixent** • 300 mg/2mL; 200 mg/1.4 mL pre-filled pen • 300 mg/2 mL; 200 mg/1.14 mL; 100 mg/0.67 mL pre-filled syringe (2017)	**Moderate-to-severe AD** that is not controlled by *topical* prescription treatment (or when these options cannot be used), <u>continuous use</u> **Age:** ≥ 6 years • Pens are only for age ≥ 12 years	**Adults:** 600 mg SQ initially[d], then 300 mg SQ Q2W **Children (6 to 17 years old):** weight-based dose • 15 to <30 kg: 600 mg SQ initially[d], then 300 mg Q4W • 30 to <60 kg: 400 mg initially[d], then 200 mg Q2W • 60 kg+: same dosing as adults	Moderate to severe asthma (eosinophilic phenotype or oral corticosteroid dependent), add-on maintenance treatment (age ≥ 6) CRwNP, add-on maintenance treatment (adults)
Systemic Selective Interleukin-13 Antagonist			
Tralokinumab **Adbry** • 150 mg/ mL pre-filled syringe (2021)	**Moderate-to-severe AD** that is not controlled by *topical* prescription treatment (or when these options cannot be used), <u>continuous use</u> **Age:** ≥ 18 years	**Adults:** 600 mg SQ initially[d], then 300 mg SQ Q2W Doses of 300 mg SQ Q4 weeks: consider for patients weighing <100 kg with response (clear or almost clear skin) after 16 weeks of treatment	None
Systemic Oral JAK Inhibitor(s)			
Abrocitinib **Cinbinqo** • 50 mg oral tablet • 100 mg oral tablet • 200 mg oral tablet	**Moderate-to-severe AD** that is not controlled by other *systemic* treatment, *including biologics* (or when these options cannot be used), <u>continuous use</u> **Age:** ≥ 18 years	**Adults:** 100 mg PO once daily Doses of 200 mg PO once daily: consider for patients not achieving an appropriate response after 12 weeks of 100 mg PO once daily	None

Table 1. FDA -Approved Agents for the Treatment of Atopic Dermatitis

(2022)	Limitation: not for combined use with other JAK inhibitors, biologic immunomodulators, or immunosuppressants (eg, azathioprine, cyclosporine)		
Upadacitinib **Rinvoq** • 15 mg oral tablet • 30 mg oral tablet (2022)	**Moderate-to-severe AD** that is not controlled by other *systemic* treatment, *including biologics* (or when these options cannot be used), continuous use **Age:** ≥ 12 years Limitation: not for combined use with other JAK inhibitors, biologic immunomodulators, or immunosuppressants (eg, azathioprine, cyclosporine)	**Children (weighing > 40 kg) and adults (< 65 years of age):** 15 mg PO once daily; may consider 30 mg PO once daily for patients not responding to 15 mg PO once daily **Adults (≥ 65 years of age) or severe renal impairment:** 15 mg PO once daily	Moderate to severe RA, with prior failure or intolerance to 1 or more TNF antagonists (adults)[15] Active PsA, with prior failure or intolerance to 1 or more TNF antagonists (adults)[15]

Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA, body surface area; CRwNP, Chronic rhinosinusitis with nasal polyposis; FDA,US Food and Drug Administration; g, gram; JAK, janus kinase; mg, milligrams; mL, milliliters; PO, by mouth; PsA, psoriatic arthritis; Q2W every other week; Q4W, every 4 weeks; SQ, subcutaneous; TNF, tumor necrosis factor;

[a] To be applied topically to affected area(s), and not for application to the eye, orally, intravaginally, etc.

[b] Apply only to area with AD. Stop treatment upon symptom resolution, and avoid long-term continuous use. Recommend seeing healthcare provider for symptoms lasting >6 weeks for confirmation of diagnosis.

[c] Stop treatment upon symptom resolution. Recommend seeing healthcare provider for symptoms lasting >8 weeks.

[d] Initial dupilumab doses are administered as 2 separate injections given together at 2 different SQ sites, and initial tralokinumab doses are given as 4 separate injections together at 4 different SQ sites. Recommended SQ sites: thigh, abdomen, upper arm (by caregiver only). Rotate injection sites.

Table 2. Emerging (Non FDA- Approved) Agent for the Treatment of Atopic Dermatitis

Generic Name ***(Proposed)*** **brand** Preparation	***Proposed*** **General AD Indication**	***Proposed*** **Dosing Recommendation**	**FDA-approved Indications**
Baricitinib **Olumiant** Tablet for oral use[9,16]	Moderate-to-severe AD[9] **Age:** adults[9]	1-2, or 4 mg PO once daily[2,30-32]	Moderate to severe RA, with prior failure or intolerance to 1 or more TNF antagonists (adults)[16] **Limitations:** not for combined use with other JAK inhibitors, biologic DMARDs, or potent immunosuppressants (eg, azathioprine, cyclosporine)[16]

Abbreviations: AD, atopic dermatitis; DMARD, disease-modifying antirheumatic drug; FDA, US Food and Drug Administration; JAK, janus kinase; mg, milligrams; PO, by mouth; TNF, tumor necrosis factor;

Methods

Systematic Literature Search

Search strategies, consisting of keyword phrases and controlled vocabulary, were developed for Ovid-Medline and Epistemonikos (see **Appendix A** for complete search strategy). Databases were searched from January 2018 to December 2021 for systematic reviews (SRs) of randomized controlled trials (RCTs). Ovid-Medline was searched for RCTs, to supplement the SR search, with a date restriction based on the latest search date of an included robust SR's search strategy, adjusted for the findings for each particular agent. The RCT search for JAK inhibitors and tralokinumab were limited to January 2021 to December 17, 2021 (based on the last search by an Institute for Clinical and Economic Review (ICER) SR),[2] pimecrolimus and crisaborole (based on the last search by Fahrbach et al),[41] and dupilumab (based on the last search by Nusbaum et al).[42] The RCT search for tacrolimus had an unrestricted timeframe due to a lack of robust SRs identified. A combination of independently derived filters and a McMaster University filter[43] were used to identify SRs in Ovid-Medline; a pre-programmed filter was used in Epistemonikos for SRs. Publication filters for RCTs were used in Ovid-Medline, obtained from the Cochrane Collaboration Handbook.[44]

Product prescribing information (ie, product labeling or package inserts) was searched on the FDA website (Drugs@FDA), dailymed.nlm.nih.gov, and/or drug sponsor's website. We additionally searched the drug sponsor's website for any preliminary information about drugs that were not approved by the FDA. As some non-FDA-approved medications have been approved in other countries, product information for these agents was searched on the regulatory site of other countries (ie, European Medicines Agency, https://www.ema.europa.eu/en/medicines) and Medicines & Healthcare products

Regulatory Agents of the United Kingdom, https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)

Authors additionally screened the references lists of related systematic reviews and other relevant websites for further information:

1. For guidelines or position statements addressing treatment of atopic dermatitis: websites of the American Academy of Dermatology (AAD), the American Academy of Allergy, Asthma & Immunology (AAAAI), ICER, and the National Institute for Health and Care Excellence (NICE)
2. Evidence-based drug information databases: Micromedex and Lexicomp

Screening

Two reviewers independently screened publication titles and abstracts for inclusion. Conflicts were resolved by consensus between reviewers. The full text for all articles receiving 2 inclusion votes were retrieved, and inclusion was determined by the lead author. **Figure 1** in **Appendix B** shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria

SRs or systematic reviews and meta-analysis (SRMAs) of RCTs, and RCTs that included direct head-to-head efficacy comparisons among the AD agents of interest were included. For the non-FDA approved agents, studies of these types with a comparison to placebo were also included. Although tralokinumab, upadacitinib, and abrocitinib are now FDA-approved, at the time of the literature search and data extraction, these agents had not yet received approval, thus these placebo comparisons are provided in **Appendix C.**

Excluded references met the following criteria: 1) review articles that did not utilize a systematic review methodology, 2) for FDA approved agents, RCTs with placebo comparison and without a comparison to another AD agent of interest, 3) network meta-analyses without direct comparisons, 4) systematic reviews containing only phase II RCTs, 5) systematic reviews not reporting efficacy-related outcomes, 6) post-hoc exploratory or subgroup analyses, pharmacokinetic studies, or observational studies, 7) studies addressing use for indications other than atopic dermatitis, 8) for the supplemental RCT search, phase II studies.

Disease Overview

Atopic dermatitis (AD), or atopic eczema, is a chronic inflammatory skin disorder characterized by pruritus, pain, and persistent or relapsing inflammatory eczematous lesions due to skin barrier dysfunction and immune system imbalances.[3-5,36,45] Symptoms (eg, skin itching, visible eczemas and sleep issues) can drastically impact a patient's health-related quality of life (QoL) due to psychological distress and difficulty with productivity at work or school.[2,3] Additionally, families and the health care system suffer a significant economic burden due to routine medical visits, treatment, and work/school related absence.[2,3]

AD predominately affects children ≤ 5 years of age (90% of cases), but may occur at any age.[1-5,36] It affects up to 20-25% of the pediatric population and approximately 1% to 3% of adults.[3,5] Among children, approximately 80% of cases are considered mild, and most (up to 70%) experience improvement or resolution in late childhood.[3,36] Distribution of skin patterns tends to be age-related with lesions manifesting on the face and extensor surfaces of the extremities in infants, flexural folds in children, and wrists, ankles, head, and upper trunk in adults.[3,36]

The pathogenesis of AD involves complex mechanisms pertaining to genetic, immunologic, and environmental factors that result in skin barrier dysfunction and immune system imbalances.[3-5,36] AD is often associated with the occurrence of other allergic conditions, such as asthma and allergic rhinitis.[1-4,36] Approximately 70% of AD patients have a family relative affected by an atopic disorder, such as allergic rhinitis, asthma, or food allergy.[3-5] A strong genetic risk factor for developing AD is the presence of null mutations in the FLG gene (filaggrin), which encodes epidermal structural proteins important for skin integrity.[3,5,36] Several environmental and lifestyle factors also play a role in developing AD, including living in urban areas with minimal sunlight and humidity, tobacco smoke, and irritants, such as soaps and detergents.[3,5,36]

Diagnosis of AD is based on the clinical features such as pruritus, skin dryness, and distribution of eczematous lesions.[3-5] The American Academy of Dermatology (AAD) recommends a simplified version of the Hanifin and Rajka criteria (2003) for diagnosis in clinical practice.[4] **Table 3** outlines the revised Hanifin and Rajka criteria for diagnosing AD in infants, children, and adults.

Table 3. Revised Hanifin and Rajka Criteria for the Clinical Diagnosis of Atopic Dermatitis[3,4]

- **Essential features** that must be present: pruritus and eczema (typical morphology with age-specific patterns; chronic or relapsing history)
- **Important features** that are present in most cases: early age of onset, atopy such as personal and/or family history and IgE reactivity, and xerosis
- **Associated features** that are suggestive of AD: atypical vascular response, keratosis pilaris, ocular/ periorbital changes
- **Exclusionary conditions** that should not be considered as AD: eg, scabies, seborrheic dermatitis, psoriasis, contact dermatitis

Abbreviations: AD, atopic dermatitis; IgE, immunoglobulin E

The most frequently used scales to measure AD disease severity are the Scoring Atopic Dermatitis (SCORAD) Index, Eczema Area Severity Index (EASI), Investigator's Global Assessment (IGA), and Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score.[3,4] The scales were developed for use in clinical trials; the ADD does not recommend them for regular clinical care.[4] Similarly, QoL scales and disease impact measurements such as the Children's Dermatology Life Quality Index (CDLQI) and the Dermatology Life Quality Index (DLQI) were not designed for use in clinical practice.[4] Nevertheless, consideration to use the SCORAD index, the EASI score, and the Patient Oriented Eczema Measure (POEM) scales in clinical practice may be warranted due to available evidence suggesting adequate testing and validation.[4] **Table 4** includes information regarding components of commonly used AD disease severity assessment tools.

An explicit definition of mild, moderate, and severe AD is not declared in the US guidelines.[4-7] Despite the lack of formal definition, mild AD tends to affect less body surface area (BSA), resolves over time, and is associated with minor pruritus intensity.[3,37] In contrast, moderate-to-severe AD tends to affect a larger BSA, expresses a continuous progression, and is associated with severe pruritus intensity.[3,37] The National Institute for Health and Care Excellence (NICE) defines mild, moderate, and severe AD based on the extent of skin lesions, intensity of pruritus, and impact on QoL.[1] The progression in disease severity requires additional treatment options for management.[5-7,17,23,37]

Table 4. Common Severity Scales for Assessing Atopic Dermatitis[3,4]

SCORAD[46]	EASI[47]	IGA[48]
Components Measured in Each Scale		
• **Severity of physical clinical symptoms[a]:** erythema, edema/induration/papulation, oozing/crusting/weeping/exudation, excoriation, and lichenification • **Disease extent:** percentage of BSA • **Symptoms[b]:** pruritus and sleep difficulties • **SCORAD > 50:** severe AD **SCORAD 25-50:** moderate AD **SCORAD <25:** mild AD	• **Severity of physical clinical symptoms[a]:** erythema, edema/induration/papulation, excoriation, and lichenification • **Disease extent[c]:** percentage of BSA affected in the head/neck, upper extremities, lower extremities, and trunk	• **Severity of physical clinical symptoms[d]:** erythema, edema/induration/papulation, oozing/crusting/weeping/exudation, excoriation, lichenification, and scaling • **Limitations:** No standardized IGA. High variability in nomenclature, definitions, and scale size between clinical trials

Abbreviations: AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area Severity Index; IGA, Investigator's Global Assessment; SCORAD, Scoring Atopic Dermatitis

[a] Scores range from 0, absence, to 3, severe

[b] Scores range from 0, none to 10, maximum severity

[c] Score ranges from 0-72, with 72 being the most aggressive and severe score

[d] Scores range from "clear" to "severe" or "very severe"

Clinical Practice Guideline Recommendations

Goals of pharmacologic treatment for AD include reducing skin inflammation and pruritus, restoring skin barrier properties, and improving patient quality-of-life (QoL).[2,5,6,17] Topical agents are considered the foundation of AD therapy recommended by the most recent US guidelines (American Academy of Dermatology (AAD) [2014] and American Academy of Allergy, Asthma & Immunology (AAAAI)/ American College of Allergy, Asthma & Immunology (ACAAI) practice parameter [2012]).[5,6] To maintain disease control in more severe cases of AD, combination therapy with topical and systemic agents and/or phototherapy is recommended.[5,7] According to the AAD guideline, non-pharmacologic interventions include topical moisturizers, bathing practices, and wet wrap therapy; pharmacologic topical treatment includes corticosteroids (TCSs) and calcineurin inhibitors (TCIs); and systemic treatment options include immunologic or anti-inflammatory agents and phototherapy.[6,7]

Overview of Topical Treatment

US guidelines address use of TCIs, but predate approval of other topicals reviewed in this report; the general approach to topical treatment is as follows. Topical moisturizers are recommended as first-line treatment for AD, regardless of disease severity.[5,6] TCSs are recommended when monotherapy with moisturizers do not achieve a desired response in skin improvement.[6] TCSs are available at low, medium, or high potency; potency selection depends on the affected area(s), age of the patient, patient preference, severity, and cost of therapy.[6] TCIs (tacrolimus ointment, and pimecrolimus 1% cream) are second-line agents recommended for acute and non-continuous chronic treatment in adults and children ≥ 2 years of age, who have failed to respond to other topical prescription treatments, or when an intolerance exists to those treatments.[5,6,17-19] Tacrolimus is available in two different concentrations, 0.03% and 0.1%, with only the lower concentration recommended for children 2 to 15 years of age.[19] The US clinical practice guidelines (AAD [2014] and (AAAAI/ACAAI) [2012] practice parameter) do not state a preference for one TCI over another; however, TCIs may be preferred to TCSs in particular clinical situations (ie, steroid resistance, involvement of sensitive areas, manifestation of steroid-induced atrophy, and long-term continuous use of TCSs).[6] During commitment use with a TCS, the TCS is administered first to control flares and reduce local skin reactions associated with TCIs.[6]

The US 2014 AAD guideline only mentioned the topical phosphodiesterase inhibitor (TPI), crisaborole, as investigational.[6] Recommendations for use of crisaborole are also not included in more recent guidelines from other countries such as the 2018 consensus-based European guidelines and the 2020 European Task Force on Atopic Dermatitis of the European Academy of Dermatology and Venerology (ETFAD/EADV) position paper, possibly due to lack of regulatory approval.[17,24] Nevertheless, the consensus-based guideline highlights that it was shown to be more efficacious than the controlled vehicle in patients ≥ 2 years of age with mild-to-moderate AD in clinical trials; however, the efficacy compared to other topicals (TCIs or TCSs) is difficult to ascertain.[17] The other topical, ruxolitinib, is approved for treatment of mild-to-moderate AD in patients ≥ 12 years of age; its use is not yet addressed by reviewed US or European guidelines, likely due to its approval in only the later part of 2021.

Overview of Systemic Treatment

Systemic immunomodulatory agents (eg, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil) and/ or phototherapy are recommended for adult and pediatric patients with AD refractory to conventional topical therapy (eg, moisturizers, TCSs, and TCIs).[3,7]

Although they are not yet addressed in US guidelines,[5,7] other therapies including dupilumab, tralokinumab, abrocitinib, and upadacitinib, are likely additional treatment options for patients requiring systemic therapy. Some European organizations have provided recommendations about the use of systemic agents not addressed by US guidelines. The National Institute for Health and Care Excellence (NICE) recommends dupilumab or baricitinib as alternative options for adults with moderate-to-severe AD, unresponsive or intolerant/contraindicated to at least one other systemic immunosuppressant agent (eg, cyclosporin, methotrexate, azathioprine, or mycophenolate mofetil).[21,22] The 2018 European guideline more narrowly recommends the use of dupilumab exclusively for moderate-to-severe AD in adults, in which disease control is not achieved with topical treatment and a contraindication exists, or is not suitable to use other systemic treatments.[17,23] The updated 2020 ETFAD/EADV position paper recommends dupilumab for individuals (≥ 12 years of age) with moderate-to-severe AD, requiring systemic therapy.[24] JAK inhibitors such as upadacitinib and the selective IL-13 antibody, tralokinumab, were only mentioned by European guidelines as systemic medications that are under development.[23,24]

Treatment Approach in Children

Treatment algorithms for pediatrics are similar to adults,[5-7] but the appropriateness of product options may vary based on the FDA approved age. In children under 12 years of age, NICE recommends a stepwise approach based on disease severity, with mild AD requiring emollients and mild potency TCSs only.[1] TCIs are reserved for moderate and severe AD and are not recommended as first-line for any disease severity.[1] Similar to adults, systemic agents and/ or phototherapy should be used in severe refractory cases of AD.[1]

Table 5 includes guideline recommendations only pertaining to the non-steroidal agents of interest for the treatment of AD. A complete summary of clinical practice guideline recommendations for the treatment of AD is provided in **Table 1** in **Appendix D.**

Table 5. Summary of Clinical Practice Guideline Recommendations Regarding Non-steroidal Agents for Atopic Dermatitis

Guideline (Sponsoring Organization; Year)	Recommendations[a]
	United States Guidelines

Guidelines of Care for the Management of Atopic Dermatitis: Part 2: Management and Treatment of Atopic Dermatitis with Topical Therapies **(AAD; 2014)[6]**	• For *children and adults*, TCIs (tacrolimus and pimecrolimus) are recommended for acute and non-continuous chronic treatment, in addition to maintenance (2-3 times per week). (**Level I, Strength A**) These agents are preferred to topical steroids in the following situations:
	  ○ Refractory to steroids
	  ○ Application to sensitive areas (eg, face, anogenital, skin folds)
	  ○ Presence of steroid-induced atrophy
	  ○ Long-term continuous topical steroid use
	• TCIs are recommended in "actively affected areas as a steroid-sparing agent" (**Level I, Strength A**)
	• "The concomitant use of a TCS with a TCI may be recommended for the treatment of AD" (**Level II, Strength B**)

The Joint Task Force on Practice Parameters on Atopic Dermatitis **(AAAAI, ACAAI, and the JCAAI; 2012)[5]**	• For the treatment of AD, TCIs (pimecrolimus and tacrolimus) may be considered (**Strength A**)
	  ○ Topical tacrolimus ointment, "unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids" (**Strength A**)
	  ○ Topical pimecrolimus cream, "safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus" (**Strength A**)

	European Guidelines
Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part 1 **(EDF, EADV, EAACI, ETFAD, EFA, ESPD. GA2LEN, UEMS; 2018)[17]**	<u>Adults</u> • Mild (SCORAD <25 or transient eczema): "Reactive therapy with topical glucocorticosteroids class II or depending on local cofactors; topical calcineurin inhibitors, antiseptics including silver, silver coated textiles" • Moderate (SCORAD 25-50/ or recurrent eczema): "Proactive therapy with topical tacrolimus or class II or III topical glucocorticosteroids, wet wrap therapy, UV therapy (UVB 311 nm), psychosomatic counseling, climate therapy • Severe (SCORAD >50 or persistent eczema): "Hospitalization, systemic immunosuppression, dupilumab" <u>Children:</u> • Mild (SCORAD <25 or transient eczema): same as adults • Moderate (SCORAD 25-50/ or recurrent eczema): same as adults

Table 5. Summary of Clinical Practice Guideline Recommendations Regarding Non-steroidal Agents for Atopic Dermatitis

Guideline (Sponsoring Organization; Year)	Recommendations[a]
	• Severe (SCORAD >50/ or persistent eczema): "Hospitalization, systemic immunosuppression: cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil" Recommendations: • Treatment with TCS should be considered for treating acute exacerbations before switching to a TCI (**Level -, Strength D**) • TCIs are indicated in sensitive skin area(s) (eg, face, intertriginous sites, anogenital) (**Level 1b, Strength A**) • Bi-weekly application of tacrolimus ointment may reduce relapses (**Level 1b, Strength A**)
Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part 2 **(EDF, EADV, EAACI, ETFAD, EFA, ESPD. GA2LEN, UEMS; 2018)[23]**	• Dupilumab is recommended in adults with moderate-to-severe AD, in which disease control is not achieved with topical treatment and a contraindication exists or it is not advisable to use other systemic treatment (**Level 1, Strength A**) ○ Should be used with emollients daily and may be used with topical anti-inflammatory agents as needed (eg, TCS) (**Level 2, Strength B**) ***Note*** *that the pediatric AD indication approval for dupilumab may have occurred after this guidelines was published.*
Guideline on Atopic Dermatitis; **(NICE; 2013)[1]**	• TCIs (tacrolimus and pimecrolimus) are not recommended as first-line agents for AD, and should be initiated after a failed response to TCSs ○ TCIs should not be used for mild AD • As second-line agents (TCIs), use is recommended when there is concern for serious adverse events from continued TCS use (eg, irreversible skin atrophy)
Dupilumab for treating moderate to severe atopic dermatitis; **(NICE; 2018)[22]** • A technology appraisal guidance	• Dupilumab is recommended for moderate-to-severe AD in adults that have an inadequate response to at least one other systemic therapy (eg, ciclosporin, methotrexate, azathioprine, mycophenolate mofetil) or a contraindication exists • Dupilumab should be stopped at 16 weeks if at least a 50% reduction in EASI and at least a 4-point reduction in the DLQI has not occurred from treatment initiation • Dupilumab may be used with or without TCS

Table 5. Summary of Clinical Practice Guideline Recommendations Regarding Non-steroidal Agents for Atopic Dermatitis

Guideline (Sponsoring Organization; Year)	Recommendations[a]
	• TCIs may be used with dupilumab, but TCI use should be reserved to sensitive areas (eg, face, neck, anogenital, skin folds)
Baricitinib for treating moderate to severe atopic dermatitis; **(NICE; 2021)**[21] • A technology appraisal guidance	• Baricitinib is recommended for moderate to severe AD in adults that have an inadequate response to at least one other systemic therapy (eg, ciclosporin, methotrexate, azathioprine, mycophenolate mofetil) or a contraindication exists • Response should be assessed at 8 weeks and stopped at 16 weeks if at least a 50% reduction in EASI and at least a 4-point reduction in the DLQI has not occurred from treatment initiation

Abbreviations: AAAAI, American Academy of Allergy, Asthma & Immunology; AAD, American Academy of Dermatology; ACAAI, American College of Allergy, Asthma & Immunology; AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EAACI, European Academy of Allergy and Clinical Immunology; EADV, European Academy of Dermatology and Venereology; EASI, Eczema Area and Severity Index; EDF, European Dermatology Forum; EFA, European Federation of Allergy and Airways Diseases Patients' Associations; ESPD, European Society of Pediatric Dermatology; ETFAD, European Task Force on Atopic Dermatitis; GA2LEN, Global Allergy and Asthma European Network; JCAAI, Joint Council of Allergy, Asthma, and Immunology; NICE, National Institute for Health and Care Excellence; PUVA, psoralen and ultraviolet; QoL, quality of life; SCORAD, Scoring Atopic Dermatitis; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; UEMS, European Union of Medical Specialists; UVB, ultraviolet B

[a] See Appendix D for complete recommendations and information about interpretation of level of evidence (LOE) and strength of recommendations

Pharmacology

Each of the agents in this report are thought to modulate inflammatory mediators involved in AD pathogenesis. Proposed mechanisms of action are shown in **Table 6** and summarized below.

Table 6. Mechanism of Action of Non-steroidal Atopic Dermatitis Products[a]

Generic Name (administration route)	Proposed Pharmacology
JAK Inhibitors	
Abrocitinib[14] (oral)	**JAK1 inhibitor** JAK1 preference over other JAK enzymes: • JAK2 – 28 fold; JAK3 – >340 fold; TYK2 – 43-fold
Baricitinib[16] (oral)	**JAK inhibitor** • Inhibits several JAK enzymes (JAK1, JAK2, TYK2) > JAK3
Ruxolitinib[35] (topical)	**JAK1 and JAK2 inhibitor**
Upadacitinib[15] (oral)	**JAK inhibitor** • Inhibits several JAK enzymes (JAK1, JAK2) > (JAK3, TYK2)
Calcineurin Inhibitors	
Pimecrolimus[18] (topical)	Mechanism for AD activity not known • Binds macrophilin-12 (FKBP-12), an intracellular protein • Inhibits calcineurin
Tacrolimus[19] (topical)	Effects T-cell signaling by inhibition of activating cytokines
PDE-4 Inhibitor	
Crisaborole[33] (topical)	Mechanism for AD activity not known • Increases intracellular cAMP through actions on PDE-4
IL-13 Inhibitors	
Tralokinumab[12] (subcutaneous injection)	**Inhibits IL-13** signaling
Dupilumab[13] (subcutaneous injection)	**Inhibits IL-13** (Type II receptor) **and IL-4** (Type I and II receptor) signaling

Abbreviations: IL, interleukin; JAK, janus kinase; PDE, phosphodiesterase; TYK, tyrosine kinase;

[a] Information is from package inserts (ie, prescribing information). For baricitinib, information is based on US approval for treatment of RA; information may change if approved for treatment of AD.

JAK inhibitors target one or more JAK enzyme subtypes, leading to modulation of downstream cytokine signal transduction. JAK inhibitors suppress the JAK/STAT (Signal Transducer and Activator of Transcription) signaling pathway. Normally, JAKs couple with a cytokine receptor and activate STAT

transcription factor proteins, affecting gene expression involved in creation of inflammatory mediators, activation of some T helper cells, and other effects (eg, hematopoiesis).[49] JAK inhibitors vary in their specificity for the different kinases as shown in **Table 7**. The relevance of these differences in terms of effectiveness is not established,[35] though it is known that downstream effects differ among the JAKs.[49]

Both pimecrolimus and tacrolimus (TCIs) are inhibitors of the phosphatase calcineurin, which occurs via complex formation between the TCI and macrophilin-12.[50] Their exact actions in AD are not known.[18,19] However, it is known that inhibition of calcineurin selectively reduces T-cell activation and subsequent creation of cytokines, leading to anti-inflammatory effects. Additionally, actions in mast cells reduce formation of proinflammatory cytokines (eg, TNF-alpha) or mediators.[19,50]

The benefits of crisaborole for AD are not fully understood. Crisaborole is established as an inhibitor of phosphodiesterase (PDE)-4; inhibition of this leads to increases in cyclic adenosine monophosphate (cAMP) within cells which may decrease production of cytokines involved in AD pathogenesis. It may also directly affect keratinocytes.[51]

Both dupilumab and tralokinumab are human monoclonal IgG4 antibodies that inhibit signaling by certain interleukins (IL) involved in the aberrant pathology of AD.[12,13] Dupilumab binds to the IL-4 receptor alpha subunit to disrupt signaling by the type 2 cytokines, IL-4 and IL-13.[13,52] Tralokinumab binds directly to IL-13 preventing its binding to certain receptors.[12] Both IL-4 and IL-13 drive mediators of the type 2 inflammatory pathway which is overactive in patients with AD.[53]

Pharmacokinetics and Use in Special Populations

Pharmacokinetics and Drug-Drug Interactions

Topical products, including ruxolitinib when applied in patients with ≤ 20% of BSA affected by AD, are considered to have a reduced or negligible risk for systemic exposure, which may lead to a lower risk for systemic adverse effects.[51,54,55]

Comparative pre-clinical (pigs, *in vitro* human) data suggest that pimecrolimus and tacrolimus reach similar concentrations in the skin,[56] but pimecrolimus has a lower potential to permeate through the skin than tacrolimus.[56,57] This is expected to translate to lower relative systemic exposure and possibly therefore less systemic immune effects for pimecrolimus[56,57]; however, that was not compared in these studies. In a pharmacokinetic (PK) study comparing treatment with pimecrolimus 1% cream or tacrolimus 0.1% ointment twice daily for 13 days among adults with severe AD, higher systemic exposure to tacrolimus was observed in patients with detectable blood concentrations. Detectable blood concentrations occurred in 36% of tacrolimus samples, and 12% of pimecrolimus samples.[55]

The elimination half-life for the oral JAK inhibitors is sufficient to facilitate once daily dosing.[15,16,34] Subcutaneously administered antibodies, dupilumab and tralokinumab have longer elimination half-lives, facilitating every other week dosing in most patients.[12,13]

Biologic products like dupilumab and tralokinumab carry a risk of immunogenicity. Among dupilumab- and tralokinumab-treated patients, anti-drug antibodies (ADA) have been detected in a small proportion of patients.[12,13] For dupilumab, high ADA titer levels have been associated with undetectable drug levels. Two adult patients who developed high titers during dupilumab treatment experienced serum sickness-like symptoms.[13] For tralokinumab, ADA were not associated with changes in drug exposure.[12]

Drug-drug interactions (DDIs) are a potential concern for most of these agents except for crisaborole.[33] For the other topical agents, labeling warns of potential DDIs between pimecrolimus, tacrolimus, and ruxolitinib and CYP3A4 inhibitors[18,19,35] or CYP3A4 inducers (for ruxolitinib).[35] Avoiding use of ruxolitinib with *strong* CYP3A4 inhibitors is recommended due to the potential increased exposure to ruxolitinib.[35] Among the systemic therapies, PK interactions with the antibodies (dupilumab, tralokinumab) are unlikely.[12,13] Each oral JAK inhibitors have the potential for DDIs, varying by product, as shown in **Table 8.** US labeling for abrocitinib, baricitinib, and upadacitinib includes that concomitant use with other specific immunosuppressant therapies (other JAK inhibitors, biologic immunomodulators, or potent immunosuppressants) are not recommended.[14-16] Live vaccinations are not recommended in patients receiving the systemic therapies.[12-16]

Table 7. Pharmacokinetic, Drug-drug Interactions and Dosage Adjustment Information[a]

Generic Name *(proposed)* brand	Select PK information	Metabolism and Excretion Dose adjustment	Drug-drug Interactions and Selected Special Populations Information
Topical therapies			
Crisaborole[33] (Eucrisa)	Systemic steady state reached by 8 days	• Hepatic metabolism (hydrolysis, oxidation) to inactive metabolites • Renal excretion No dose adjustments reported	**DDIs:** Not expected to interact with metabolizing enzymes (eg, CYP450) or transporters to a clinically significant degree **SP:** use not established for age <3 months old
Pimecrolimus[18,58] (Elidel)	Minimal to no systemic accumulation after repeated use	• Hepatic metabolism • Excretion: feces (78.4% metabolite, <1% unchanged) No dose adjustments reported	**DDIs:** CYP3A4 substrate; DDIs after topical use are unlikely, but not impossible. Exercise caution with CYP3A4 inhibitors (eg, erythromycin, itraconazole, ketoconazole). **SP:** numerically more children with detectable blood levels (at least one) than adults. Use not established for age <2 years.
Ruxolitinib[35] (Opzelura)	Minimal to no systemic accumulation after repeated use **Terminal $T_{1/2}$:** 116h	• Metabolism by CYP3A4, and CYP2C9 (minor) • Excretion (mostly as metabolites, <1% unchanged drug): urine (74%), feces (22%) No dose adjustments reported	**DDIs**: CYP3A4 inhibitors increase systemic exposure; CYP3A4 inducers reduce systemic exposure • Avoid use with strong CYP3A4 inhibitors **SP:** use in children <12 years old not established. At supratherapeutic doses, growth/bone toxicity observed in juvenile rats.
Tacrolimus[19] (Protopic)	Minimal to no systemic accumulation after repeated use • **BA** ~0.5% **$T_{1/2}$** (after oral use)**:** ~32 to 48 h	• Metabolism by CYP3A4 (extensive) • Excretion (based on oral administration): fecal (93%), urine (2%) No dose adjustments reported	**DDI** after topical use are unlikely, but not impossible. Exercise caution with CYP3A4 inhibitors. **SP:** low blood concentrations detected in children, with exposure declining after longer duration of use. Use in children <2 years old not established.
Oral therapies			

Table 7. Pharmacokinetic, Drug-drug Interactions and Dosage Adjustment Information[a]

Generic Name *(proposed)* brand	Select PK information	Metabolism and Excretion Dose adjustment	Drug-drug Interactions and Selected Special Populations Information
Abrocitinib[14] (Cinbinqo)	**BA** (absolute): 60% **$T_{1/2}$:** ~3 to 5 h	• Metabolism: extensive (by CYP2C19 [53%], CYP2C9 [30%], CYP3A4 [11%], CYP2B6 [6%]) to active and inactive metabolites • Excretion: metabolic clearance (primary; <1% unchanged in urine); metabolites eliminated renally Reduce dose for moderate RI • Use not recommended: severe RI or severe HI	**DDI:** Substrate of multiple CYP enzymes, and P-gp inhibitor. Metabolites are OAT3 substrates. • Strong CYP2C19 inhibitors: reduce dose • Moderate to strong CYP2C19/CYP2C9 inducers: use not recommended • P-gp substrates: caution • Vaccinations: no data. Avoid live vaccines. **SP:** No data for children <12 years old. Systemic exposure increased with mild to severe RI; *not studied in patients with ESRD on RRT or severe HI.*
Baricitinib[16] (Olumiant)	**BA** (absolute): 80% **$T_{1/2}$** (RA patients)**:** ~12 h	• Hepatic metabolism by CYP3A4 (~6%) • Excretion: primarily renal (75% urine [69% unchanged], 20% feces [15% unchanged] Reduce dose for moderate RI • Use not recommended: severe RI or severe HI	**DDI**: substrate of CYP3A4, OAT3, P-gp, BCRP, MATE2-K. • Reduce dose with strong OAT3 inhibitors (eg, probenecid) • Not studied in combination with other JAK inhibitors or biologic DMARDs • Vaccinations: avoid live vaccines. **SP:** Systemic exposure increased with mild to severe RI. Use not established in children.

Table 7. Pharmacokinetic, Drug-drug Interactions and Dosage Adjustment Information[a]

Generic Name *(proposed)* brand	Select PK information	Metabolism and Excretion Dose adjustment	Drug-drug Interactions and Selected Special Populations Information
Upadacitinib[15] (Rinvoq)	**BA:** NR **Terminal $T_{1/2}$:** 8 to 14 h	• Metabolized by CYP3A4 (major) and CYP2D6 (minor) to inactive metabolites • Excretion: unchanged (urine, 24%; feces, 38%); as metabolites, 34% Reduce dose for severe RI • Use not recommended: severe HI	**DDI:** Substrate of multiple CYP enzymes • Strong CYP3A4 inhibitors, chronic use: caution • Strong CYP3A4 inducers: use not recommended • Not recommended: use with other JAK inhibitors, biologic immunomodulators or potent immunosuppressants **SP:** Higher rates of AE observed in elderly. *Not studied in patients with ESRD.*
Subcutaneous Therapies			
Dupilumab[13] (Dupixent)	**BA:** 61 to 64% **Time to SS:** reached by week 16 **Median time to undetectable levels** (after last SS dose): 10-12 weeks (300 mg Q2W last dose); or 9 weeks (200 mg Q2W last dose)	• Not characterized; expected: catabolism into peptides No dose adjustments reported	**DDIs** that affect the PK of other drugs are unlikely • Avoid live vaccines • Immune responses to non-live vaccines occur **SP:** lower troughs among people with higher body weight. Use not established for children <6 years old. **Immunogenicity:** Ab to dupilumab have been detected (~5%); ADA with neutralizing Ab detected (~1 to 5%). High titers associated with undetectable dupilumab levels.

Table 7. Pharmacokinetic, Drug-drug Interactions and Dosage Adjustment Information[a]

Generic Name *(proposed)* brand	Select PK information	Metabolism and Excretion Dose adjustment	Drug-drug Interactions and Selected Special Populations Information
Tralokinumab[12] (Adbry)	**BA** (absolute): 76% **Time to SS:** reached by week 16 **$T_{1/2}$:** 22 days	• Catabolism into peptides via non-saturable proteolysis No dose adjustments for RI/HI reported. There is limited data for severe RI or moderate to severe HI. • *High body weight (>100 kg):* may consider NOT reducing dosing frequency if positive response after 16W	**DDIs:** No data on effect on PK of other drug entities • Avoid live vaccines • Immune responses to non-live vaccines occur **SP:** lower troughs among people with higher body weight. No PK studies available for children, use not established for children <18 years old. **Immunogenicity:** ADA detected (4.6%); persistent ADA (0.9%), neutralizing Ab (1%). ADA did not affect tralokinumab levels.

Abbreviations: Ab, antibodies; AD, atopic dermatitis; ADA, antidrug antibodies; BA, bioavailability; BCRP, Breast Cancer Resistance Protein; CYP, cytochrome P450; DDI, drug-drug interaction; ESRD, end stage renal disease; h, hour; HI, hepatic impairment; MATE, multidrug toxic extrusion protein; NR, not reported; OAT, organic anion transporting polypeptide; P-gp, P-glycoprotein; PK, pharmacokinetic; RA, rheumatoid arthritis; RI, renal impairment; RRT, renal replacement therapy (eg, hemodialysis); SP, special populations; SS, steady state; $T_{1/2}$, elimination half-life; Q2W, every 2 weeks; W, weeks

[a] Information is from package inserts (ie, prescribing information). For baricitinib, information is based on US approval for treatment of RA; information may change if approved for treatment of AD.

Patients with Renal or Hepatic Impairment

As shown in **Table 7,** most of the agents do not require adjustment for renal or hepatic impairment, according to product labeling.[12-16,18,19,33,35] Dose adjustments are required among the oral JAK inhibitors. Abrocitinib and baricitinib (per treatment of RA) require reduced doses for moderate renal impairment and use is not recommended in patients with severe renal impairment.[14,16] No dosage adjustment is necessary for upadacitinib in mild or moderate renal impairment; however, a reduced dose (15 mg once daily) is recommended for patients with severe renal impairment.[15] For upadacitinib, baricitinib, and abrocitinib use is not recommended in patients with severe hepatic impairment (ie, Child Pugh class C).[14-16]

Pediatric and Geriatric Use

Crisaborole has the youngest age of approval, with supportive evidence for use in children as young as 3 months old.[33,38] Among non-topical therapies, dupilumab has the youngest age with supportive evidence for use, among children as young as 6 years old.[13]

Regarding use in older adults (age ≥ 65 years), product labeling for crisaborole, pimecrolimus, dupilumab, and tralokinumab states that there is insufficient evidence to determine if there are meaningful differences and safety or efficacy compared to younger patients.[12,13,18,33] For dupilumab, the minimal available data does not suggest meaningful differences.[13] For tacrolimus, no differences in the adverse event profile compared to other populations were observed.[19] Similarly, for ruxolitinib, no meaningful differences in safety or efficacy compared to younger patients have been observed.[35] For tralokinumab, the product labeling does not suggest dose adjustments for older adults, but note that evidence in adults ≥ 65 years old is limited.[12] For the oral JAK inhibitors, labeling supports that the safety profile in older adults may be worse compared to younger patients.[14-16] For baricitinib, no differences have been observed (among RA patients), but possible differences have not been eliminated.[16] Since baricitinib is renally eliminated, older adults with poor renal function may be more sensitive to its effects.[16] More frequent adverse events were observed among older adults versus younger patients treated with upadacitinib.[15] Similarly, older adults were more sensitive to adverse events, including serious events, with abrocitinib; higher rates of low platelets and herpes zoster infection occurred compared to younger populations in clinical studies.[14]

Pregnancy and Breastfeeding

In general, there is a paucity of data to guide use of these agents during pregnancy or breastfeeding. **Table 8** includes information about use of these products during pregnancy or lactation according to prescribing information from the manufacturer.

AD may present as a new diagnosis or may worsen during pregnancy. Lack of appropriate treatment may increase maternal and fetal risks for complications of AD such as eczema herpeticum or staphylococcus aureus infections, and exacerbate maternal stress which could have deleterious effects.[20] The European Task Force on Atopic Dermatitis (ETFAD, 2019) proposed an algorithm for management of pregnant women with AD.[20] This approach includes stepwise therapy according to patient response; first is use of emollients, followed by class II/III TCS for 2 weeks, then narrow-band

UVB or natural sunlight. TCIs (or proactive class II TCS) are listed as an option if the patient initially responds to the 2 weeks of TCS but relapses within 1 week. Systemic therapies (cyclosporin [1st line], systemic corticosteroids [2nd line], or azathioprine [at a reduced dose]) are an option after failure of UVB/natural sunlight therapy. Systemics should be initiated based on shared decision-making between patients and providers in acknowledgement of potential risks and benefits to the patient and neonate. Some systemic therapies (mycophenolate mofetil, methotrexate) are contraindicated during pregnancy.[20]

According to the manufacturer, there is a lack of information about human use of crisaborole during pregnancy, though animal studies did not indicate adverse risks.[33] It is also not known if it is present in human milk. Risks versus benefits for use should be considered.[33] The ETFAD does not recommend use of crisaborole during pregnancy or breastfeeding owing to the lack of information.[20]

ETFAD lists TCIs as an option during pregnancy based on supportive evidence for use of systemic calcineurin inhibitors during pregnancy, and expected minimal systemic absorption. Topical tacrolimus is favored over topical pimecrolimus due to the greater amount of data with systemic use during pregnancy.[20] Package inserts recommend caution, and weighing the risks versus benefits given the lack of information.[18,19] During breastfeeding, ETFAD also considers TCIs to be an option, recommending that they are applied immediately after breastfeeding.[20] Manufacturers recommend weighing the risks versus benefits to use while breastfeeding.[18,19] Tacrolimus is known to be in human milk,[19] and it is unknown if pimecrolimus is present in human milk.[18]

Regarding use of the antibody dupilumab during pregnancy, the limited human data do not suggest fetal harm.[13] There is insufficient information about the use of tralokinumab during pregnancy.[12] Both are IgG antibodies which are expected to cross the placenta and be present in human milk,[20] though there is a lack of information on dupilumab and tralokinumab specifically.[12,13] Product labeling for both dupilumab and tralokinumab recommend considering risks versus benefits to determine whether they should be used during breastfeeding.[12,13] ETFAD (in 2018) only commented on dupilumab, recommending that other systemic therapies options should be used during pregnancy due to minimal experience with dupilumab and greater relative experience with the other options; they also, do not recommend its use during breastfeeding.[20]

There is insufficient human data on the use of JAK inhibitors during pregnancy.[14-16,35] Animal studies for ruxolitinib, abrocitinib, baricitinib, and upadacitinib indicate the potential for fetal harm (see **Table 9)** when given orally at supratherapeutic doses.[14-16,35] Labeling for upadacitinib advises using contraception during treatment with upadacitinib.[15] It is unknown if JAK inhibitors are present in human milk.[14-16,35] They are known to be in animal milk (abrocitinib, ruxolitinib, baricitinib, upadacitinib),[14-16,35] suggesting that they may be secreted into human milk. Manufacturer labeling does not advise their use while breastfeeding.[14-16,35] Treatment with JAK inhibitors during pregnancy or lactation were not addressed by the 2019 ETFAD position statement.[20]

Table 8. Recommendations during Pregnancy or Breastfeeding from Product Information[a]

Generic Name *(proposed)* brand	Pregnancy	Breastfeeding
Topical therapies		
Crisaborole[33] (Eucrisa)	• No human data • Animal studies of *oral use* during organogenesis at doses > humans did not demonstrate adverse effects on fetal development	• Unknown if secreted in human milk • No data on use during breastfeeding • Consider risks versus benefits
Pimecrolimus[18] (Elidel)	• Insufficient human data • Animal studies during organogenesis at doses > humans, no teratogenicity was observed. Slight skeletal toxicity was observed at the highest doses in rabbits. • Crossed rat and rabbit placenta after oral use • Exercise caution; use if benefits > risks	• Unknown if secreted in human milk • Infant risk unknown, but there is a potential for AE • Consider risks vs benefits
Ruxolitinib[35] (Opzelura)	• Insufficient human data • In animal studies of *oral use* during organogenesis at doses > humans, adverse developmental outcomes occurred (decreased fetal weight) at the highest doses studied	• Unknown if secreted in human milk; it is present in rat milk • Infant risk unknown, but there is a potential for AE • **Breastfeeding NOT recommended** during use and for at least 4 weeks after stopping use
Tacrolimus[19] (Protopic)	• Insufficient human data; tacrolimus crosses the placenta. Systemic tacrolimus is associated with fetal toxicity (hyperkalemia, renal dysfunction). • In animal studies of *oral use* during organogenesis, infant toxicity was observed (including abortions), particularly at doses that also caused maternal toxicity • Exercise caution; use if benefits > risks	• Present in human milk • Infant risk unknown, but there is a potential for AE • Consider risks vs benefits
Oral therapies		

Table 8. Recommendations during Pregnancy or Breastfeeding from Product Information[a]

Generic Name *(proposed)* brand	Pregnancy	Breastfeeding
Abrocitinib[14] (Cinbinqo)	• No or insufficient human data • In animal studies at doses > human doses, developmental toxicity (skeletal variations) occurred	• Unknown if secreted in human milk; it is present in animal milk • No data on use during breastfeeding • **Breastfeeding NOT recommended** during use and for at least 1 day after the last dose (about 5 to 6 half-lives)
Baricitinib[16] (Olumiant)	• Insufficient human data • In animal studies during organogenesis at doses > human doses , baricitinib was teratogenic (skeletal malformations) at the higher range but not lower range of administered doses. Reduced fetal body weight, and embryo lethality (in rabbits but not rats) were observed.	• Unknown if secreted in human milk; it is present in rat milk • Infant risk unknown, but there is a potential for AE • **Breastfeeding NOT recommended**
Upadacitinib[15] (Rinvoq)	• Insufficient human data • In animal studies (rats, rabbits) during organogenesis at doses > human doses, adverse fetal effects occurred (skeletal malformations at higher doses, cardiovascular malformations in rabbits, post-implantation loss in rabbits, and decreased fetal body weights). • **Recommended that females of reproductive potential use contraception during and for up to 4 weeks post-last dose**	• Unknown if secreted in human milk; it is present in animal milk • Infant risk unknown, but there is a potential for AE • **Breastfeeding NOT recommended** during use and for at least 6 days after the last dose (about 10 half-lives)
Subcutaneous Therapies		
Dupilumab[13] (Dupixent)	• Available human data does not suggest increased maternal or fetal risk • Expected to cross the placenta • In animal studies of *subcutaneous use* of a similar Ab during organogenesis at doses > humans, no adverse developmental effects were observed	• No data on presence in human milk, but IgG antibodies are known to be in human milk • Potential effects on the infant are unknown • Consider risks vs benefits

Table 8. Recommendations during Pregnancy or Breastfeeding from Product Information[a]

Generic Name *(proposed)* brand	Pregnancy	Breastfeeding
Tralokinumab[12] (Adbry)	• Insufficient, limited human data • Animal studies do not suggest fetal harm	• Unknown if present in human milk • Consider risks vs benefits

Abbreviations: AE, adverse event; EU, European Union; IgG, immunoglobulin G; vs, versus; UK, United Kingdom;

[a] Information is from package inserts (ie, prescribing information). For baricitinib, information is based on US approval for treatment of RA; information may change if approved for treatment of AD.

Direct Comparative Evidence

Literature searches for SRs and SRMAs of RCTs, and RCTs identified 448 unique records, of which 11 SRs and 12 RCTs met inclusion criteria for the qualitative synthesis. The PRISMA flow diagram for publication screening is available in **Appendix B**. The majority of the identified direct head-to-head comparison evidence evaluated TCIs compared to each other in adults and children with varying AD disease severity. Two additional head-to-head RCT comparisons were identified (1 study each) for the oral JAK inhibitors (abrocitinib and upadacitinib) compared to dupilumab. Nonactive comparators (placebo or vehicle) were included for the emerging non-steroidal agents. Although tralokinumab, upadacitinib, and abrocitinib are now FDA-approved, at the time of the literature search and data extraction, these agents had not received approval, thus these placebo comparisons are provided in **Appendix C.** The most common primary efficacy endpoints that were used in clinical trials included IGA (vIGA-AD) and EASI. Common secondary endpoints included QoL outcomes, measured by Peak Pruritus Numerical Rating Scale (PP-NRS) response, Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure (POEM), Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD), and the Children's Dermatology Life Quality Index (CDLQI).

A direct head-to-head comparison with the other target agents of this report was not identified for the following agents: topical ruxolitinib, tralokinumab, baricitinib, and crisaborole.

Table 9 summarizes characteristics and results of the included SRs. For SRs that were used only to identify eligible RCTs, efficacy and safety results are not reported. Please refer to the agent specific RCT summary table in **Appendix C. Table 1** in **Appendix C** shows a comparison of the RCTs identified among the included SRs that evaluated the same agents.

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
Le, 2021[59] SR	Adults and/or children (≥12 years of age) with moderate-to-severe AD who failed to have an	ABO (100 mg, 200 mg) daily +TCS vs. DUP 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=838)	<u>Abrocitinib</u> **Bieber et al. *N Engl J Med*. 2021; 384(12):1101– 1112. **JADE Compare** *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2**	Ovid MEDLINE, Embase (Ovid), and PubMed (search date: from inception to **June 2021**)	Refer to agent specific RCT summary table

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
	adequate response to TCS/TCI or/and failed or required systemic therapies	ABO (100 mg, 200 mg) daily vs. PBO (N= 778) BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239) BAR (2 mg, 4 mg) daily +TCS vs. PBO+TCS (N= 453) UPA (15 mg, 30 mg) daily vs. PBO (N=1683) UPA 15 mg daily +TCS vs. PBO+TCS (N= 901)	Gooderham et al. *JAMA Dermatol.* 2019; 155:1371–9. <u>Baricitinib</u> *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2** *Reich et al. *JAMA Dermatol.* 2020; 156:1333–43. **BREEZE-AD7** Guttman-Yassky et al. *J Am Acad Dermatol.* 2019; 80:913–21.e9. <u>Upadacitinib</u> *Reich et al. *Lancet.* 2021; 397:2169-81 **AD Up** *Guttman-Yassky et al. *Lancet.* 2021; 397:2151-68. **Measure Up 1 and Measure Up 2** Guttman-Yassky et al. *J Allergy Clin Immunol*. 2020; 145:877–84.		
Meher, 2021[60] SRMA	Adults and/or children (≥12 years of age) with moderate-to-severe[a] AD for ≥ 1 year, who failed to have an adequate response to	ABO (100 mg, 200 mg) daily +TCS vs. DUP 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=838) ABO (100 mg, 200 mg) daily vs. PBO (N= 778)	<u>Abrocitinib</u> **Bieber et al. *N Engl J Med*. 2021; 384(12):1101– 1112. **JADE Compare** *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2** Gooderham et al. *JAMA Dermatol.* 2019; 155:1371–9.	PubMed, Cochrane, and the International Clinical Trials Registry Platform (search date: from inception to **April 30, 2021**)	**<u>ABO vs. PBO: RR (95% confidence interval)</u>** Primary Outcome • IGA response[b] at 12W: RR= 3.52 (2.78,4.46) Secondary Outcomes • EASI-75 response[c] at 12W: RR=3.35 (2.54,4.41)

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
	topical therapies		*Note:* These phase 3 RCTs included in **Meher 2021** are also included in **Le 2021**		• PP-NRS response[d] at 12W: RR=2.54 (1.95,3.30) • TEAEs: RR=1.17 (1.06,1.29)
Fadlalmola, 2021[61] SRMA	Adults and/or children (≥12 years of age) with moderate-to-severe[a] AD for at least 1 year, who failed to have an adequate response to topical therapies	ABO (100 mg, 200 mg) daily +TCS vs. DUP 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=838) ABO (100 mg, 200 mg) daily vs. PBO (N=778)	<u>Abrocitinib</u> **Bieber et al. *N Engl J Med*. 2021; 384(12):1101– 1112. **JADE Compare** *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2** Gooderham et al. *JAMA Dermatol.* 2019; 155:1371–9. *Note:* These phase 3 RCTs included in **Fadlalmola 2021** are also included in **Meher 2021** and **Le 2021**	PubMed, Cochrane, Web of Science, Scopus, and Global Resource for Eczema Trials (search date: from inception to **February 1, 2021**)	**<u>ABO 100 mg vs. PBO: RR/MD (95% confidence interval)</u>** • IGA response[b] at 12W: RR= 3.03 (2.14, 4.30) • EASI-75 response[c] at 12W: RR=2.74 (1.99, 3.79) • PP-NRS response[d] at 12W: RR= 2.17 (1.51, 3.13) • SCORAD at 12W: MD= –13.33 (–14.62, –12.05) • PSAAD index at 12W: MD= –1.23 (–1.54, –0.92) • POEM index at 12W: MD= –6.72 (–7.79, –5.65) • DLQI score at 12W: MD= –2.99 (–3.88, –2.09)

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
					• CDLQI score at 12W: MD= –2.49 (–4.90, –0.07) **<u>ABO 200 mg vs. PBO: RR/MD (95% confidence interval)</u>** • IGA response[b] at 12W: RR= 4.44 (3.16, 6.24) • EASI-75 response[c] at 12W: RR=4.04 (2.55, 6.42) • PP-NRS response[d] at 12W: 2.60 (1.34, 5.04) • SCORAD at 12W: MD= –24.70 (–25.98, –23.42) • PSAAD index at 12W: MD= –2.08 (–2.39, –1.77) • POEM index at 12W: MD= –7.33 (–8.39, –6.26) • DLQI score at 12W: MD= –5.07 (–5.94, –4.20) • CDLQI score at 12W: MD= –3.71 (–6.13, –1.30)

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
					Safety • No significant difference between ABO and PBO for serious adverse events of any cause • Compared to PBO, ABO 100 or 200 mg was associated with a higher incidence of nausea (*p=0.01*) • ABO 200 mg was associated with a higher incidence of headache compared to PBO (*p=0.01*), however ABO 100 mg had no significant difference
Fahrbach, 2020[41] SRNMA	Children (≥2 years of age) and adults diagnosed with mild- to-moderate AD[e]	Tacrolimus 0.1% vs. Pimecrolimus 1% (N= 188) Tacrolimus 0.03% vs. Pimecrolimus 1% (N=1206)	Crisaborole Paller et al. *J Am Acad Dermatol*.2016;75(3):494–503.e6. Tacrolimus vs. Pimecrolimus **Abramovits et al. *J Drugs Dermatol.* 2008;7(12):1153–8. ** Paller et al. *J Am Acad Dermatol.* 2005;52(5):810–22. **Kempers et al. *J Am Acad Dermatol.* 2004;51(4):515–25. Tacrolimus	MEDLINE, Embase, the Cochrane Collection Central Register of Clinical Trials, Database of Abstracts of Reviews of Effects (searched date: from inception to	**Tacrolimus 0.1% vs Pimecrolimus 1%: HR (95% credible interval)** • Achieving ISGA 0-1 Score at 28-42 days: HR= 1.37 (0.96, 2.22) **Tacrolimus 0.03% vs Pimecrolimus 1%: HR (95% credible interval)**

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
			Schachner et al. *Pediatrics*. 2005;116(3):e334–e342. Chapman et al. *J Am Acad Dermatol.* 2005;53(2 Suppl 2):S177–S185185. Levy et al. *J Allergy Clin Immunol.* 2005;115(2):S103. <u>Pimecrolimus</u> Eichenfield et al. *J Am Acad Dermatol.* 2002;46(4):495–504.	**March 10, 2020**)	• Achieving ISGA 0-1 Score at 28-42 days: HR= 1.20 (0.98, 1.49)
Tsai, 2021[62] SRNMA	Children (≥12 years of age) and adults with moderate-to-severe[a] AD who failed to have an adequate response to TCS/TCI or/and failed or required systemic therapies	ABO (100 mg, 200 mg) daily vs. PBO N= 778 BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239) BAR (2 mg, 4 mg) daily +TCS vs. PBO+TCS (N= 453)	<u>Abrocitinib</u> *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2** Gooderham et al. *JAMA Dermatol.* 2019; 155:1371–9. <u>Baricitinib</u> *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2** *Reich et al. *JAMA Dermatol.* 2020; 156, 1333–1343. **BREEZE-AD7** Guttman-Yassky et al. *J. Am. Acad. Dermatol.* 2019; 80, 913–921.e9. <u>Upadacitinib</u> Guttman-Yassky, et al. *J. Allergy Clin. Immunol.* 2020; 145, 877–884. *Includes BREEZE AD4 (NCT03428100), which is an ongoing RCT	MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Web of Science (searched date: from inception to **February 1, 2021**)	Refer to agent specific RCT summary table

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
			Note: These phase 3 RCTs included in **Tsai 2021** are also included in **Le 2021**		
Mostafa, 2021[63] SRNMA	Adults and/or children (≥12 years of age) with moderate-to-severe[a] AD	ABO (100 mg, 200 mg) daily vs. PBO (N=387) ABO (100 mg, 200 mg) daily +TCS vs. DUP 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=838) BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239) BAR (2 mg, 4 mg) daily +TCS vs. PBO+TCS (N= 453) TRA 600 mg LD, then 300 mg Q2W vs. PBO (N= 1596) TRA 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=380)	<u>Abrocitinib</u> *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** **Bieber et al. *N Engl J Med*. 2021; 384(12):1101– 1112. **JADE Compare** <u>Baricitinib</u> *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2** *Reich et al. *JAMA Dermatol.* 2020; 156, 1333–1343. **BREEZE-AD7** <u>Upadacitinib</u> Guttman-Yassky et al. *J Allergy Clin Immunol.*2020;145:877–884 <u>Tralokinumab</u> *Wollenberg et al. *Br J Dermatol*.2021 ;184(3):437–449. **ECZTRA 1 and ECZTRA 2** *Silverberg et al. *Br J Dermatol*.2021;184:450–463. **ECZTRA 3** <u>Upadacitinib</u> Guttman-Yassky et al. *J Allergy Clin Immunol.*2020;145:877–884	Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, and Database of Abstracts of Review of Effectiveness (searched date: from inception to **March 21, 2021**)	**<u>DUP 300 mg Q2W vs. ABO 200 mg: LSM (95% credible interval)</u>** • DLQI score at 12W: 1.10 (–0.62, 2.82) • POEM score at 12W: –1.80 (–5.77, 2.17) **<u>DUP 300 mg Q2W vs. ABO 100 mg: LSM (95% credible interval)</u>** • DLQI score at 12W: –1.20 (–2.92, 0.52) • POEM score at 12W: –1.20 (–5.17, 2.77) **<u>ABO 200 mg vs. PBO: LSM (95% credible interval)</u>** • DLQI score at 12W: –4.06 (–5.28, –2.83) • POEM score at 12W: –7.20 (–10.01, –4.39) **<u>ABO 100 mg vs. PBO: LSM (95% credible interval)</u>** • DLQI score at 12W: –2.65 (–3.87, –1.43) • POEM score at 12W: –3.80 (–6.61, –0.99)

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
Nusbaum, 2021[42] SRMA	Adults and/or children (≥12 years of age) with moderate-to-severe[a] AD requiring systemic immunomodulatory therapies	ABO (100 mg, 200 mg) daily +TCS vs. DUP 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=838) ABO (100 mg, 200 mg) daily vs. PBO (N= 778) BAR (1 or 2 mg) daily vs. PBO (N=440) BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239) BAR (2 mg, 4 mg) daily +TCS vs. PBO+TCS (N= 453) UPA (15 mg, 30 mg) daily vs. PBO (N=1683) TRA 600 mg LD, then 300 mg Q2W vs. PBO (N= 1596)	<u>Abrocitinib</u> **Bieber et al. *N Engl J Med*. 2021; 384(12):1101– 1112. **JADE Compare** *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2** Gooderham et al. *JAMA Dermatol.* 2019; 155:1371–9. <u>Baricitinib</u> *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2** *Simpson et al. *J Am Acad Dermatol*. 2021;85:62–70. **BREEZE-AD5** *Reich et al. *JAMA Dermatol.* 2020; 156, 1333–1343. **BREEZE-AD7** Guttman-Yassky et al. *J Am Acad Dermatol.* 2019;80(4):913–921. <u>Tralokinumab</u> *Wollenberg et al. *Br J Dermatol*.2021 ;184(3):437–449. **ECZTRA 1 and ECZTRA 2** *Silverberg et al. *Br J Dermatol*.2021;184:450–463. **ECZTRA 3** Wollenberg et al. *J Allergy Clin Immunol.* 2019;143(1):135–141. <u>Upadacitinib</u> *Guttman-Yassky et al. *Lancet.* 2021; 397:2151-68. **Measure Up 1 and Measure Up 2**	Embase, Medline, and Cochrane Central Register of Clinical Trials (searched date: from inception to **March 26, 2021**)	**<u>UPA vs. PBO: Prevalence (95% confidence interval)</u>** UPA 30 mg • EASI response[c] at 16W: 0.76 (0.70, 0.82) • PP-NRS response[d] at 16W: 0.59 (0.55, 0.63) UPA 15 mg • EASI response[c] at 16W: 0.64 (0.55, 0.74) • PP-NRS response[d] at 16W: 0.48 (0.38, 0.57) **<u>ABO 200 mg vs. PBO: Prevalence (95% confidence interval)</u>** • EASI response[c] at 12W: 0.63 (0.58, 0.67) • PP-NRS response[d] at 12W: 0.57 (0.52, 0.62) **<u>BAR vs. PBO: Prevalence (95% confidence interval)</u>** BAR 1 mg • EASI response[c] at 16W: 0.14 (0.11, 0.18) • PP-NRS response[d] at 16W: 0.11 (0.06, 0.17) BAR 2 mg

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
		TRA 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=380)	Guttman-Yassky et al. *American Academy of Dermatology Annual Meeting*; 2018, Feb 16–20; San Diego (CA).		• EASI response[c] at 16W: 0.19 (0.14, 0.24) ○ +TCS: 0.40 (0.27, 0.53) • PP-NRS response[d] at 16W: 0.18 (0.11, 0.26) BAR 4 mg • EASI response[c] at 16W: 0.23 (0.18, 0.29) ○ +TCS: 0.44 (0.31, 0.58) • PP-NRS response[d] at 16W: 0.20 (0.15, 0.26) **ABO 100 mg vs. PBO: Prevalence (95% confidence interval)** • PP-NRS response[d] at 12W: 0.43 (0.36, 0.49) **ABO 100 mg vs. PBO: SMD (95% confidence interval)** • DLQI score at 12W: 4.92 (2.48, 7.36) **ABO 200 mg vs. PBO: SMD (95% confidence interval)** • DLQI score at 12W: 8.28 (5.10, 11.45)

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
Miao, 2021[64] SRMA	Children (≥12 years of age) and adults with moderate-to-severe[a] AD who failed to have an adequate response to TCS/TCI or/and failed or required systemic therapies	ABO (100 mg, 200 mg) daily vs. PBO (N= 391) BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239)	Abrocitinib *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2** Baricitinib *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2** Guttman-Yassky et al. *J Am Acad Dermatol.* 2019;80(4):913–921. Upadacitinib Guttman-Yassky et al. *J Allergy Clin Immunol.* 2020;145(3):877–884.	PubMed, The Cochrane Library, Embase, Web of Science, CNKI, CBM, VIP, and WanFang Database (searched date: from inception to **January 2, 2021**)	Refer to agent specific RCT summary table
Li, 2021[65] SRMA	Children (≥12 years of age) and adults with moderate-to-severe[a] AD who failed to have an adequate response to TCS/TCI or/and failed or required systemic therapies	ABO (100 mg, 200 mg) daily vs. PBO (N= 778) BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239) BAR (2 mg, 4 mg) daily +TCS vs. PBO+TCS (N= 453)	Abrocitinib *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2** Gooderham et al. *JAMA Dermatol.* 2019; 155:1371–9. Baricitinib *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2** *Reich et al. *JAMA Dermatol.* 2020; 156, 1333–1343. **BREEZE-AD7** Guttman-Yassky et al. *J Am Acad Dermatol.* 2019;80(4):913–921. Upadacitinib	PubMed, Embase, The Cochrane Controlled Register of Trials, Web of Science, the Global Resource of Eczema Trials database, and ClinicalTrials.gov (searched date: from inception to **September 1, 2020**)	Refer to agent specific RCT summary table

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
			Guttman-Yassky et al. *J Allergy Clin Immunol.* 2020;145(3):877–884.		
Zhang, 2021[66] SRNMA	Children (≥12 years of age) and adults with moderate-to-severe[a] AD who failed to have an adequate response to TCS/TCI or/and failed or required systemic therapies	ABO (100 mg, 200 mg) daily vs. PBO (N= 387) BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239)	Abrocitinib *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** Baricitinib *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2** Upadacitinib Guttman-Yassky et al. *J Allergy Clin Immunol.* 2020;145(3):877–884.	PubMed, Embase, Web of Science, and Cochrane Library (searched date: from inception to **March 28, 2021**)	Refer to agent specific RCT summary table
Atlas, 2021[2] SRNMA	Adults and/or children (≥12 years of age) with moderate-to-severe[a] AD who failed to have an adequate response to TCS/TCI or/and failed or required systemic therapies	ABO (100 mg, 200 mg) daily +TCS vs. DUP 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=838) ABO (100 mg, 200 mg) daily vs. PBO (N= 778) BAR (1 or 2 mg) daily vs. PBO (N=440)	Abrocitinib **Bieber et al. *N Engl J Med*. 2021; 384(12):1101– 1112. **JADE Compare** *Simpson et al. *Lancet.* 2020; 396:255–66. **JADE MONO-1** *Silverberg et al. *JAMA Dermatol.* 2020; 156:863–73. **JADE MONO-2** Gooderham et al. *JAMA Dermatol.* 2019; 155:1371–9. Baricitinib *Simpson et al. *Br J Dermatol.* 2020; 183:242–55. **BREEZE-AD1 and BREEZE-AD2**	Medline, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (searched date: from inception to **May 26, 2021**)	Refer to agent specific RCT summary table

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA
		BAR (1 mg, 2 mg, 4 mg) daily vs. PBO (N= 1239) BAR (2 mg, 4 mg) daily +TCS vs. PBO+TCS (N= 453) UPA (15 mg, 30 mg) daily vs. PBO (N=1683) UPA 15 mg daily +TCS vs. PBO+TCS (N= 901) TRA 600 mg LD, then 300 mg Q2W vs. PBO (N= 1596) TRA 600 mg LD, then 300 mg Q2W +TCS vs. PBO+TCS (N=380) DUP 600 mg LD, then 300 mg Q2W vs. UPA 30 mg daily (N=692)	*Simpson et al. *J Am Acad Dermatol*. 2021;85:62–70. **BREEZE-AD5** *Reich et al. *JAMA Dermatol.* 2020; 156, 1333–1343. **BREEZE-AD7** <u>Tralokinumab</u> *Wollenberg et al. *Br J Dermatol*.2021 ;184(3):437–449. **ECZTRA 1 and ECZTRA 2** *Silverberg et al. *Br J Dermatol*.2021;184:450–463. **ECZTRA 3** <u>Upadacitinib</u> *Reich et al. *Lancet.* 2021; 397:2169-81 **AD Up** *Guttman-Yassky et al. *Lancet.* 2021; 397:2151-68. **Measure Up 1 and Measure Up 2** **Blauvelt et al. *JAMA Dermatol.* 2021; 157(9):1047-1055. **Heads Up**		

Abbreviations: ABO, abrocitinib; AD, atopic dermatitis; BAR, baricitinib; BSA, body surface area; CBM, Chinese Biomedical Literature Database; CDLQI, Children's Dermatology Life Quality Index; CNKI, China Academic Journals; DLQI, Dermatology Life Quality Index; DUP, dupilumab; EASI, Eczema Area and Severity Index; HR, hazard ratio; IGA, Investigator's Global Assessment; ISGA, Investigator's Static Global Assessment; LD, loading dose; LSM, least square means difference; MA, meta-

Table 9. Characteristics and Results of Included Systematic Reviews

First author, year, study design	Population	Intervention of Interest (N, number of participants)	List of trials of interest identified by SR	Literature search databases (search dates)	Efficacy and safety endpoints/ results from MA

analysis; MD, mean differences; mg, milligrams; NR, not reported; PBO, placebo; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Score; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; Q2W, every other week; RCT, randomized controlled trial; RR, risk ratio; SCORAD, Scoring Atopic Dermatitis; SMD, standardized mean difference; SR, systematic review; SRMA, systematic review and meta-analysis; SRNMA, systematic review and network meta-analysis; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; TRA, tralokinumab; UPA, upadacitinib; VIP, Chinese Science and Technology Periodicals Database; W, weeks

***phase 3 randomized placebo-controlled trials for non-FDA approved agents at the time of extraction (baricitinib, abrocitinib, upadacitinib, and tralokinumab). Abrocitinib, upadacitinib, and tralokinumab are currently approved for the treatment of AD.**
****head-to-head randomized controlled trials**

[a] Defined as IGA ≥ 3, EASI score ≥16, BSA ≥10%, and PP-NRS ≥4; [b] IGA with at least a two-point reduction from baseline; [c] More than 75% improvement from baseline EASI; [d] An improvement of more than four points from baseline PP-NRS; [e] All diagnostic scales/scores for disease severity and diagnostic criteria for AD were eligible for inclusion

Summary of Comparative Evidence in the Treatment of Atopic Dermatitis

Comparative Evidence of Abrocitinib vs. Dupilumab

No head-to-head SR evidence was identified for abrocitinib in regard to objective efficacy outcomes.[2,42,59-63,65,66] However, **Mostafa et al (2021)** conducted an SR and NMA of RCTs including direct pairwise comparisons between abrocitinib and dupilumab evaluating QoL outcomes (based on data from the JADE COMPARE trial).[63] Pairwise comparisons between agents of interest were only reported based on DLQI and POEM scores. The dupilumab 300 mg every other week arm had greater improvements in the DLQI score compared to abrocitinib 200 mg daily, and abrocitinib 100 mg daily.[63] However, the abrocitinib 200 mg daily arm had the greatest improvement in the POEM score compared to dupilumab 300 mg every other week and abrocitinib 100 mg daily.[63]

The JADE COMPARE RCT compared abrocitinib to dupilumab (in addition to placebo arm), but statistical comparisons between abrocitinib and dupilumab were only performed for secondary efficacy outcomes (eg, itch,) and not primary (IGA or EASI-75 response at week 12).[29] Patients were **18 years and older**, diagnosed with moderate-to-severe AD for at least 1 year, and had an established prior failure with topical medications. Abrocitinib 200 mg daily was superior to dupilumab 300 mg subcutaneously every other week (post 600 mg loading dose) regarding itch response at week 2.[29] By week 16, abrocitinib, regardless of dose (200 mg or 100 mg daily) was not statistically different from dupilumab regarding IGA response and EASI-75 response (EASI-75: 71%, 60%, 66%, respectively; IGA: 48%, 35%, 39%, respectively).[29] Abrocitinib significantly improved symptoms of AD compared to placebo during the trial duration of 12 weeks in patients receiving concomitant topical therapy.[29] The most frequently reported adverse events among abrocitinib treatment groups were nausea, nasopharyngitis, upper respiratory tract infection (URTI), headache, and acne, whereas conjunctivitis was more common in the dupilumab treatment group.[29]

Table 10 outlines the primary efficacy endpoints, key secondary endpoints, and pertinent safety information for the JADE COMPARE trial.

Table 2 in **Appendix C** outlines the primary and selected key secondary endpoints, and pertinent safety information from the identified abrocitinib placebo-controlled trials.

Comparative Evidence of Baricitinib vs. Placebo

There are currently no head-to-head SR and SRMA comparisons between baricitinib and other non-steroidal treatments for AD.[2,42,59,62-66] In the absence of head-to-head evidence, placebo controlled SRs and RCTs are discussed.

The SR by **Nusbaum et al (2021)** contains a pooled analysis of the pivotal phase III placebo controlled RCTs BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, and BREEZE-AD7 (see **Table 3** in **Appendix C**).[30-32,42] Patients were adults (≥ 18 years of age) diagnosed with moderate-to-severe AD for at least 1 year that failed to have an adequate response to or had an intolerance to TCS therapy.[30-32,42] Baricitinib monotherapy improved signs and symptoms of AD compared to placebo, with a larger effect size

observed for the highest dose compared to the lower dose; a higher prevalence of patients achieved a 75% reduction in EASI taking baricitinib 4 mg daily compared to baricitinib 1 mg daily (0.23 vs 0.14, respectively).[42] Similar results were observed for baricitinib in combination with TCS versus placebo.[42] A dose dependent trend was observed for patient-reported pruritis, with higher baricitinib doses achieving a greater prevalence of patients experiencing a reduction in itch intensity.[42]

Two short-term (16 week) phase III, placebo-controlled, randomized, multicenter, double-blind trials (BREEZE-AD1 and BREEZE-AD2) demonstrated baricitinib monotherapy improved disease severity, itch intensity, skin pain, and sleep disruptions (due to pruritis) compared to placebo.[30] Patients were adults (≥ 18 years of age) diagnosed with moderate-to-severe AD for at least 1 year that failed to have an adequate response or were intolerant to TCS therapy.[30] The primary efficacy endpoint measured the validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD) response at 16 weeks between varying doses of baricitinib (1 mg, 2 mg, and 4 mg) compared to placebo. The likelihood of achieving a v-IGA response of clear or almost clear and a higher proportion of EASI (eg, EASI-90, EASI-100) increased in a dose-proportional manner.[30] The most robust response was observed for baricitinib 4 mg, which showed improvements as early as week 1 and a sustained the response until the end of the trials.[30] In the trials, the most commonly reported adverse events (≥ 2% in any treatment group) included nasopharyngitis, URTIs, creatine phosphokinase (CPK) elevations, headaches, and herpes simplex infections.[30] No major adverse cardiovascular events (MACEs), deaths, malignancies, or venous thromboembolisms (VTEs) occurred in patients treated with baricitinib.[30]

Another short-term (16 week) phase III, placebo-controlled, randomized, multicenter, double-blind trial (BREEZE-AD 5) demonstrated that baricitinib improved signs and symptoms of AD in a dose-dependent manner compared to placebo, including for patient-reported outcomes.[31] Patients were adults (≥ 18 years of age) diagnosed with moderate-to-severe AD for at least 1 year with a history of a failed response or intolerance to TCS therapy.[31] Patients treated with baricitinib 2 mg daily began to have an observable EASI response by week 2, and by week 4 the response was approximately 80% of those that achieved the response at week 16.[31] Similar to the BREEZE-AD1 and BREEZE-AD2, baricitinib 1 mg resulted in non-significant results compared to placebo; however, in BREEZE-AD 5 this occurred across all outcomes, including EASI and IGA response.[31] The most frequently reported adverse events among treatment groups were URTIs, nasopharyngitis, diarrhea, and nausea.[31] An increase in the incidence of herpes simplex was observed in patients treated with baricitinib compared to placebo.[31] No reported cases of malignancies, gastrointestinal perforation, VTEs, MACEs, or deaths occurred in patients treated with baricitinib.[31]

An additional RCT, BREEZE-AD 7, assessed the efficacy and safety of baricitinib (2 mg or 4 mg daily) compared to placebo among patients taking low-to-moderate potency TCSs.[32] Patients were adults (≥ 18 years of age) diagnosed with moderate-to-severe AD for at least 1 year with a history of a failed response or intolerance to TCS therapy.[32] Similar primary endpoint results (for vIGA-AD response) as the other monotherapy trials were observed for baricitinib 4 mg in combination with TCS relative to placebo.[32] However, baricitinib 2 mg failed to achieve a statistically significant difference versus placebo for the primary efficacy endpoint.[32] Baricitinib 4 mg daily in combination with TCSs also significantly improved symptoms and patients' QoL compared to placebo.[32] The most commonly reported adverse events were nasopharyngitis, URTIs, folliculitis, acne, and diarrhea. A VTE event (pulmonary embolism)

was reported for a 51 year old patient (former smoker) treated with baricitinib 4 mg daily on concurrent oral contraceptive therapy, leading to treatment discontinuation.[32] Similar to the previously mentioned studies, higher incidences of herpes simplex were reported for baricitinib-treated patients compared to patients receiving placebo.[32]

Table 3 in **Appendix C** outlines the primary and selected key secondary endpoints, and pertinent safety information from the identified baricitinib placebo-controlled trials.

Comparative Evidence Among TCIs

Direct comparative evidence was found for tacrolimus (0.03% and 0.1%) versus pimecrolimus among the NMA by **Fahrbach et al (2020)**.[41] This SR and NMA, included 9 RCTs, including 3 trials with a direct comparison between tacrolimus and pimecrolimus.[41] Patients were children (≥2 years of age) and adults with mild-to- moderate AD.[41] The primary efficacy outcome of interest was achieving improvement in disease severity based on an Investigator's Static Global Assessment (ISGA) score of 0 or 1 (clear or almost clear) at 28-42 days.[41] The pooled analysis demonstrated that a higher proportion of patients achieved an ISGA score of 0 or 1 with tacrolimus, at either dose (0.03% or 0.1%), compared to pimecrolimus 1% cream.[41]

- *Tacrolimus 0.03% ointment vs. pimecrolimus 1% cream*

  An RCT **(Kempers et al 2004)** showed that pimecrolimus 1% cream was associated with fewer application-site reactions during early treatment initiation compared to tacrolimus 0.03% ointment among children 2 to 17 years of age with moderate AD.[67] Four days into treatment, patients experienced less erythema/irritation, pruritis, and fewer reactions lasting longer than 30 minutes while using pimecrolimus compared to tacrolimus. However, the incidence of warmth and stinging/burning was similar between both treatment groups. Pimecrolimus cream was favored over tacrolimus ointment for ease of application and formulation attributes (eg, non-greasy).[67] No statistical difference was observed between the efficacy of tacrolimus 0.03% ointment compared to pimecrolimus 1% cream measured by obtaining an IGA response of 0 or 1.[67]

- *Tacrolimus 0.1% ointment vs. pimecrolimus 1% cream*

  An RCT conducted by **Abramovits et al (2008)** showed that tacrolimus 0.1% ointment is more efficacious than pimecrolimus cream at improving EASI score among adults with moderate AD at 6 weeks.[25] In addition, a faster onset of action was observed with tacrolimus compared to pimecrolimus.[25] Local application-site reactions (eg, burning, pruritus, pain, warmth, erythema) were not statistically different between treatment groups, but numerically more events occurred in the tacrolimus-treated group compared to the pimecrolimus-treated group.[25] Treatment discontinuation was rarely due to adverse events among both groups.[25] However, significantly more pimecrolimus-treated patients discontinued treatment due to a lack of efficacy compared to patients receiving tacrolimus (5 vs 0, respectively).[25]

Another RCT **(Fleischer 2007)** reported similar results, showing that adults with moderate to very severe AD treated with tacrolimus 0.1% ointment displayed greater improvement in the EASI score and BSA affected compared to pimecrolimus 1% cream at 6 weeks.[26] In addition, more patients treated with topical tacrolimus experienced treatment success, defined as an Investigator's Global Atopic Dermatitis Assessment (IGADA) of clear or almost clear, compared to patients treated with pimecrolimus.[26] However, both treatment groups had comparable improvements in pruritus.[26] Local application-site reactions, including burning, pruritus, pain, and warmth had a numerically higher incidence in patients receiving topical tacrolimus compared to patients receiving pimecrolimus; however, this was not statistically different between treatment groups.[26] Study withdrawal due to lack of efficacy occurred more often in patients treated with pimecrolimus compared to patients treated with topical tacrolimus ointment (10 vs. 1, respectively).[26]

- *Tacrolimus 0.03%/0.1% ointment vs. pimecrolimus 1% cream*

  A RCT **(Paller 2005)** demonstrated that tacrolimus (0.03% and 0.1%) ointments are more efficacious than pimecrolimus 1% cream at improving EASI score among children and adults with varying disease severity (mild to very severe) at 6 weeks.[27] In addition, children and adult patients receiving tacrolimus achieved a more rapid clinical response in relief of itch compared to patients treated with pimecrolimus.[27] The occurrence of application site-reactions such as pain, erythema, and pruritus were similar between treatment groups. However, burning occurred more frequently in the adult population treated with tacrolimus 0.1% compared to the adult patients treated with pimecrolimus.[27]

  A second RCT **(Onumah 2013)** had a small sample size (N=20), but showed that pimecrolimus was more efficacious than tacrolimus at improving IGA response among children and adults with moderate AD at 4 weeks.[68] Additionally, patients preferred the formulation of pimecrolimus compared to tacrolimus ointment in terms of ease of use, moisturizing, quick absorption and penetration, ability to easily apply to large surface areas, and lack of residue and greasiness.[68]

Comparative Evidence of Upadacitinib vs. Dupilumab

Only one SR (ICER report) included a direct comparison between upadacitinib and another non-steroidal agent, dupilumab.[2] This SR included the 1 head-to-head RCT comparing upadacitinib to dupilumab, and 3 RCTs comparing upadacitinib to placebo.[2] In the SR, included patients were adolescents (12 to 17 years of age) and adults diagnosed with moderate-to-severe AD that previously failed topical therapies (TCIs or TCS) or recently received systemic therapy.[2] Upadacitinib improved the severity of AD as measured by EASI response and patient-reported itch compared to placebo, with the higher dose of 30 mg daily being more efficacious than 15 mg daily.[2] In addition, upadacitinib 30 mg daily achieved superiority compared to dupilumab at improving EASI scores at 16 weeks (based on data from Heads Up trial).[2,28]

The Heads Up trial evaluated the superiority of upadacitinib 30 mg daily to subcutaneous dupilumab 300 mg every other week (after a 600 mg loading dose).[28] At 16 weeks, significantly more patients treated with upadacitinib 30 mg achieved ≥75% improvement in EASI score from baseline compared to patients treated with dupilumab (71% vs. 61%; p=0.006). [28] Additionally, all ranked secondary efficacy endpoints

demonstrated a greater improvement with upadacitinib compared to dupilumab.[28] A greater proportion of patients receiving upadacitinib achieved AD lesion clearance (ie, EASI-90 or EASI-100) exceeding the minimum standard of at least 75% reduction (ie, EASI-75) compared to dupilumab.[28] Additionally, upadacitinib demonstrated a faster onset of action compared to dupilumab, with skin improvement observed as early as week 2 of treatment (44% vs. 17%, respectively), and pruritis relief reported as early as week 1 (31% vs 9%, respectively).[28] Rates of acne, serious infection, eczema herpeticum, and herpes zoster were higher in patients treated with upadacitinib, whereas rates of conjunctivitis (mild or moderate) and injection site reactions were higher among patients that received dupilumab.[28] Among either treatment group, no VTE events, MACEs, or gastrointestinal perforations were observed.[28] One death associated to upadacitinib treatment occurred in a 40 year old due to influenza associated bronchopneumonia.[28]

Table 10 outlines the primary efficacy endpoints, key secondary endpoints, and pertinent safety information for the Heads Up trial.

Table 4 in **Appendix C** outlines the primary and selected key secondary endpoints, and pertinent safety information from the identified upadacitinib placebo-controlled trials.

Comparative Evidence of Dupilumab vs. Upadacitinib or Abrocitinib

Two identified SRs, the 2021 ICER report (**Atlas et al, 2021)**[2] and **Mostafa et al (2021)**[63], included a direct comparison between dupilumab and another non-steroidal agent for the treatment of AD. The ICER report included 6 dupilumab RCTs, including a phase II study, evaluating the efficacy and safety of dupilumab compared to an active comparator (upadacitinib or abrocitinib) or placebo.[2] Excluding placebo-controlled studies, only 2 RCTs were of interest (JADE COMPARE and Heads Up).[28,29] Mostafa et al also included results from the JADE COMPARE trial, but for QoL outcomes (DLQI and POEM).[63]

Results from both of the RCTs with direct comparisons between dupilumab and another AD agent of interest, which enrolled patients 18 years or older with moderate to severe AD with an indication for systemic therapy, are summarized in the abrocitinib or upadacitinib sections of this report. These trials indicate that higher doses of upadacitinib and perhaps abrocitinib (for rapid itch response) are more effective than dupilumab at improving the severity of AD.[2,28,29] Rates of acne, serious infection, and serious adverse events were numerically higher with either JAK inhibitor (at the higher dose), whereas rates of conjunctivitis (mild or moderate) were higher among patients that received dupilumab.[28,29]

Briefly, JADE COMPARE, which was not designed to statistically compare the primary efficacy endpoints between abrocitinib and dupilumab, demonstrated similar efficacy results between abrocitinib (200 mg or 100 mg) and dupilumab (300 mg every other week after a 600 mg loading dose) for improving physical symptoms of AD at 16 weeks.[29] A benefit for abrocitinib over dupilumab was seen for itch response at 2 weeks. QoL outcomes failed to clearly distinguish between dupilumab and abrocitinib; benefits on the DLQI score were observed for dupilumab compared to abrocitinib (both 100 mg and 200 mg), but abrocitinib 200 mg (and not 100 mg) was superior to dupilumab for improvement based on the POEM score.[63] However, the safety profile may favor dupilumab over abrocitinib in terms of overall

adverse events, particularly for acne and nausea.[29] Still, conjunctivitis occurred most frequently in the dupilumab arm.

The other head-to-head phase III RCT with a dupilumab arm, Heads Up, compared upadacitinib 30 mg daily to subcutaneous dupilumab 300 mg every other week (after a 600 mg loading dose).[28] Upadacitnib 30 mg daily was superior to dupilumab at improving physical symptoms of AD at 16 weeks; efficacy results favoring upadacitinib were also observed for all secondary endpoints (eg, itching). The onset of effect may also be faster for upadacitinib compared to dupilumab.[28] However, rates of acne (mild or moderate), serious infection, eczema herpeticum, and herpes zoster were reported more frequently in patients treated with upadacitinib, whereas rates of conjunctivitis (mild or moderate) and injection site reactions were higher among patients that received dupilumab.[28]

Table 10 outlines the primary and secondary endpoints, and pertinent safety information regarding dupilumab compared to abrocitinib (JADE COMPARE) and upadacitinib (Heads Up).

Table 10. Head-to-head Randomized Controlled Trials of Dupilumab

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
Multicenter, randomized, double-blind, double-dummy, placebo controlled (Bieber, 2021, **JADE COMPARE**)[29]	Patients ≥18 years of age diagnosed with moderate-to-severe AD[a] for ≥1 year, uncontrolled by topical therapies	**ABO 200 mg** po daily (N=226) or **ABO 100 mg** po daily (N=238) **vs** **DUP** 300 mg subQ every other week (after a LD of 600 mg) (N=242) **vs** **PBO** (N=131) Duration: 16W	Co-primary endpoints: IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 12W modified ITT population **Not designed to assess superiority of abrocitinib compared to dupilumab** EASI-75 Response: ≥75% improvement in EASI score at week 12 from baseline **Not designed to assess superiority of abrocitinib compared to dupilumab** Key secondary endpoints: Itch (PP-NRS) Response: (≥4 point improvement from baseline in score) at week 2 • ABO 100 mg vs DUP 300 mg: treatment difference=5.2% (95%CI -2.9% to 13.4%); p=0.20 • ***ABO 200 mg vs DUP 300 mg:*** treatment difference= 22.1% (95%CI 13.5% to 30.7%); p=<0.001 IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline at **week 16** • ABO 100 mg vs DUP 300 mg: treatment difference= -3.5% (95%CI -12.2% to 5.2%); p=NR • ABO 200 mg vs DUP 300 mg: treatment difference= 9.4% (95%CI 0.4% to 18.5%); p=NR EASI-75 Response: ≥75% improvement in EASI score at **week 16** from baseline	Most frequently reported TEAEs (≥5% in any treatment group) • Nausea ABO 100 (4.2%) vs ABO 200 (11.1%) vs DUP 300 (2.9%) vs PBO (1.5%) • Conjunctivitis ABO 100 (0.8%) vs ABO 200 (1.3%) vs DUP 300 (6.2%) vs PBO (2.3%) • Nasopharyngitis ABO 100 (9.2%) vs ABO 200 (6.6%) vs DUP 300 (9.5%) vs PBO (6.9%) • URTI ABO 100 (5.0%) vs ABO 200 (4.0%) vs DUP 300 (3.7%) vs PBO (4.6%) • Headache ABO 100 (4.2%) vs ABO 200 (6.6%) vs DUP 300 (5.4%) vs PBO (4.6%) • Acne ABO 100 (2.9%) vs ABO 200 (6.6%) vs DUP 300 (1.2%) vs PBO (0%) Discontinued Treatment due to AEs ABO 100 (2.5%) vs ABO 200 (4.4%) vs DUP 300 (3.3%) vs PBO (3.8%) SAEs[b] ABO 100 (2.5%) vs ABO 200 (0.9%) vs DUP 300 (0.8%) vs PBO (3.8%) Reported herpes viral infection: • Herpes zoster ABO 100 (0.8%) vs ABO 200 (1.8%) vs DUP 300 (0%) vs PBO (0%) • Eczema herpeticum

Table 10. Head-to-head Randomized Controlled Trials of Dupilumab

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ABO 100 mg vs DUP 300 mg: treatment difference= -5.1% (-13.9% to 3.7%); p= NR • ABO 200 mg vs DUP 300 mg: treatment difference= 5.5% (95%CI -3.1% to 14.1%); p=NR	ABO 100 (0.4%) vs ABO 200 (0%) vs DUP 300 (0%) vs PBO (0.8%)
Multicenter, randomized, double-blind, double-dummy, active-controlled (Blauvelt, 2021, **Heads Up**)[28]	Adults (18 to 75 years of age) diagnosed with moderate-to-severe AD[a] ≥ 3 years, uncontrolled by TCI or TCS therapies or previously receiving systemic AD treatment within prior 6 months	**UPA 30 mg** po daily (N= 348) **vs** **DUP 300 mg** subQ Q2W (after a LD of 600 mg) (N=344) Duration: 16W Patients continued topical emollients	Primary endpoint: EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline • ***UPA 30 mg vs DUP 300 mg:*** 247 patients (71%) vs 210 patients (61%); adj. difference = 10.0%; (95% CI 2.9% to 17.0%); p=0.006 Selected key secondary endpoint(s) WP-NRS Response: (≥4 point improvement from baseline in score) at week 16 • ***UPA 30 mg vs DUP 300 mg:*** adj. difference = 19.3% (95% CI NR); p=<0.001 EASI-90 Response: ≥90% improvement in EASI score at week 16 • ***UPA 30 mg vs DUP 300 mg:*** adj. difference = 21.8% (95% CI NR); p=<0.001 EASI-100 Response: 100% improvement in EASI score at week 16 • ***UPA 30 mg vs DUP 300 mg:*** adj. difference = 20.3% (95% CI NR); p=<0.001 LSM change in (weekly average) WP-NRS score: from baseline to week 16 • ***UPA 30 mg vs DUP 300 mg:*** adj. LSM difference = – 17.8 (95% CI NR); p<0.0001	Most frequently reported TEAEs (≥5% in any treatment group) • Acne UPA 30 (15.8%) vs DUP 300 (2.6%) • AD worsening UPA 30 (6.9%) vs DUP 300 (8.4%) • URTI UPA 30 (6.3%) vs DUP 300 (3.8%) • Increased plasma CPK UPA 30 (6.6%) vs DUP 300 (2.9%) • Nasopharyngitis UPA 30 (5.7%) vs DUP 300 (6.4%) • Headache UPA 30 (4.0%) vs DUP 300 (6.1%) • Conjunctivitis UPA 30 (1.4%) vs DUP 300 (8.4%) Discontinued treatment due to AEs UPA 30 (2.0%) vs DUP 300 (1.2%) SAEs UPA 30 (2.9%) vs DUP 300 (1.2%) Severe AE UPA 30 (7.2%) vs DUP 300 (4.1%) Deaths: 1 death occurred in UPA 30 Reported infections: • Serious infection UPA 30 (1.1%) vs DUP 300 (0.6%) • Eczema herpecitum

Table 10. Head-to-head Randomized Controlled Trials of Dupilumab

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
				UPA 30 (0.3%) vs DUP 300 (0%) • Herpes zoster UPA 30 (2.0%) vs DUP 300 (0.9%) <u>Selected other AEs of interest:</u> • Non-NMSC malignancy UPA 30 (0%) vs DUP 300 (0.3%) • Neutropenia UPA 30 (1.7%) vs DUP 300 (0.6%)

Abbreviations: AD, atopic dermatitis; Adj, adjusted; BW, bodyweight; CI, confidence interval; CPK, creatine phosphokinase; EASI, Eczema Area and Severity Index; ITT, intention-to-treat; LD, loading dose; LSM, least squares mean; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; Q2W, every two weeks; pt, point; SAEs, serious adverse events; subQ, subcutaneously; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; TEE, thromboembolic event; UPA, upadacitinib; URTI, upper respiratory tract infection; vIGA-AD, validated Investigator's Global Assessment for Atopic Dermatitis; W, weeks; WP-NRS, Worst Pruritis Numerical Rating Scale.

[a] Diagnosis of AD per the Hanifin and Rajka criteria. Must be "candidates for systemic therapy" based on lack of sufficient response to or intolerance/inappropriateness for topical treatments. Moderate-to-severe AD criteria: ≥ 10% BSA with AD *and* EASI score ≥ 16 *and* vIGA-AD ≥ 3 *and* WP-NRS ≥ 4.
Italicized bold comparator names signifies statistically significant results

Comparative Evidence of Ruxolitinib

No direct head-to-head SR or RCT efficacy comparisons were identified between ruxolitinib and other non-steroidal agents for the treatment of AD.[2,42,59-63,65,66] Ruxolitinib cream has been proven safe and effective by the FDA for the treatment of mild-to-moderate AD in patients 12 years of age and older, unresponsive to topical therapies.[35] Compared to TCSs (medium potency), ruxolitinib numerically improved EASI-75 and IGA responses, and itch NRS scores from baseline; however, tests for statistical significance were not reported.[2] Due to the topical formulation, ruxolitinib may exhibit fewer adverse reactions compared to other JAK inhibitors which need to be taken orally, but the risk of systemic absorption may still exist.[62] When applied in patients with ≤ 20% of BSA affected by AD, the risk for systemic exposure is considered to be reduced or negligible.[51,54,55]

Comparative Evidence of Crisaborole

There are currently no direct head-to-head SR or RCT efficacy comparisons between crisaborole and other non-steroidal agents for the treatment of AD.[2,42,59-63,65,66] Crisaborole ointment has been proven safe and effective by the FDA for mild-to-moderate AD in patients 3 months of age and older.[33] Crisaborole may be used as an alternative option to TCIs in patients ≥ 2 years of age with mild-to-moderate AD.[41]

Comparative Evidence of Tralokinumab

There are currently no direct head-to-head SR or RCT efficacy comparisons between tralokinumab and other non-steroidal agents for the treatment of AD.[2,42,59-63,65,66] Tralokinumab subcutaneous injection has been approved by the FDA to be safe and effective for the treatment of moderate-to-severe AD in adult patients inadequately controlled with *topical* prescription therapies (or when these medications are not suitable).[12]

Table 5 in **Appendix C** outlines the primary and selected key secondary endpoints, and pertinent safety information from the identified tralokinumab placebo-controlled trials.

Safety

Below is a summary of commonly reported adverse events (AEs) as reported in prescribing information. For products approved in children, information about the AE profile in children is noted. Some AEs may occur more frequently in older adults receiving systemic JAK inhibitors (abrocitinib, upadacitinib).[14,15]

Common Adverse Events (AEs) as Reported in Prescribing Information

Therapies with FDA approval for AD

- Crisaborole (AE ≥ 1%): application site pain (eg, burning or stinging)
    - Similar safety profile in pediatric patients (≥ 3 months)[33]
- Pimecrolimus (most common AE ≥ 1%): burning at application site, headache, nasopharyngitis, cough, influenza, pyrexia, viral infection
    - Generally similar safety profile in children (≥2 years); numerically greater URTIs in children[18]
- Tacrolimus (most common treatment-related AE ≥ 1%): skin burning, pruritis, flu-like symptoms, headache, folliculitis, rash, alcohol intolerance, acne, vesiculobullous rash, skin tingling, dyspepsia, hyperesthesia, back pain, varicella/herpes zoster, myalgia, cyst
    - Generally similar safety profile in children (≥ 2 years, using the 0.03% ointment); most common AE in children: skin burning, pruritis, varicella zoster, vesiculobullous rash[19]
- Ruxolitinib (AE ≥ 1%): nasopharyngitis, diarrhea, bronchitis, ear infection, increased eosinophil count, urticaria, folliculitis, tonsillitis, rhinorrhea
    - Similar safety profile in children (≥ 12 years)[35]
- Dupilumab (AE ≥ 1% in patients with AD): injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritis, other herpes simplex viral infection, dry eye
    - Generally similar safety profile in children (≥ 6 years)[13]
- Tralokinumab (AE ≥ 1% in adult AD patients treated with a 600 mg SQ loading dose followed by 300 mg SQ every 2 weeks): URTIs, injection site reactions, conjunctivitis, and eosinophilia[12]
- Upadacitinib (AE ≥ 1% in patients with AD): URTIs, acne, herpes infections simplex
    - Higher rates of AEs, including infections, among older adults (≥ 65 years) versus younger[15]
    - Similar safety profile (at 15 mg or 30 mg dose) in adolescents as adults[15]
- Abrocitinib (AE ≥ 1%): nasopharyngitis, nausea, headache, herpes simplex, increased blood creatine phosphokinase, dizziness, urinary tract infection (UTI)
    - AEs were more frequent in older adults (≥ 65 years old), such as low platelets and herpes zoster infections[14]

Therapies with FDA approval for a *non-AD* indication

- Baricitinib (AE ≥ 1% in adults with RA with a dose of 2 mg once daily): URTIs, nausea, herpes infections (simplex or zoster)[16]

Warnings and Precautions

These products carry some labeled warnings and precautions as summarized in **Table 11** (abrocitinib, baricitinib, upadacitinib, and ruxolitinib) and **Table 12** (crisaborole, pimecrolimus, tacrolimus, dupilumab, tralokinumab). *Note that warnings for baricitinib were extrapolated from labeling based on FDA approval for its indication for RA; this may or may not change if this product is approved for AD in the US.*

The JAK inhibitors generally carry similar warnings with regard to the risk for serious infections, morality, malignancy, major adverse cardiovascular events, thrombosis, and changes in hematologic and lipid parameters.[14-16,35] Systemic JAK inhibitors should not be started in patients with certain hematologic cytopenias (varies by agent) at baseline.[14-16] Owing to immunosuppressive effects, live vaccination during treatment with systemic JAK inhibitor treatment is not recommended.[14-16] Warnings unique to baricitinib and upadacitinib are the risk of gastrointestinal perforation and liver enzyme elevations.[15,16] Baricitinib additionally warns of hypersensitivity reactions[16] and specific to upadacitinib, the risk for embryo-fetal toxicity.[15]

Among the other agents, topical crisaborole only carries a warning regarding the risk of hypersensitivity reactions.[33] TCIs carry a black box warning regarding a possible increased risk of malignancy. Other warnings are a possible risk of immunosuppression, evaluating for discontinuation if lymphadenopathy occurs, avoiding sun exposure, and avoiding application in certain situations (to pre-malignant lesions or bacterial/viral infections, and in people with insufficient skin barriers that could increase systemic absorption).[18,19] TCIs should not be used in people who are immunocompromised or who have a developing immune system (including people <2 years old).[18,19] Burning or stinging sensations at the site of TCI application are common during the first few days of treatment.[18,19] Unlike pimecrolimus, tacrolimus carries a warning for renal insufficiency due to post-market reports of acute renal failure during its use.[19] These cases have occurred in patients with and without other risk factors, but tacrolimus ointment should be used cautiously in patients at risk for renal impairment.[19] The systemic monoclonal antibodies, dupilumab and tralokinumab carry warnings for hypersensitivity reactions, and development of ocular side effects.[12,13] Owing to the effects of IL-13 in the immune response to helminth infections, it is recommended to treat parasitic infections before treatment with dupilumab or tralokinumab.[12,13] Patients should receive any necessary live vaccinations before receipt of dupilumab or tralokinumab.[12,13] Dupilumab carries additional warnings related to use in patients with asthma, and to avoid abruptly stopping corticosteroids (topical or systemic) when starting dupilumab.[13] In patients with asthma and chronic sinusitis with nasal polyps treated with dupilumab, serious systemic eosinophilic conditions have occurred; providers should monitor for rashes, pulmonary or cardiac symptoms, or neuropathy in people presenting with eosinophilia.[13]

Regarding **contraindications,** crisaborole, pimecrolimus, tacrolimus, upadacitinib, dupilumab, and tralokinumab should not be used in patients with a prior hypersensitivity reaction.[12,13,15,18,19,33] In the US, there are not labeled contraindications for baricitinib or ruxolitinib.[16,35] Labeling for abrocitinib states that during the first 3 months of treatment, it is contraindicated in patients taking antiplatelet therapies, except for low-dose aspirin (≤ 81 mg daily).[14]

Below is a discussion about **black box warnings** for these products, and additional details regarding the conjunctivitis warning for dupilumab and tralokinumab.

Black box warning for JAK inhibitors: risk for infections, mortality, major adverse cardiovascular events, malignancy, and thrombosis

Infection risk: Serious and sometimes fatal bacterial, invasive fungal, viral, or other opportunistic pathogens have occurred during treatment with oral JAK inhibitors.[14-16] Topical ruxolitinib also carries this warning, noting that serious lower respiratory infections occurred with its use during clinical trials.[35] Owing to these risks, initiation of JAK inhibitors (oral or topical) is not recommended in patients with serious active infections, and clinicians should consider the risks vs benefits in patients with risk factors for infection (eg, chronic/recurrent infections, history of serious infection, underlying conditions, travel/exposure to tuberculosis or mycoses).[14-16,35] Screening for active/latent Tuberculosis (Tb) and viral hepatitis is recommended before use[14-16,35]; do not use oral JAK inhibitors in patients with active Tb[14-16] or oral/topical JAK inhibitors in patients with active viral hepatitis.[14-16,35] Treatment of latent Tb is recommended before initiation of oral JAK inhibitors.[14-16] Patients should be monitored for infection during treatment, and any infection should be treated appropriately.[14-16,35] *The following are rates of infection in clinical trials per prescribing information:*

- Baricitinib (among RA patients between 0 to 52 weeks; 2 mg dose, 4 mg dose):
    - Overall infections: 58.6, 55.3 events per 100 patient-years. Most common types: viral URTI, URTI, UTI, bronchitis.[16]
    - Serious infections: 4.2, 3.7 events per 100 patient-years. Most common types: pneumonia, herpes zoster, UTI.[16] Per EU labeling that includes AD treatment, the overall incidence of serious infections in clinical trials for AD was 2.1 per 100 patient-years.[8]
- Upadacitinib (among RA patients after 12 months- this information is not reported for AD patients, but overall types of AEs are considered similar; 15 mg dose, 30 mg dose):
    - Overall infections: 83.8, 99.7 events per 100 patient-years.[15] Per EU labeling that includes AD treatment, the long-term rates of infections was 98.5 and 109.6 events per 100 patient-years for the 15 mg and 30 mg dose, respectively.[69]
    - Serious infections: 3.5, 5.6 per 100 patient-years. Most common types: pneumonia, cellulitis.[15] Per EU labeling that includes AD treatment, the long-term rates of serious infections were 2.3 and 2.8 events per 100 patient-years for the 15 mg and 30 mg dose, respectively.[69]
- Abrocitinib (long-term extension; 100 mg dose, 200 mg dose):
    - Overall infections: 91.8, 103.2 per 100 patient-years.[14]
    - Serious infections: 2.3, 2.3 per 100 patient-years. Most common: herpes simplex or zoster, pneumonia.[14]
- Ruxolitinib: Details about incidence of infections are not reported. Through 8 weeks of treatment, 3% of patients reported nasopharyngitis, 1% reported bronchitis, and 1%, an ear infection. Cases of Tb were not observed. Impact on chronic hepatitis is unknown.[35]

Table 11. Contraindications, Warnings and Precautions for JAK inhibitors from Prescribing Information[a]

Abrocitinib[14]	Baricitinib[16]	Upadacitinib[15]	Ruxolitinib[35]
Contraindications			
During the first 3 months of treatment, antiplatelet therapies except for low-dose aspirin (≤ 81 mg daily)	None	Hypersensitivity to active substance or components	None
Warnings and Precautions			
Risk for Serious Infections, Mortality, Malignancy, Major Adverse Cardiovascular Events (MACE), and Thrombosis • Serious infections (eg, active tuberculosis, invasive fungal infections), or other opportunistic infections (bacterial, viral, other) resulting in hospitalization or death have occurred. Often, patients were taking concurrent immunosuppressants. o Monitor patients for infection. Interrupt treatment should a serious or opportunistic infection, or herpes zoster infection (or may continue treatment per ruxolitinib labeling) occur. o Consider risks vs benefits in patients with chronic or recurrent infection. Avoid use in patients with active serious infections (localized or disseminated) ▪ Test for latent Tb, and treat it appropriately before use ▪ Test for viral hepatitis before use. Effects of treatment on viral hepatic infections are unknown as patients with active infections were not in clinical studies. Ruxolitinib labeling specifies treatment is not recommended for patients with active hepatitis B/C infection. • Mortality and MACE o Higher rates of all-cause mortality, including MACE (ie, CV death, MI, stroke) events, have been observed (in RA patients age 50+ with at least 1 CV risk factor) treated with another JAK inhibitor (tofacitinib) compared to TNF antagonists. Smoking history increases the risk. Use (of upadacitinib, abrocitinib, or baricitinib) should be stopped in patients with a history of these events (ie, MI or stroke). • Lymphoproliferative disorders and other malignancies have occurred during treatment with some JAK inhibitors o Consider risks vs benefits in patients with a history of a neoplasm (other than NMSC), patients who develop a malignancy, and current/past smokers o Monitor skin for cancer • Serious venous thromboembolic and arterial thrombotic events have occurred more frequently than with placebo (for some JAK inhibitors) o Evaluate patients with thrombosis symptoms. Use cautiously inpatients with other risk factors for thrombosis.			
	<u>Gastrointestinal Perforation</u> • Events occurred during clinical trials, often in patients taking concomitant NSAIDs. Use cautiously in patients at risk for GI perforation (eg, NSAID use, history of diverticulitis) • Evaluate patients presenting with symptoms suggesting a GI perforation		

Table 11. Contraindications, Warnings and Precautions for JAK inhibitors from Prescribing Information[a]

Abrocitinib[14]	Baricitinib[16]	Upadacitinib[15]	Ruxolitinib[35]
	Hypersensitivity reactions, including serious reactions have occurred. D/c treat while evaluating the HS cause	**Embryo-fetal toxicity** is possible, based on animal studies. Use effective contraception	
	Liver Enzyme Elevations • Liver enzyme increases associated with use o Monitor at baseline, and as indicated thereafter o If DILI is suspected, interrupt treatment until it is ruled out		
Hematologic Laboratory Abnormalities			
Lymphopenia and *thrombocytopenia* were observed in clinical trials. Do not start in patients with low platelets, low erythrocytes, low lymphocytes or low neutrophils. Check a complete blood count 4 weeks after treatment start, and 4 weeks after dose increases	*Lymphopenia, neutropenia, and anemia* were observed in clinical trials. Avoid starting or interrupt treatment with low absolute neutrophil count, low absolute lymphocyte count, or low hemoglobin. Evaluate these labs at baseline, and as clinically needed thereafter.	*Lymphopenia, neutropenia, and anemia* were observed in clinical trials. Avoid starting or interrupt treatment with low absolute neutrophil count, low absolute lymphocyte count, or low hemoglobin. Evaluate these labs at baseline, and as clinically needed thereafter.	*Neutropenia, thrombocytopenia, and anemia* were observed in clinical trials. Consider risks vs benefits in patients with a history of these hematologic abnormalities. Monitor these labs as clinically indicated. Consider treatment d/c if significant events occur.
Lipid Parameter Increases			
Dose-dependent increases in lipid parameters observed. Check lipid parameters 4 weeks after treatment start. Monitor and treat any hyperlipidemia according to guideline recommendations	• Increases in various lipid parameters (total, HDL and LDL cholesterol) have occurred with treatment o Measure lipid panel about 12 weeks after starting treatment. Treat hyperlipidemia according to guideline recommendations	• Increases in various lipid parameters (total, HDL and LDL cholesterol) have occurred with treatment o Measure lipid panel about 12 weeks after starting treatment. Treat hyperlipidemia according to guideline recommendations	Increases in various lipid parameters (total and LDL cholesterol, triglycerides) have occurred with treatment

Table 11. Contraindications, Warnings and Precautions for JAK inhibitors from Prescribing Information[a]

Abrocitinib[14]	Baricitinib[16]	Upadacitinib[15]	Ruxolitinib[35]
Vaccinations			
Avoid live vaccines during, right before, and after treatment • Ensure vaccinations are up-to-date (including for herpes zoster) before starting treatment	Avoid live vaccinations during use • Ensure vaccinations are up-to-date before starting treatment	Avoid live vaccines during or right before starting treatment • Ensure vaccinations are up-to-date (including for herpes zoster) before starting treatment	

Grey shading indicates it is a **black box warning.** Striped yellow pattern indicates that this therapy is not yet FDA-approved for AD
Abbreviations: BBW, black box warning; D/c, discontinue; DILI, drug-induced liver injury; GI, gastrointestinal; HS, hypersensitivity; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; NSAID, nonsteroidal anti-inflammatory drug; Tb, tuberculosis

[a] Based on package inserts for products approved for AD in the US. For products lacking FDA approval for AD, but with another FDA-approved use, information is based on the labeling prior to AD approval (ie, for baricitinib).

Risk of thrombosis, cardiac events, malignancy, and death with JAK inhibitors

In 2021, the FDA required updates to the labeling for baricitinib and upadacitinib in light of a higher rate of thrombosis, major cardiovascular events (myocardial infarction, stroke), certain cancers and death compared to patients treated with an alternative therapy (TNF antagonists) in a randomized safety trial for another JAK inhibitor (tofacitinib [Xeljanz]) among patients 50 years or older with RA and at least 1 cardiovascular disease risk factor (ie, the Oral Surveillance trial).[11] The elevated risk was observed at the recommended dose of tofacitinib for treatment of RA. The FDA considers other JAK inhibitors used to treat inflammatory conditions to possibly carry a similar risk.[11] They do not mention topical ruxolitinib in their safety briefing,[11] though its labeling does list these black box warnings, noting that they have occurred with other oral JAK inhibitors used to treat inflammatory conditions.[35]

In the large post-marking Oral Surveillance trial of patients with a median age of 60 years and a duration of a median of 4 years, tofacitinib failed to meet its noninferiority primary cardiovascular safety endpoint and malignancy endpoint (to meet the endpoint the confidence interval [CI] must exclude a hazard ratio [HR] of 1.8) for the comparison to TNF antagonists. The HR of the composite endpoint of major adverse cardiovascular events (MACE: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) for tofacitinib compared to TNF antagonists was 1.33 (95% CI; 0.91 to 1.94). For malignancy (excluding nonmelanoma skin cancer), for tofacitinib compared to TNF antagonists, the HR was 1.48 (95% CI 1.05 to 2.09). The risk of thrombosis and cardiac events increased in a dose-dependent manner whereas the risk of malignancy (lymphoma, lung cancer) occurred regardless of dose.[11]

Whether the safety profile of tofacitinib in RA patients will extend to other JAK inhibitors when used to treat AD patients remains to be determined. Pooled analyses of shorter-term placebo controlled trials, and open-label extension studies for treatment of AD with baricitinib (median exposure duration of 310 days, maximum of 736 days)[70] and abrocitinib (mean exposure of 90 days in placebo-controlled trials; total exposure of 1617 person-years with a maximum of 756 days)[71] have been published. Among all patients receiving baricitinib (1 to 4 mg dose) 2 cases of venous thromboembolism (VTE) occurred (incidence rate [IR], 0.40 per 100 person-years at risk [PY]), 5 non-NMSC cases including 3 lymphoma cases (IR 0.22 per 100 PY), 6 cases of NMSC (IR 0.26 per 100 PY), and 1 MACE event (IR 0.17 per 100 PY) in a patient with multiple cardiovascular risk factors.[70] During treatment with baricitinib, 1 death occurred (gastrointestinal bleed), and 1 hemorrhagic stroke occurred; no gastrointestinal perforations were reported.[70] Among all patients receiving abrocitinib (100 or 200 mg dose), 5 VTE events occurred (IR 0.12 per 100 PY) in patients on the 200 mg dose, 7 cases of NMSC occurred, 3 other malignancies occurred (2 prostate cancer, 1 gastro adenocarcinoma), and 3 MACE events (IR 0.18 per 100 PY) including 2 MI and 1 sudden death occurred, all in older adults with other cardiovascular risk factors.[71] In total, 3 deaths were reported during abrocitinib treatment including 1 sudden death, 1 death due to gastro adenocarcinoma and 1 death due to COVID-19 infection.[71] This suggests systemic JAK inhibitors used to treat AD could be associated with malignancy and cardiac events like tofacitinib, but whether risk is increased beyond background risk is not discernable. Authors point out that people with RA have an increased risk of cardiovascular events compared to the general population, and the observed MACE incidence with baricitinib and abrocitinib is similar to or lower than the background incidence of these events.[70,71] Of note, on average, patients in these clinical trials were younger than those in the tofacitinib safety study (median age of 31 years and mean age of 36.4 years in all abrocitinib or baricitinib cohorts, respectively),[70,71] which likely influences risks for these events.

Thromboembolic events: US labeling for baricitinib and upadacitinib warns of an elevated risk of venous thromboembolism (VTE) and arterial thrombosis. Serious events, including death, have occurred.[15,16] Labeling for abrocitinib warns of similar risks, specifically, the risk for VTE.[14] If symptoms suggestive of a thromboembolic event occur, treatment with these agents should be discontinued, and appropriate treatment should be initiated. Their use should be avoided in patients with risk factors for thrombosis.[14-16] The topical ruxolitinib also carries this warning based on events with the oral JAK inhibitors, though cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) have occurred during treatment with topical ruxolitinib too; it should be used cautiously in at-risk patients.[35] *The following are rates of thrombotic events in clinical trials per prescribing information:*

- Baricitinib (among RA patients between 0 to 52 weeks; 2 mg dose, 4 mg dose):
    - Venous thromboembolism: 0.6, 0.7 per 100 patient-years
    - Arterial thrombosis: 0.9, 0.3 events per 100 patient-years[16]
- Upadacitinib (among RA patients after 12 months- this information is not reported for AD patients, but overall types of AEs are considered similar; 15 mg dose, 30 mg dose):
    - Venous thromboembolism: 0.5, 0.4 per 100 patient-years
    - Arterial thrombosis: 0, 0.2 per 100 patient-years[15]
- Abrocitinib (among AD patients in all clinical studies; 100 mg, 200 mg dose):
    - DVT: 0, 0.3 per 100 patient-years
    - PE: 0, 0.4 per 100 patient-years[14]
- Ruxolitinib: event rates not reported in prescribing information[35]

Major adverse cardiovascular events: US labeling for baricitinib, abrocitinib, and upadacitinib warns of the increased risk of cardiovascular events relative to TNF antagonists that were observed with another JAK inhibitor among RA patients (in the Oral Surveillance study mentioned above).[14-16] Ruxolitinib also carries a similar warning.[35] Providers should consider the risks versus benefits of these therapies based on patient's cardiovascular risk. Cardiovascular risks are increased in patients with a current or prior history of smoking.[14-16] Use of baricitinib, abrocitinib, or upadacitinib is not recommended for patients with a history of a myocardial infarction or stroke.[14-16]

Malignancy and lymphoproliferative disorders: US labeling for baricitinib, abrocitinib, upadacitinib, and ruxolitinib warns of an elevated risk of malignancies[14-16,35] (especially lymphoma, and lung cancer in current/prior smokers) compared to TNF antagonists in that prior study of another oral JAK inhibitor among RA patients (the Oral Surveillance study mentioned above).[14-16] Malignancies, including non-melanoma skin cancer (NMSC), occurred in clinical studies with abrocitinib, baricitinib, and upadacitinib.[14-16] Risks versus benefits of these therapies should be considered, particularly in patients with a history of malignancy (other than treated NMSC), people with an emergent malignancy, and people with a current or past history of smoking. Periodic monitoring of skin for cancer is recommended in people at risk for skin cancer.[14-16,35] *The following are rates of malignancy in clinical trials per prescribing information:*

- Baricitinib (among RA patients between 0 to 52 weeks; 2 mg dose, 4 mg dose):
    - Malignancy (other than NMSC): 0.6, 0.7 per 100 patient-years[16]
- Upadacitinib (among RA patients after 12 months- this information is not reported for AD patients, but overall types of AEs are considered similar; 15 mg dose, 30 mg dose):
    - Malignancy (other than NMSC): 1.2, 1.3 per 100 patient-years[15]

- Abrocitinib (among AD patients in all clinical studies; 100 mg, 200 mg dose)
    - Malignancy (including NMSC): 0.5, 0.3 per 100 patient-years[14]
- Ruxolitinib: no malignancies reported in prescribing information[35]

Mortality: US labeling for baricitinib, abrocitinib, upadacitinib, and ruxolitinib warns of a higher rate of all-cause mortality, including sudden cardiac death, that was observed in the Oral Surveillance study (mentioned above) during treatment with another oral JAK inhibitor compared to TNF antagonists in a cohort of patients with RA.[14-16,35] Potential risks of these therapies for an individual patient should be weighed against the benefits.[14-16,35]

Black box warning for Topical Calcineurin Inhibitors (TCIs): risk for malignancy

Both topical tacrolimus and pimecrolimus carry warnings for the risk for malignancy, and advise avoiding *continuous* long-term use in light of the lack of established long-term safety (ie, it is not established for >1 year of non-continuous use).[18,19] The FDA required this warning as of 2006[72,73] due to evidence of increased risk for malignancies (and infection) after *systemic* use of calcineurin inhibitors in animal studies and among transplant recipients.[18,19] Proposed mechanisms of risk include lack of immune system detection of cancer due to immunosuppression or possibly direct stimulation of tumors.[72] A causal relationship with the TCIs is not established.[18,19] To mitigate risk, labeling advises to not use these products among people who are immunocompromised and in children less than 2 years of age, and to confirm the diagnosis of AD if there is not improvement after treatment with topical tacrolimus or pimecrolimus after 6 weeks.[18,19]

Whether TCIs with limited systemic exposure actually increase the risk for cancers, particularly lymphoma, is controversial. A systematic review (SR) from 2016 failed to find an increased risk of lymphoma in pediatric clinical trials ≥ 12 weeks long, and based on a review of the literature.[73] However, Lam et al (2021) and Wu et al (2020) found an increased risk of lymphoma based on meta-analysis of observational (cohort or case-control) studies in patients receiving TCIs compared to those without TCIs.[72,74] In cohort studies with a follow-up duration ranging from a mean of 1.5 years to up to 10 years, any TCI use (in patients with any disease state) significantly increased the risk for lymphoma compared to nonactive comparators (relative risk [RR] 1.86; 95% CI 1.39 to 2.49) and TCSs (RR 1.35; 1.13 to 1.61).[72] An increased risk of melanoma or keratinocyte carcinoma was not observed.[72] Authors suggest that the absolute risk of lymphoma is low, thus "the potential increased risk attributable to TCI use for any individual patient is likely very small."[72] Risk of lymphoma in general is related to degree of immunosuppression.[75] Factors which increase systemic absorption of TCIs (eg, more body involvement, more compromised skin barrier) could theoretically increase risk.[74]

Warning for dupilumab and tralokinumab: risk for ocular side effects

US labeling for dupilumab and tralokinumab carry a warning regarding the risk of ocular side effects including conjunctivitis and keratitis.[12,13] For dupilumab, a higher frequency of these events compared to placebo occurred among patients with AD, but not in clinical trials to treat other conditions.[13] Patients should monitor and report new or worsening ocular symptoms.[12,13] In most cases, long term treatment of the ocular surface disorder without discontinuation of the offending agent will resolve the symptoms.[76] For some patients, the ocular effects led to discontinuation of dupilumab.[76]

According to a systemic review, ocular surface disorders commonly occur in AD patients treated with dupilumab, but long-term ocular complications are rare.[76] In dupilumab RCTs, 10.9% of treated patients experienced this effect,[76] and among 5 tralokinumab RCTs, 7.5% of treated patients experienced conjunctivitis.[77] Rates of dupilumab-induced ocular effects appear higher with real-life use compared to rates in clinical trials.[78] The cause of these disorders is not known. Proposed mechanisms include mucosal barrier dysfunction induced by blockade of IL-13 leading to hypoplasia of mucin-secreting goblet cells, and a shift toward the Th1 immune response owing to downregulation of the Th2 immune response by dupilumab/tralokinumab.[76]

Table 12. Contraindications, Warnings and Precautions for Topical Calcineurin Inhibitors and Biologic Products from Prescribing Information

Crisaborole[33]	Pimecrolimus[18]	Tacrolimus[19]	Dupilumab[13]	Tralokinumab[12]
Contraindications				
Hypersensitivity to active substance or any product components				
Warnings and Precautions				
Hypersensitivity Reactions • Discontinue treatment, and treat the reaction Clinical trials: contact urticaria in <1% of patients	**Possible Risk for Malignancy; Unknown Long-Term Safety** • Rare skin and lymphoma malignancies reported with use Avoid: continuous use and application to sites other than those with atopic dermatitis • Not indicated for children < 2 (that have developing immune systems)		**Hypersensitivity Reactions** • Clinical trials: <1% of patients; 1 case of anaphylaxis occurred • Discontinue treatment, and treat the reaction	**Hypersensitivity Reactions** • Discontinue treatment, and treat the reaction
	Immunosuppression Risk Systemic use increases risk for infections and malignancy, and there is a theoretical risk with topical use. Avoid: continuous long-term use (safety for durations >1-year of noncontinuous use is unknown); use in immunocompromised people		**Conjunctivitis and Keratitis** Observed among AD patients in trials. For most patients, it resolved during treatment. Monitor for eye symptoms	
	Unstudied in Immunocompromised Individuals **Avoid applying to (pre-) malignant skin lesions** (eg, cutaneous T-cell lymphoma which can have symptoms similar to AD)		**Treatment of Parasitic (Helminth) Infections Prior to Starting Biologic Treatment** It is unknown how the immune system of patients with these infections will react with dupilumab/tralokinumab treatment If a helminth infection occurs and do not respond to antiparasitic treatment, temporarily discontinue dupilumab/tralokinumab until resolution.	
	Avoid Use in Patients with Insufficient Skin Barriers (eg, Netherton's syndrome, lamellar ichthyosis, generalized erythroderma, cutaneous GVHD) • Avoid due to potential increased systemic exposure		**Abrupt Discontinuation of Corticosteroids** Abrupt discontinuation can cause withdrawal symptoms. Gradually	**Update Live Vaccinations Prior to Use** Immune response may be altered after the administration of live vaccinations. Avoid

Table 12. Contraindications, Warnings and Precautions for Topical Calcineurin Inhibitors and Biologic Products from Prescribing Information

Crisaborole[33]	Pimecrolimus[18]	Tacrolimus[19]	Dupilumab[13]	Tralokinumab[12]
			reduce dose under medical provider supervision	administering live vaccines during treatment due to the increase risk of infection
	Do Not Apply to Bacterial or Viral Infections • Ensure infections at AD sites are resolved before use; safety/efficacy not established for use on AD lesions with infections. Use may lead to superficial infections. • If skin warts worsen, or do not improve with treatment, temporarily discontinue pimecrolimus until wart resolution.		**Asthma Comorbidity** Patients treating AD who have asthma should not stop/adjust other asthma treatments unless told by medical provider	
	Evaluate for Discontinuation in Cases of Lymphadenopathy • Cases of lymphadenopathy (0.9%) occurring in trials, usually due to infections that was treatable with antibiotics. • Discontinue treatment if lymphadenopathy due to unknown etiology, or due to acute mononucleosis occurs.		**Serious Eosinophilic Conditions** (eg, eosinophilic pneumonia) Observed in asthma patients	
	Burning or Pruritis Usually, symptoms improve quickly within minutes to hours, and improve as AD symptoms resolve		**Not for Treatment of Acute Asthma Symptoms** Medical advice should be obtained if asthma remains uncontrolled or worsens	
	Avoid Sun Exposure Potential effects with ultraviolet light exposure unknown; avoid/minimize exposure (to natural or artificial sunlight)			
		Renal Failure Risk • Rare AKF reported Exercise caution in patients with risk factors: patients where larger systemic		

Table 12. Contraindications, Warnings and Precautions for Topical Calcineurin Inhibitors and Biologic Products from Prescribing Information

Crisaborole[33]	Pimecrolimus[18]	Tacrolimus[19]	Dupilumab[13]	Tralokinumab[12]
		absorption is expected, OR patients at risk for renal impairment		

Grey shading indicates it is a **black box warning.**

Abbreviations: BBW, black box warning; D/c, discontinue; GI, gastrointestinal; HS, hypersensitivity; MACE, major adverse cardiovascular events; NSAID, nonsteroidal anti-inflammatory drug; Tb, tuberculosis

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Appendix A: Literature Searches

Literature Searches for Systematic Reviews

Table 1. Ovid Medline Literature Search Strategy for Systematic Reviews

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to November 08, 2021>
Search strategy (date of search: November 9, 2021)

#	Searches	Results
1	exp *Dermatitis, Atopic/ or exp *Eczema/ or (atopic-dermatitis or eczema).ti,ab,kw,kf	42797
2	(abrocitinib or Cibinqo or baricitinib or Olumiant or crisaborole or Eucrisa or dupilumab or Dupixent or pimecrolimus or Elidel or ruxolitinib or Opzelura or tralokinumab or Adtralza or tacrolimus or Protopic or upadacitinib or Rinvoq).ti,ab,kw,kf. or exp Tacrolimus/	28049
3	*Dermatologic Agents/ or Janus Kinase Inhibitors/ or (Antibodies, Monoclonal/ and (Interleukin-13/ or Dermatologic Agents/)) or Phosphodiesterase 4 Inhibitors/ or Protein Kinase Inhibitors/ or Calcineurin Inhibitors/	79177
4	(PF-04965842 or PF04965842 or CAT-354 or CAT-354 or INCB028050 or INCB-028050 or ABT-494 or ABT494 or INCB018424 or INCB-018424).ti,ab,kw,kf	96
5	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw	423484
6	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	394680
7	2 or 3 or 4	104190
8	5 or 6	495465
9	1 and 7 and 8	222
10	limit 9 to yr="2018 -Current"	**131**

Table 2. Epistemonikos Search Strategy for Systematic Reviews

Database(s): Epistemonikos Session Results
Search strategy (date of search: December 2, 2021)

#	Searches	Results
1	(atopic dermatitis) or eczema	2529
2	**AND** abrocitinib or Cibinqo or baricitinib or Olumiant or crisaborole or Eucrisa or dupilumab or Dupixent or pimecrolimus or Elidel or ruxolitinib or Opzelura or tralokinumab or Adtralza or tacrolimus or Protopic or upadacitinib or Rinvoq or (janus kinase inhibitor*) or (monoclonal antibod*) or (phosphodiesterase 4 inhibitor*) or (phosphodiesterase inhibitor*) or (protein kinase inhibitor*) or (calcineurin inhibitor*) or (PF-04965842 OR PF04965842 OR CAT-354 OR CAT-354 OR INCB028050 OR INCB-028050 OR ABT-494 OR ABT494 OR INCB018424 OR INCB-018424)	267
Filter publication year	From 2018 to 2021	106

Filter publication type	Systematic Review	**60**

Literature Searches for Randomized Controlled Trials

Table 3. Ovid Medline Literature Search Strategy for Janus Kinase Inhibitors and Tralokinumab Randomized Controlled Trials

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 17, 2021>
Search strategy (date of search: December 17, 2021)

#	Searches	Results
1	exp *Dermatitis, Atopic/ or exp *Eczema/ or (atopic-dermatitis or eczema).ti,ab,kw,kf	43109
2	(abrocitinib or Cibinqo or baricitinib or Olumiant or ruxolitinib or Opzelura or tralokinumab or Adtralza or upadacitinib or Rinvoq).ti,ab,kw,kf.	2695
3	*Dermatologic Agents/ or Janus Kinase Inhibitors/ or (Antibodies, Monoclonal/ and (Interleukin-13/ or Dermatologic Agents/))	22442
4	(PF-04965842 or PF04965842 or CAT-354 or CAT354 or INCB028050 or INCB-028050 or ABT-494 or ABT494 or INCB018424 or INCB-018424).ti,ab,kw,kf	97
5	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1301022
6	2 or 3 or 4	24834
7	1 and 5 and 6	363
8	limit 7 to yr="2021 -Current"	**55**

Table 4. Ovid Medline Literature Search Strategy for Pimecrolimus and Crisaborole Randomized Controlled Trials

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 17, 2021>
Search strategy (date of search: December 17, 2021)

#	Searches	Results
1	exp *Dermatitis, Atopic/ or exp *Eczema/ or (atopic-dermatitis or eczema).ti,ab,kw,kf	43109
2	(crisaborole or Eucrisa or pimecrolimus or Elidel).ti,ab,kw,kf.	979
3	*Dermatologic Agents/ or Phosphodiesterase 4 Inhibitors/ or Calcineurin Inhibitors/	26569
4	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1301022
5	2 or 3	27125
6	1 and 4 and 5	395
7	limit 6 to yr="2020 -Current"	**41**

Table 5. Ovid Medline Literature Search Strategy for Dupilumab Randomized Controlled Trials

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 17, 2021>

Search strategy (date of search: December 17, 2021)

#	Searches	Results
1	exp *Dermatitis, Atopic/ or exp *Eczema/ or (atopic-dermatitis or eczema).ti,ab,kw,kf	43109
2	(dupilumab or dupixent).ti,ab,kw,kf.	1338
3	*Dermatologic Agents/ or (Antibodies, Monoclonal/ and (Interleukin-13/ or Dermatologic Agents/))	21668
4	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1301022
5	2 or 3	22887
6	1 and 4 and 5	388
7	limit 6 to yr="2021 -Current"	**48**

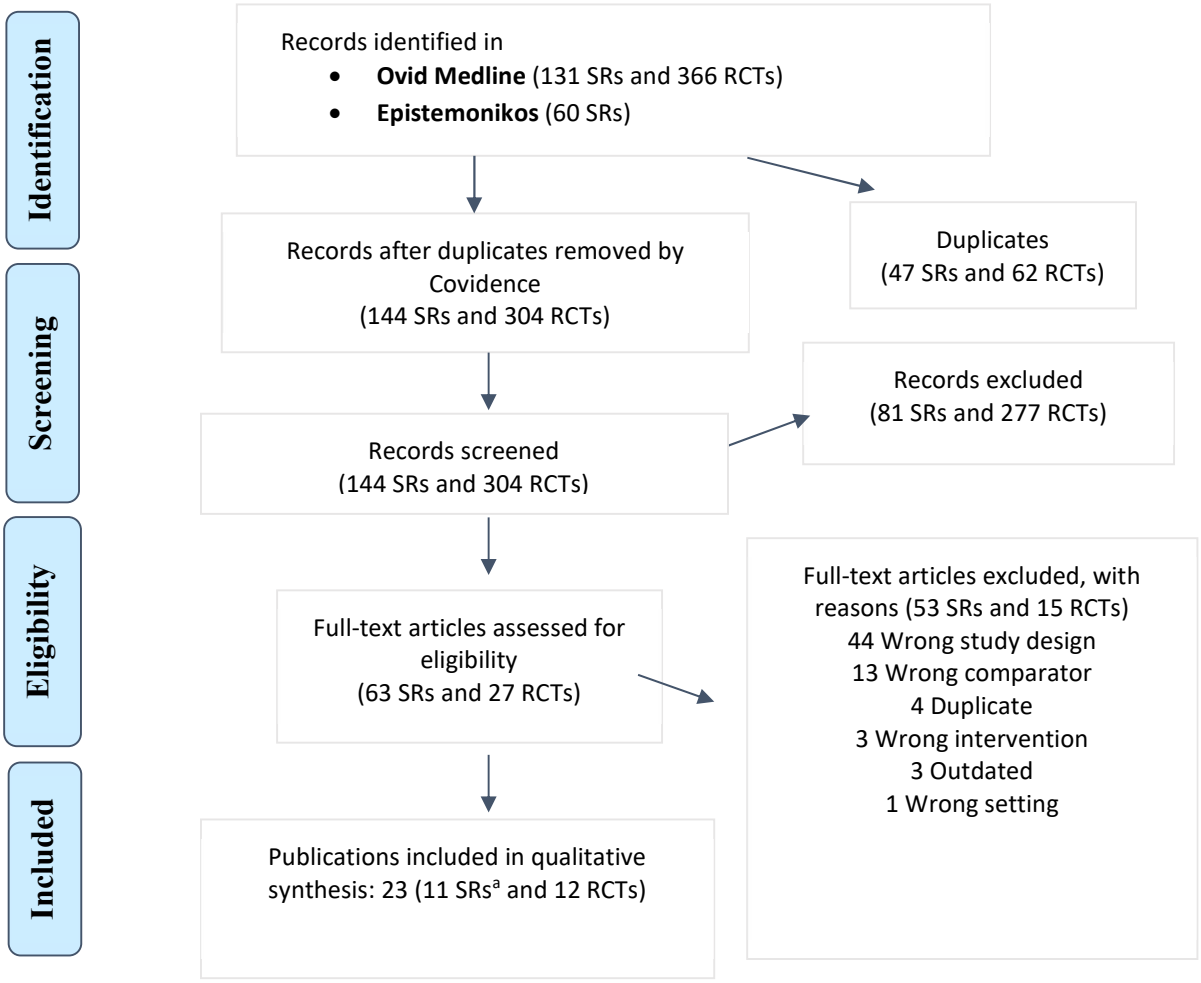
Table 6. Ovid Medline Literature Search Strategy for Tacrolimus Randomized Controlled Trials

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 17, 2021>
Search strategy (date of search: December 17, 2021)

#	Searches	Results
1	exp *Dermatitis, Atopic/ or exp *Eczema/ or (atopic-dermatitis or eczema).ti,ab,kw,kf	43109
2	(tacrolimus or Protopic).ti,ab,kw,kf. or *Tacrolimus/	20585
3	*Calcineurin Inhibitors/	1893
4	((topica* adj2 administer*) or topica* or ointment).ti,ab,kw,kf.	121348
5	*Administration, Cutaneous/	1847
6	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1301022
7	4 or 5	123116
8	2 or 3	21552
9	1 and 6 and 7 and 8	**222**

Appendix B: Screening of Studies

Figure 1. PRISMA Flow Chart for Publication Screening



Abbreviations: RCT, randomized controlled trial; SR, systematic review

[a] Includes SRs were only the SR portion was extracted, and the ICER report identified from https://icer.org/

Appendix C: Supplementary Evidence Tables

Table 1. Randomized Controlled Trials (of the Same Agents) Included in Systematic Reviews for the Treatment of Atopic Dermatitis

Author last name, year, trial name	Doses Tested in RCTs	SR/MA									
		Le, 2021[59]	Meher, 2021[60]	Fadlalmola, 2021[61]	Tsai, 2021[62]	Mostafa, 2021[63]	Nusbaum, 2021[42]	Miao, 2021[64]	Li, 2021[65]	Zhang, 2021[66]	Atlas, 2021[2]
Abrocitinib											
Bieber, 2021. JADE Compare[29]	ABO (100 mg or 200 mg) vs. DUP 300 mg Q2W vs. PBO	✓	✓	✓		✓	✓				✓
Simpson, 2020 JADE MONO-1[79]	ABO (100 mg or 200 mg) vs. PBO	✓	✓	✓	✓	✓	✓		✓	✓	✓
Silverberg, 2020 JADE MONO-2[80]	ABO (100 mg or 200 mg) vs. PBO	✓	✓	✓	✓		✓	✓	✓		✓
Baricitinib											
Simpson, 2020 BREEZE-AD1 and BREEZE-AD2[30]	BAR (1 mg, 2 mg, or 4 mg) vs. PBO	✓			✓	✓	✓	✓	✓	✓	✓
Reich, 2020 BREEZE-AD7[32]	BAR (1 mg, 2 mg, or 4 mg) +TCS vs. PBO+TCS	✓			✓	✓	✓		✓		✓
Simpson, 2021 BREEZE-AD5[31]	BAR (1mg or 2 mg) vs. PBO						✓				✓
Upadacitinib											
Reich, 2021 AD Up[81]	UPA 15 mg +TCS vs. PBO+TCS	✓									✓
Guttman-Yassky, 2021 Measure Up 1 and Measure UP 2[82]	UPA (15 mg or 30 mg) vs. PBO	✓					✓				✓

Table 1. Randomized Controlled Trials (of the Same Agents) Included in Systematic Reviews for the Treatment of Atopic Dermatitis

Author last name, year, trial name	Doses Tested in RCTs	SR/MA									
		Le, 2021[59]	Meher, 2021[60]	Fadlalmola, 2021[61]	Tsai, 2021[62]	Mostafa, 2021[63]	Nusbaum, 2021[42]	Miao, 2021[64]	Li, 2021[65]	Zhang, 2021[66]	Atlas, 2021[2]
Blauvelt, 2021 Heads Up[28]	DUP 300 mg vs. UPA 30 mg										✓
	Tralokinumab										
Wollenberg, 2021 ECZTRA 1 and ECZTRA 2[83]	TRA 300 mg Q2W vs. PBO					✓	✓				✓
Silverberg, 2021 ECZTRA 3[84]	TRA 300 mg Q2W vs. PBO					✓	✓				✓

Abbreviations: ABO, abrocitinib; BAR, baricitinib; DUP, dupilumab; mg, milligrams; PBO, placebo; Q2W, every other week; SR, systematic review; TCS, topical corticosteroids; TRA, tralokinumab; UPA, upadacitinib;

Comparative Evidence of Abrocitinib vs. Placebo

The included SRs conducted by **Atlas et al (2021), Meher et al (2021)**, **Nusbaum et al (2021)**, and **Fadlalmola et al (2021)** contain pooled analysis of a phase II trial, in addition to the pivotal phase III trials, JADE MONO-1, JADE MONO-2, and JADE COMPARE.[2,29,42,60,61,79,80] Patients were adults and/or children (≥12 years of age) with moderate-to-severe AD who failed to have an adequate response to topical therapies. The pooled analysis showed that patients treated with abrocitinib achieved a higher rate of IGA response, EASI-75 response, and PP-NRS response at 12 weeks compared to placebo.[42,60,61] Additionally, patients treated with abrocitinib experienced an improvement in QoL compared to placebo as measured by the POEM, PSAAD, and the CDLQI scores.[42,61,85] However, patients treated with abrocitinib had a higher risk of developing adverse events, which seems to be dose related, when compared to placebo.[60,61] The most commonly reported adverse events included nausea, nasopharyngitis, URTI, and headache.[29,60,61,79,80]

An additional, 4 placebo-controlled phase III RCTs were identified for abrocitinib, 2 of which were not included in the SRs.[79,80,86,87] All identified studies demonstrated an improvement in IGA, EASI, and PP-NRS response for patients receiving abrocitinib compared to patients receiving placebo.[79,80,86] Although a smaller proportion of adolescents were included in the trials, results seem similar to the adult population, according to the SR by ICER.[2,79,80,86,87] The JADE REGIMEN trial, a randomized withdrawal study, showed that a majority of patients with an initial response to abrocitinib 200 mg daily were less likely to experience a flare relapse compared to those receiving a reduced dose (100 mg daily).[87] It further supports the most effective dose for disease control is abrocitinib 200 mg daily compared to abrocitinib 100 mg, but is associated with a higher risk of adverse events.[87]

Table 2 includes population, efficacy, and pertinent safety information summarized from identified placebo-controlled abrocitinib RCTs. For key secondary endpoints, when multiple timepoints were collected, only the last timepoint endpoints were reported in the table.

Table 2. Randomized Placebo-Controlled Trials of Abrocitinib

RCT Design (author, year, trial name)	***Population***	***Intervention***	***Efficacy Results (% of patients)***	***Safety Results***
Multicenter, double-blind, randomized, placebo-controlled (Simpson, 2020, **JADE MONO-1**)[79]	Patients (≥12 years of age) diagnosed with moderate-to-severe AD[a] ≥1 year, uncontrolled by topical therapies	**ABO 100 mg** po daily (N=156) **vs** **ABO 200 mg** po daily (N=154) **vs** **PBO** po daily (N=77) Duration: 12W	Co-primary endpoints: IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 12W • ***ABO 100 mg vs PBO:*** 37 patients (24%) vs 6 patients (8%); treatment difference =15.8%; (95% CI 6.8% to 24.8%); p=0.0037 • ***ABO 200 mg vs PBO:*** 67 patients (44%) vs 6 patients (8%); treatment difference =36.0%; (95% CI 26.2% to 45.7%); p=<0.0001 EASI-75 Response: ≥75% improvement in EASI score at week 12 from baseline • ***ABO 100 mg vs PBO:*** 62 patients (40%) vs 9 patients (12%); treatment difference =27.9%; (95% CI 17.4% to 38.3%); p=<0.0001 • ***ABO 200 mg vs PBO:*** 96 patients **(**63%) vs 9 patients (12%); treatment difference =51.0%; (95% CI 40.5% to 61.5%); p=<0.0001 Key secondary endpoints: PP-NRS Response: (≥4 point improvement from baseline in score) at week 12 • ***ABO 100 mg vs PBO:*** treatment difference =22.5%; (95% CI 10.3% to 34.8%); p=0.0003 • ***ABO 200 mg vs PBO:*** treatment difference =41.7%; (95% CI 29.6% to 53.9%); p=<0.0001 PSAAD Total Score Change: Difference in least squares mean change from baseline at week 12	Most frequently reported TEAEs (≥5% in any treatment group) • Nausea ABO 100 (9%) vs ABO 200 (20%) vs PBO (3%) • Nasopharyngitis ABO 100 (15%) vs ABO 200 (12%) vs PBO (10%) • Headache ABO 100 (8%) vs ABO 200 (10%) vs PBO (3%) • URTI ABO 100 (7%) vs ABO 200 (7%) vs PBO (7%) • AD ABO 100 (14%) vs ABO 200 (5%) vs PBO (17%) Discontinued treatment due to AEs ABO 100 (6%) vs ABO 200 (6%) vs PBO (9%) SAEs ABO 100 (3%) vs ABO 200 (3%) vs PBO (4%) • Only 2 were treatment-related [ABO 100: acute pancreatitis and ABO 200: IBD] Reported herpes viral infection: • Any herpes viral infection ABO 100 (3%) vs ABO 200 (3%) vs PBO (0%) • Eczema herpeticum ABO 100 (1%) vs ABO 200 (0%) vs PBO (1%)

Table 2. Randomized Placebo-Controlled Trials of Abrocitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***ABO 100 mg vs PBO:*** treatment difference= 1.1 (95% CI -1.7 to -0.4); p=0.0010 • ***ABO 200 mg vs PBO:*** treatment difference= -2.1 (95% CI -2.7 to -1.4); p=<0.0001	
Multicenter, international, randomized, double-blinded, placebo-controlled (Silverberg, 2020, **JADE MONO-2**)[80]	Patients (≥12 years of age) diagnosed with moderate-to-severe AD[a] ≥1 year, uncontrolled by topical therapies	**ABO 100 mg** po daily (N=158) **vs** **ABO 200 mg** po daily (N=155) **vs** **PBO** po daily (N=78) Duration: 12W	Co-primary endpoints: IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 12W • ***ABO 100 mg vs PBO:*** 44 patients (28%) vs 7 patients (9%); treatment difference =19.3%; (95% CI 9.6% to 29.0%); p=0.001 • ***ABO 200 mg vs PBO:*** 59 patients (38%) vs 7 patients (9%); treatment difference =28.7%; (95% CI 18.6% to 38.8%); p=<0.001 EASI-75 Response: ≥75% improvement in EASI score at week 12 from baseline • ***ABO 100 mg vs PBO:*** 69 patients (45%) vs 8 patients (10%); treatment difference =33.9%; (95% CI 23.3% to 44.4%); p=<0.001 • ***ABO 200 mg vs PBO:*** 94 patients **(**61%) vs 8 patients (10%); treatment difference =50.5%; (95% CI 40.0% to 60.9%); p=<0.001 Key secondary endpoints: PP-NRS Response: (≥4 point improvement from baseline in score) at week 12 • ***ABO 100 mg vs PBO:*** treatment difference =33.7%; (95% CI 22.8% to 44.7%); p=<0.0001	Most frequently reported TEAEs (≥3% in any treatment group) • Nausea ABO 100 (7.6%) vs ABO 200 (14.2%) vs PBO (2.6%) • Nasopharyngitis ABO 100 (12.7%) vs ABO 200 (7.7%) vs PBO (6.4%) • Headache ABO 100 (5.7%) vs ABO 200 (7.7%) vs PBO (2.6%) • URTI ABO 100 (8.9%) vs ABO 200 (3.2%) vs PBO (3.8%) • Worsening AD ABO 100 (5.7%) vs ABO 200 (3.9%) vs PBO (15.4%) Discontinued treatment due to AEs ABO 100 (3.8%) vs ABO 200 (3.2%) vs PBO (12.8%) SAEs ABO 100 (3.2%) vs ABO 200 (1.3%) vs PBO (1.3%) • Only 2 were treatment-related [ABO 100: herpangina and pneumonia] Reported herpes viral infection:

Table 2. Randomized Placebo-Controlled Trials of Abrocitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***ABO 200 mg vs PBO:*** treatment difference =43.9%; (95% CI 32.9% to 55.0%); p=<0.0001 PSAAD Total Score Change: Difference in least squares mean change from baseline at week 12 • ***ABO 100 mg vs PBO:*** treatment difference= –1.7 (95% CI –2.3 to –1.1); p=<0.0001 • ***ABO 200 mg vs PBO:*** treatment difference= –2.2 (95% CI –2.8 to –1.6); p=<0.0001	• Any herpes viral infection ABO 100 (0%) vs ABO 200 (1.3%) vs PBO (0%) • Eczema herpeticum ABO 100 (1.3%) vs ABO 200 (0%) vs PBO (1.3%)
Multicenter, international, randomized, placebo-controlled (Eichenfield, 2021, **JADE TEEN**)[86]	Patients (12 to 17 years of age) diagnosed with moderate-to-severe AD[a], uncontrolled by topical therapies or requiring systemic therapy	**ABO 100 mg** po daily (N=95) **vs** **ABO 200 mg** po daily (N=94) **vs** **PBO** po daily (N=96) Duration: 12W	Co-primary endpoints: IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 12W • ***ABO 100 mg vs PBO:*** 37 patients (42%) vs 23 patients (25%); treatment difference =16.7%; (95% CI 3.5% to 29.9%); p=<0.05 • ***ABO 200 mg vs PBO:*** 43 patients (46%) vs 23 patients (25%); treatment difference =20.6%; (95% CI 7.3% to 33.9%); p=<0.05 EASI-75 Response: ≥75% improvement in EASI score at week 12 from baseline • ***ABO 100 mg vs PBO:*** 61 patients (69%) vs 39 patients (42%); treatment difference =26.5%; (95% CI 13.1% to 39.8%); p=<0.05 • ***ABO 200 mg vs PBO:*** 67 patients **(**72%) vs 39 patients (42%); treatment difference =29.4%; (95% CI 16.3% to 42.5%); p=<0.0001 Key secondary endpoints:	Most frequently reported TEAEs (≥3% in any treatment group) • Nausea ABO 100 (7.4%) vs ABO 200 (18.1%) vs PBO (1.0%) • URTI ABO 100 (9.5%) vs ABO 200 (10.6%) vs PBO (10.4%) • Headache ABO 100 (5.3%) vs ABO 200 (8.5%) vs PBO (7.3%) • Nasopharyngitis ABO 100 (8.4%) vs ABO 200 (8.5%) vs PBO (9.4%) • Dizziness ABO 100 (0%) vs ABO 200 (6.4%) vs PBO (1.0%) Discontinued treatment due to AEs ABO 100 (1.1%) vs ABO 200 (2.1%) vs PBO (2.1%) SAEs

Table 2. Randomized Placebo-Controlled Trials of Abrocitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			PP-NRS Response: (≥4 point improvement from baseline in score) at week 12 • ABO 100 mg vs PBO: treatment difference =22.8%; (95% CI 8.0% to 37.7%); p=NS • ***ABO 200 mg vs PBO:*** treatment difference =25.6%; (95% CI 10.6% to 40.6%); p=<0.05 PSAAD Total Score Change: Difference in least squares mean change from baseline at week 12 • ABO 100 mg vs PBO: treatment difference= –0.5 (95% CI –1.1 to 0.0); p=NS • ABO 200 mg vs PBO: treatment difference= –0.7 (95% CI –1.3 to –0.1); p=NS	ABO 100 (0%) vs ABO 200 (1.1%) vs PBO (2.1%) Reported herpes viral infection: • Herpes zoster ABO 100 (1.1%) vs ABO 200 (0%) vs PBO (0%) • Herpes simplex ABO 100 (0%) vs ABO 200 (1.1%) vs PBO (0%) • Oral herpes ABO 100 (1.1%) vs ABO 200 (2.1%) vs PBO (0%) • Eczema herpeticum ABO 100 (1.1%) vs ABO 200 (0%) vs PBO (0%)
Multicenter, double-blinded, placebo-controlled, randomized, withdrawal study (Blauvelt, 2021, **JADE REGIMEN**)[87]	Patients (≥12 years of age) diagnosed with moderate-to-severe AD[a], uncontrolled by topical therapies	Open-label induction period of **ABO 200 mg** po daily (N=1235) Blinded maintenance period **ABO 200 mg** po daily (N=266) **vs** **ABO 100 mg** po daily (N=265) **vs**	Primary endpoint: Loss of response (flare) during maintenance period requiring rescue treatment[c]: ≥50% loss of initial EASI response at week 12 with a new IGA score of ≥2 • ***ABO 100 mg vs PBO:*** 105 patients (40%) vs 207 patients (78%); HR=0.27; (95% CI 0.21 to 0.34); p=<0.0001 • ***ABO 200 mg vs PBO:*** 44 patients (17%) vs 207 patients (78%); HR=0.10; (95% CI 0.07 to 0.14); p=<0.0001 Key secondary endpoint: Loss of IGA 0/1 response during maintenance period: • ***ABO 100 mg vs PBO:*** HR=0.35; (95% CI 0.29 to 0.42); p=<0.0001	Most frequently reported TEAEs (≥2% in any treatment group) • Nasopharyngitis ABO 100 (3.8%) vs ABO 200 (6.8%) vs PBO (1.9%) • Nausea ABO 100 (0.8%) vs ABO 200 (3.0%) vs PBO (0.4%) • Headache ABO 100 (0.4%) vs ABO 200 (2.6%) vs PBO (0.4%) • URTI ABO 100 (3.0%) vs ABO 200 (3.0%) vs PBO (2.2%) • Worsening AD ABO 100 (19.2%) vs ABO 200 (12.4%) vs PBO (31.1%)

Table 2. Randomized Placebo-Controlled Trials of Abrocitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
		PBO po daily (267) Duration: 40W	• ***ABO 200 mg vs PBO:*** HR=0.63; (95% CI 0.50 to 0.78); p=<0.0001	Discontinued treatment due to AEs ABO 100 (1.9%) vs ABO 200 (6.0%) vs PBO (1.5%) SAEs ABO 100 (1.5%) vs ABO 200 (4.9%) vs PBO (0.7%) Reported herpes viral infection: • Herpes zoster ABO 100 (0.8%) vs ABO 200 (2.6%) vs PBO (0.4%) • Herpes simplex ABO 100 (0.8%) vs ABO 200 (2.6%) vs PBO (0%)

Abbreviations: ABO, abrocitinib; AD, atopic dermatitis; AE, adverse event; BSA, body surface area; DUP, dupilumab; EASI, eczema area and severity index; IGA, Investigator Global Assessment; IBD, inflammatory bowel disease; ITT, intention-to-treat; LD, loading dose; NR, not reported; NS, not significant; PBO, placebo; PO, by mouth; PP-NRS, peak pruritus numerical rating scale; PSAAD, pruritus and symptoms assessment for atopic dermatitis; TEAE, treatment-emergent adverse event; SAE, serious adverse event; subQ, subcutaneous; URTI, upper respiratory tract infection; W, weeks

[a] Moderate-to-severe AD criteria: IGA score ≥3, EASI score ≥16, BSA affected ≥10%, and PP-NRS score ≥4

[b] SAEs are reported according to the data presented within the article. A lack of clarity exists between the incidence of SAEs reported within the article and the supplementary appendix (Table S19). The supplementary appendix reports 3 more SAEs in the abrocitinib 100 mg group and 4 more SAEs in the placebo group. Additionally, the incident of squamous-cell carcinoma within the abrocitinib 200 mg group is not mentioned in Table S19.

[c] Rescue treatment was abrocitinib 200 mg daily combined with medicated topical therapy

Italicized bold comparator names signifies statistically significant results

Comparative Evidence of Baricitinib vs. Placebo

For a text summary of the included trials listed in **Table 3**, please refer to page 57 to 58 the report. **Table 3** outlines the primary and selected key secondary endpoints from the identified placebo-controlled baricitinib trials, and pertinent safety information. Selected key secondary endpoints were chosen for inclusion in the table based on consistency with reported outcomes of other pivotal phase III trials, and clinical relevance.

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	***Population***	***Intervention***	***Efficacy Results (% of patients)***	***Safety Results***
Multicenter, randomized, double-blind, parallel-group, placebo-controlled (Simpson, 2020, **BREEZE-AD 1**)[30]	Patients ≥18 years of age diagnosed with moderate-to-severe AD[a] for ≥1 year, uncontrolled by TCS therapy[b]	**BAR 1 mg** po daily (N=127) **vs** **BAR 2 mg** po daily (N=123) **vs** **BAR 4 mg** (N=125) **vs** **PBO** (N=249) Duration: 16W Patients continued topical emollients	Primary endpoint: vIGA-AD Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 16W • ***BAR 1 mg vs PBO:*** 15 patients (12%) vs 12 patients (5%); OR= 2.7 (95% CI 1.2 to 6.0); p=<0.05 • ***BAR 2 mg vs PBO:*** 14 patients (11%) vs 12 patients (5%); OR= 2.6 (95% CI 1.2 to 5.8); p=<0.05 • ***BAR 4 mg vs PBO:*** 21 patients (17%) vs 12 patients (5%); OR= 4.1 (95% CI 1.9 to 8.7); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: 21 patients (17%) vs 25 patients (10%); OR= 1.8 (95% CI 1.0 to 3.4); p=0.065 • ***BAR 2 mg vs PBO:*** 21 patients (17%) vs 25 patients (10%); OR= 1.9 (95% CI 1.0 to 3.6); p=<0.05 • ***BAR 4 mg vs PBO:*** 28 patients (22%) vs 25 patients (10%); OR= 2.7 (95% CI 1.5 to 4.9); p=<0.01 Selected key secondary endpoint(s)	Most frequently reported TEAEs (> 2% in any treatment group) • Nasopharyngitis BAR 1 (17.3%) vs BAR 2 (9.8%) vs BAR 4 (9.6%) vs PBO (10.4%) • Diarrhea BAR 1 (7.1%) vs BAR 2 (0%) vs BAR 4 (3.2%) vs PBO (2.8%) • Headache BAR 1 (5.5%) vs BAR 2 (11.4%) vs BAR 4 (8.0%) vs PBO (6.4%) • URTI BAR 1 (0.8%) vs BAR 2 (2.4%) vs BAR 4 (3.2%) vs PBO (2.4%) • Increased plasma CPK BAR 1 (0.8%) vs BAR 2 (0.8%) vs BAR 4 (3.2%) vs PBO (0.8%) • UTI BAR 1 (0.8%) vs BAR 2 (1.6%) vs BAR 4 (3.2%) vs PBO (1.6%) Discontinued treatment due to AEs BAR 1 (1.6%) vs BAR 2 (0.8%) vs BAR 4 (0.8%) vs PBO (1.6%) SAEs

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline • ***BAR 1 mg vs PBO:*** OR= 2.0 (95% CI 1.1 to 3.9); p=<0.05 • ***BAR 2 mg vs PBO:*** OR= 2.5 (95% CI 1.3 to 4.7); p=<0.01 • ***BAR 4 mg vs PBO:*** OR= 3.7 (95% CI 2.0 to 6.9); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: OR= 1.5 (95% CI 0.9 to 2.5); p=0.104 • ***BAR 2 mg vs PBO:*** OR= 2.0 (95% CI 1.2 to 3.3); p=<0.01 • ***BAR 4 mg vs PBO:*** OR= 2.4 (95% CI 1.5 to 3.9); p=<0.001 EASI-90 Response: ≥90% improvement in EASI score at week 16 • BAR 1 mg vs PBO: OR= 1.7 (95% CI 0.7 to 4.1); p=0.210 • ***BAR 2 mg vs PBO:*** OR= 2.5 (95% CI 1.1 to 5.7); p=<0.05 • ***BAR 4 mg vs PBO:*** OR= 4.1 (95% CI 1.9 to 8.9); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: OR= 1.7 (95% CI 0.8 to 3.6); p=0.151 • ***BAR 2 mg vs PBO:*** OR= 2.3 (95% CI 1.1 to 4.7); p=<0.05 • ***BAR 4 mg vs PBO:*** OR= 3.7 (95% CI 1.9 to 7.3); p=<0.001 LSM change in EASI score: from baseline to week 16	BAR 1 (0.8%) vs BAR 2 (0%) vs BAR 4 (1.6%) vs PBO (2.4%) Deaths: none Reported infections: • Skin infection requiring antibiotic treatment BAR 1 (0.8%) vs BAR 2 (4.9%) vs BAR 4 (3.2%) vs PBO (4.4%) • Herpes simplex BAR 1 (5.5%) vs BAR 2 (3.3%) vs BAR 4 (7.2%) vs PBO (1.2%) • Herpes zoster One case[e]

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***BAR 1 mg vs PBO:*** adj. LSM difference = – 13.4 (95% CI – 24.8 to – 2.0); p=<0.05 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 17.1 (95% CI – 28.1 to – 6.1); p=<0.01 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 24.5 (95% CI – 34.8 to – 14.2); p=<0.001 **With TCS Rescue[c]:** • ***BAR 1 mg vs PBO:*** adj. LSM difference = – 13.1 (95% CI – 20.7 to – 5.5); p=<0.001 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 16.0 (95% CI – 23.7 to – 8.4); p=<0.001 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 21.6 (95% CI – 29.1 to – 14.0); p=<0.001 Itch NRS Response: (≥4 point improvement from baseline in score) at week 16 • BAR 1 mg vs PBO: OR= 1.6 (95% CI 0.7 to 3.6); p=0.246 • BAR 2 mg vs PBO: OR= 1.7 (95% CI 0.8 to 3.8); p=0.169 • ***BAR 4 mg vs PBO:*** OR= 3.6 (95% CI 1.8 to 7.2); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: OR= 1.6 (95% CI 0.9 to 2.8); p=0.099 • ***BAR 2 mg vs PBO:*** OR= 1.8 (95% CI 1.1 to 3.2); p=<0.05 • ***BAR 4 mg vs PBO:*** OR= 1.9 (95% CI 1.1 to 3.2); p=<0.05 LSM change in Item 2[d] of the ADSS: from baseline to week 16 • BAR 1 mg vs PBO: adj. LSM difference = – 0.4 (95% CI – 0.8 to 0.1); p=0.103	

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• BAR 2 mg vs PBO: adj. LSM difference = – 0.2 (95% CI – 0.7 to 0.2); p=0.352 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 0.6 (95% CI – 1.0 to – 0.2); p=<0.01 **With TCS Rescue[c]:** • ***BAR 1 mg vs PBO:*** adj. LSM difference = – 0.8 (95% CI – 1.3 to – 0.2); p=<0.01 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 0.7 (95% CI – 1.2 to – 0.1); p=<0.05 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 0.9 (95% CI – 1.5 to – 0.4); p=<0.001 LSM change in Skin Pain NRS: from baseline to week 16 • ***BAR 1 mg vs PBO:*** adj. LSM difference = – 1.1 (95% CI – 1.8 to – 0.3); p=≤ 0.01 • BAR 2 mg vs PBO: adj. LSM difference = – 0.7 (95% CI – 1.5 to 0.0); p=0.051 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 1.1 (95% CI – 1.8 to – 0.4); p=<0.01 **With TCS Rescue[c]:** • ***BAR 1 mg vs PBO:*** adj. LSM difference = – 0.5 (95% CI – 1.0 to 0.0); p=<0.05 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 0.6 (95% CI – 1.1 to – 0.1); p=<0.05 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 0.8 (95% CI – 1.3 to – 0.3); p=≤ 0.001	
Multicenter, randomized, double-blind, parallel-group, placebo-controlled (Simpson, 2020, **BREEZE-AD 2**)[30]	Patients ≥18 years of age diagnosed with moderate-to-severe	**BAR 1 mg** po daily (N=125) **vs** **BAR 2 mg** po daily (N=123) **vs**	Primary endpoint: vIGA-AD Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 16W	Most frequently reported TEAEs (> 2% in any treatment group) • Nasopharyngitis BAR 1 (10.5%) vs BAR 2 (13.0%) vs BAR 4 (8.1%) vs PBO (12.3%) • Headache

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
	AD[a] for ≥1 year, uncontrolled by TCS therapy[b]	**BAR 4 mg** (N=123) **vs** **PBO** (N=244) Duration: 16W Patients continued topical emollients	• BAR 1 mg vs PBO: 11 patients (9%) vs 11 patients (5%); OR= 2.1 (95% CI 0.9 to 5.0); p=0.108 • ***BAR 2 mg vs PBO:*** 13 patients (11%) vs 11 patients (5%); OR= 2.6 (95% CI 1.1 to 5.9); p=<0.05 • ***BAR 4 mg vs PBO:*** 17 patients (14%) vs 11 patients (5%); OR= 3.6 (95% CI 1.6 to 8.1); p=<0.01 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: 15 patients (12%) vs 27 patients (11%); OR= 1.1 (95% CI 0.6 to 2.3); p=0.710 • ***BAR 2 mg vs PBO:*** 24 patients (20%) vs 27 patients (11%); OR= 2.1 (95% CI 1.1 to 3.8); p=<0.05 • ***BAR 4 mg vs PBO:*** 27patients (22%) vs 27 patients (11%); OR= 2.5 (95% CI 1.4 to 4.6); p=<0.01 Selected key secondary endpoint(s) EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline • ***BAR 1 mg vs PBO:*** OR= 2.4 (95% CI 1.1 to 4.9); p=<0.05 • ***BAR 2 mg vs PBO:*** OR= 3.5 (95% CI 1.7 to 7.0); p=<0.001 • ***BAR 4 mg vs PBO:*** OR= 4.4 (95% CI 2.2 to 8.8); p=<0.001 **With TCS Rescue[c]:** • ***BAR 1 mg vs PBO:*** OR= 1.7 (95% CI 1.0 to 2.9); p=<0.05	BAR 1 (4.8%) vs BAR 2 (7.3%) vs BAR 4 (8.9%) vs PBO (2.0%) • URTI BAR 1 (4.8%) vs BAR 2 (4.1%) vs BAR 4 (3.3%) vs PBO (2.0%) • Increased plasma CPK BAR 1 (3.2%) vs BAR 2 (0.8%) vs BAR 4 (5.7%) vs PBO (0.4%) • Diarrhea BAR 1 (1.6%) vs BAR 2 (2.4%) vs BAR 4 (2.4%) vs PBO (1.6%) • UTI BAR 1 (0%) vs BAR 2 (0%) vs BAR 4 (1.6%) vs PBO (1.2%) Discontinued treatment due to AEs BAR 1 (5.6%) vs BAR 2 (2.4%) vs BAR 4 (1.6%) vs PBO (0.8%) SAEs BAR 1 (7.3%) vs BAR 2 (2.4%) vs BAR 4 (0.8%) vs PBO (3.7%) Deaths: none Reported infections: • Skin infection requiring antibiotic treatment BAR 1 (4.8%) vs BAR 2 (7.3%) vs BAR 4 (4.9%) vs PBO (7.8%) • Herpes simplex BAR 1 (4.8%) vs BAR 2 (5.7%) vs BAR 4 (4.1%) vs PBO (4.5%) • Herpes zoster Two cases[e]

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***BAR 2 mg vs PBO:*** OR= 2.6 (95% CI 1.6 to 4.3); p=<0.001 • ***BAR 4 mg vs PBO:*** OR= 2.5 (95% CI 1.5 to 4.1); p=<0.001 EASI-90 Response: ≥90% improvement in EASI score at week 16 • BAR 1 mg vs PBO: OR= 2.8 (95% CI 1.0 to 8.0); p=0.053 • ***BAR 2 mg vs PBO:*** OR= 3.9 (95% CI 1.4 to 10.4); p=<0.01 • ***BAR 4 mg vs PBO:*** OR= 6.2 (95% CI 2.4 to 15.9); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: OR= 1.6 (95% CI 0.7 to 3.4); p=0.256 • ***BAR 2 mg vs PBO:*** OR= 3.2 (95% CI 1.6 to 6.4); p=<0.001 • ***BAR 4 mg vs PBO:*** OR= 4.2 (95% CI 2.2 to 8.2); p=<0.001 LSM change in EASI score: from baseline to week 16 • BAR 1 mg vs PBO: adj. LSM difference = – 12.8 (95% CI – 26.2 to 0.7); p=0.06 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 25.9 (95% CI – 38.8 to – 13.0); p=<0.001 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 26.0 (95% CI – 38.3 to – 13.7); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: adj. LSM difference = – 6.8 (95% CI – 15.2 to 1.6); p=0.11 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 11.3 (95% CI – 19.7 to – 3.0); p=<0.01	

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***BAR 4 mg vs PBO:*** adj. LSM difference = – 13.4 (95% CI – 21.7 to – 5.2); p=≤0.001 Itch NRS Response: (≥4 point improvement from baseline in score) at week 16 • BAR 1 mg vs PBO: OR= 1.4 (95% CI 0.5 to 3.9); p=0.505 • ***BAR 2 mg vs PBO:*** OR= 3.6 (95% CI 1.6 to 8.3); p=<0.01 • ***BAR 4 mg vs PBO:*** OR= 4.9 (95% CI 2.2 to 10.9); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: OR= 0.8 (95% CI 0.4 to 1.5); p=0.477 • ***BAR 2 mg vs PBO:*** OR= 2.0 (95% CI 1.2 to 3.3); p=<0.05 • ***BAR 4 mg vs PBO:*** OR= 1.9 (95% CI 1.1 to 3.2); p=<0.05 LSM change in Item 2[d] of the ADSS: from baseline to week 16 • BAR 1 mg vs PBO: adj. LSM difference = – 0.3 (95% CI – 0.6 to 0.1); p=0.123 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 0.5 (95% CI – 0.9 to – 0.2); p=<0.01 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 0.6 (95% CI – 1.0 to – 0.3); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: adj. LSM difference = – 0.3 (95% CI – 0.6 to 0.0); p=0.074 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 0.4 (95% CI – 0.7 to – 0.1); p=<0.05 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 0.6 (95% CI – 0.8 to – 0.3); p=<0.001	

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			LSM change in Skin Pain NRS: from baseline to week 16 • BAR 1 mg vs PBO: adj. LSM difference = – 0.2 (95% CI – 1.1 to 0.6); p= 0.58 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 1.8 (95% CI – 2.5 to – 1.0); p=<0.001 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 1.6 (95% CI – 2.4 to – 0.9); p=<0.001 **With TCS Rescue[c]:** • BAR 1 mg vs PBO: adj. LSM difference = 0.0 (95% CI – 0.5 to 0.5); p=0.98 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 0.9 (95% CI – 1.4 to – 0.4); p=<0.001 • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 0.7 (95% CI – 1.2 to – 0.2); p=≤ 0.01	
Multicenter, randomized, double-blind, parallel-group, placebo-controlled (Simpson, 2021, **BREEZE-AD 5**)[31]	Patients ≥18 years of age diagnosed with moderate-to-severe AD[a] for ≥1 year, uncontrolled by TCS therapy[b]	**BAR 1 mg** po daily (N=147) **vs** **BAR 2 mg** po daily (N=146) **vs** **PBO** (N=147) Duration: 16W	Primary endpoint: EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline in ITT population • BAR 1 mg vs PBO: 19 patients (13%) vs 12 patients (8%); adj. difference = NR; (95% CI NR); p= NS • ***BAR 2 mg vs PBO:*** 44 patients (30%) vs 12 patients (8%); adj. difference = NR; (95% CI NR); p=≤ 0.001 Selected key secondary endpoint(s) vIGA-AD Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 16 weeks in ITT population • BAR 1 mg vs PBO: 13% vs 5%; adj. difference = NR; (95% CI NR); nominal p=≤ 0.05	Most frequently reported TEAEs (≥ 3% in any treatment group) • URTI BAR 1 (6.1%) vs BAR 2 (7.6%) vs PBO (6.2%) • Nasopharyngitis BAR 1 (2.0%) vs BAR 2 (4.8%) vs PBO (7.5%) • Diarrhea BAR 1 (2.0%) vs BAR 2 (4.1%) vs PBO (1.4%) • Nausea BAR 1 (2.0%) vs BAR 2 (3.4%) vs PBO (2.1%) • UTI BAR 1 (0.7%) vs BAR 2 (3.4%) vs PBO (2.1%) • Headache BAR 1 (3.4%) vs BAR 2 (2.1%) vs PBO (1.4%) Discontinued treatment due to AEs BAR 1 (2.7%) vs BAR 2 (2.8%) vs PBO (2.7%) SAEs

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***BAR 2 mg vs PBO:*** 24% vs 5%; adj. difference = NR; (95% CI NR); p=≤ 0.001 Itch NRS Response: (≥4 point improvement from baseline in score) at week 16 in ITT population • BAR 1 mg vs PBO: 16% vs 6%; adj. difference = NR; (95% CI NR); p= NS • ***BAR 2 mg vs PBO:*** 25% vs 6%; adj. difference = NR; (95% CI NR); p=≤ 0.001 EASI-90 Response: ≥90% improvement in EASI score at week 16 • BAR 1 mg vs PBO: 8% vs 3%; adj. difference = NR; (95% CI NR); p= NS • ***BAR 2 mg vs PBO:*** 21% vs 3%; adj. difference = NR; (95% CI NR); p=≤ 0.001 LSM change in EASI score: from baseline to week 16 • BAR 1 mg vs PBO: adj. LSM difference = – 46.6 (95% CI – 26.5 to 1.4); p= NS • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 54.4 (95% CI – 33.9 to – 6.8); p=≤ 0.01 LSM change in Item 2[d] of the ADSS: from baseline to week 16 • BAR 1 mg vs PBO: adj. LSM difference = – 0.62 (95% CI – 0.75 to 0.32); p= NS • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 0.99 (95% CI – 1.12 to – 0.06); p=≤ 0.05 LSM change in Skin Pain NRS: from baseline to week 16 • ***BAR 1 mg vs PBO:*** adj. LSM difference = – 32.93 (95% CI – 30.34 to – 3.81); p=≤ 0.05 • ***BAR 2 mg vs PBO:*** adj. LSM difference = – 36.59 (95% CI – 33.84 to – 7.77); p=≤ 0.01	BAR 1 (0.7%) vs BAR 2 (1.4%) vs PBO (2.1%) Deaths: none Reported infections: • Serious infection BAR 1 (0%) vs BAR 2 (0.7%) vs PBO (0.7%) • Herpes zoster BAR 1 (0.7%) vs BAR 2 (0%) vs PBO (0%) • Herpes simplex BAR 1 (2.0%) vs BAR 2 (1.4%) vs PBO (0.7%)

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
Multicenter, randomized, double-blind, parallel-group, placebo-controlled (Reich, 2020, **BREEZE-AD 7**)[32]	Patients ≥18 years of age diagnosed with moderate-to-severe AD[a] for ≥1 year, uncontrolled by TCS therapy[b]	**BAR 2 mg** po daily **+TCS** (N=109) **vs** **BAR 4 mg** po daily **+TCS** (N=111) **vs** **PBO +TCS** (N=109) Duration: 16W Patients continued topical emollients and low-to-moderate TCSs	Primary endpoint: vIGA-AD Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline measured at 16 weeks in the ITT population[f] • BAR 2 mg vs PBO: 26 patients (24%) vs 16 patients (15%); OR= 1.9 (95% CI 0.9 to 3.9); p=0.08 • ***BAR 4 mg vs PBO:*** 34 patients (31%) vs 16 patients (15%); OR= 2.8 (95% CI 1.4 to 5.6); p=<0.01 Selected key secondary endpoint(s) EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline in the ITT population[f] • BAR 2 mg vs PBO: OR= 2.6 (95% CI 1.4 to 4.8); p=NA[h] • ***BAR 4 mg vs PBO:*** OR= 3.3 (95% CI 1.8 to 6.0); p=<0.001 LSM change in EASI score: from baseline to week 16 in the ITT population[f] • BAR 2 mg vs PBO: adj. LSM difference = – 13.1 (95% CI – 23.4 to – 2.7); p= NA[g] • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 22.1 (95% CI – 32.5 to – 11.8); p=< 0.001 Itch NRS Response: (≥4 point improvement from baseline in score) at week 16 in the ITT population[f] • BAR 2 mg vs PBO: OR= 2.9 (95% CI 1.5 to 5.6); p=NA[g] • ***BAR 4 mg vs PBO:*** OR= 3.8 (95% CI 2.0 to 7.5); p=<0.001 LSM change in Item 2[d] of the ADSS: from baseline to week 16 in the ITT population[f]	Most frequently reported TEAEs (≥ 2% in any treatment group) • Nasopharyngitis BAR 2 (11%) vs BAR 4 (15%) vs PBO (12%) • URTI BAR 2 (7%) vs BAR 4 (3%) vs PBO (2%) • Folliculitis BAR 2 (4%) vs BAR 4 (5%) vs PBO (0%) • Acne BAR 2 (1%) vs BAR 4 (4%) vs PBO (1%) • Diarrhea BAR 2 (1%) vs BAR 4 (3%) vs PBO (1%) • Oropharyngeal pain BAR 2 (2%) vs BAR 4 (2%) vs PBO (3%) • Increased plasma CPK BAR 2 (3%) vs BAR 4 (0%) vs PBO (0%) Discontinued treatment due to AEs BAR 2 (0%) vs BAR 4 (5%) vs PBO (1%) SAEs BAR 2 (2%) vs BAR 4 (4%) vs PBO (4%) Deaths: none Reported infections: • Serious infection BAR 2 (0%) vs BAR 4 (0%) vs PBO (2%) • Herpes zoster BAR 2 (2%) vs BAR 4 (0%) vs PBO (1%) • Herpes simplex BAR 2 (1%) vs BAR 4 (3%) vs PBO (3%) Selected other AEs of interest: • Pulmonary embolism BAR 2 (0%) vs BAR 4 (1%) vs PBO (0%)

Table 3. Randomized Placebo-Controlled Trials of Baricitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• BAR 2 mg vs PBO: adj. LSM difference = – 0.8 (95% CI – 1.2 to – 0.4); p= NA[g] • BAR 4 mg vs PBO: adj. LSM difference = – 0.9 (95% CI – 1.3 to – 0.5); p= NS EASI-90 Response: ≥90% improvement in EASI score at week 16 in the ITT population[f] • BAR 2 mg vs PBO: OR= 1.2 (95% CI 0.6 to 2.6); p=NA[g] • BAR 4 mg vs PBO: OR= 2.1 (95% CI 1.0 to 4.2); p= NS LSM change in Skin Pain NRS: from baseline to week 16 in the ITT population[f] • BAR 2 mg vs PBO: adj. LSM difference = – 1.2 (95% CI – 1.8 to – 0.5); p= NA[g] • ***BAR 4 mg vs PBO:*** adj. LSM difference = – 1.7 (95% CI – 2.3 to – 1.0); p=<0.001	

Abbreviations: AD, atopic dermatitis; ADSS, Atopic Dermatitis Sleep Scale; Adj, adjusted; BAR, baricitinib; CI, confidence interval; CPK, creatine phosphokinase; EASI, Eczema Area and Severity Index; ITT, intention-to-treat; LSM, least squares mean; NR, not reported; NRS, numeric rating scale; NS, not significant; OR, odds ratio; PBO, placebo; SAEs, serious adverse events; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection; vIGA-AD, validated Investigator's Global Assessment for Atopic Dermatitis; W, weeks

[a] Diagnosis per American Academy of Dermatology criteria. Moderate-to-severe AD criteria: vIGA-AD score ≥3, EASI score ≥16, and BSA affected ≥10%
[b] Defined as failure to achieve mild disease or better after use of at least a medium potency TCS for ≥ 4 weeks, or for the maximum duration recommended by the prescribing information (whichever is shorter). Surrogates for inadequate response to topical therapies include lack of response to systemic immunosuppressant therapies within 6 months of study screening, or "clinically significant adverse reactions to TCS"
[c] Rescue therapy consisted of TCS use at any potency or systemic therapy
[d] Item 2 of the Atopic Dermatitis Sleep Scale assess the number of night-time awakenings due to itch
[e] Herpes zoster events are not yet unblinded to the investigators
[f] Results were analyzed according to a prespecified statistical analysis plan with a graphical testing procedure; results are shown for the US and Japan graphical testing procedure
[g] Secondary endpoint statistical analysis for baricitinib 2 mg was not performed because it failed to achieve statistical significance in the primary endpoint
Italicized bold comparator names signifies statistically significant results

Comparative Evidence of Upadacitinib vs. Placebo

One additional SR, **Nusbaum et al (2021)**, included 2 pivotal phase III placebo controlled RCTs (Measure Up 1 and Measure Up 2), and a phase II trial using the same doses of upadacitinib 15 mg or 30 mg daily.[42,82] Patients were adolescents (12 to 17 years of age) and adults diagnosed with moderate-to-severe AD that previously failed topical therapies (TCIs or TCS) or recently received systemic therapy.[42,82] Upadacitinib improved EASI and patient reported itch response in a dose dependent manner compared to placebo.[42] The prevalence of patients that achieved a 75% reduction in EASI at 16 weeks receiving 30 mg daily was 0.76 (95% CI 0.70 to 0.82) and among patients receiving 15 mg daily was 0.64 (95% CI 0.55 to 0.74).[42] In addition, the prevalence of patients achieving at least a 4-point reduction on the PP-NRS at 16 weeks among patients receiving 30 mg daily was 0.59 (95% CI 0.55 to 0.63) and among patients receiving 15 mg daily was 0.48 (0.38 to 0.57).[42]

Three short-term (16 week) phase III, placebo-controlled, randomized, multicenter, double-blind trials (Measure Up 1, Measure Up 2, and Ad Up) demonstrated superiority of upadacitinib (15 mg or 30 mg daily) to placebo in reducing physical signs of AD.[81,82] Enrolled patients were between 12 and 75 years old (mean age of 32 to 35 years), had moderate-to-severe chronic AD for at least 3 years, and either could not tolerate or failed topical treatments (TCIs or TCS) or recently used other systemic treatment.[81,82] Primary efficacy results showed a dose-dependent magnitude of benefit versus placebo (greatest improvements with upadacitinib 30 mg),[81,82] and similar benefit as monotherapy (Measure Up 1 or 2 trials)[82] or when combined with TCS ± TCI (Ad Up trial).[81] Efficacy for physical signs of AD and pruritis relative to placebo emerged within days to 1-2 weeks of treatment, with a similar proportion of patients responding by 4 weeks compared to final 16 week endpoint on primary efficacy measures.[81,82] As monotherapy, upadacitinib also significantly improved patient-oriented eczema symptoms, measures of patient QoL, and other comorbid symptoms (sleep, anxiety, depression) compared to placebo.[82] Few adolescents were included in the studies (approximately 12 to 15% of participants),[81,82] but according to an ICER review, results seem similar to the adult population.[2]

The short-term safety profile for upadacitinib compared to placebo was generally favorable; results were similar as monotherapy or when combined with TCS ± TCI. In each trial, a similar proportion of patients in each group discontinued treatment due to adverse effects (between 1-4% across the studies). Serious adverse events were relatively rare (1-3%) and occurred at a similar frequency as placebo (3%). No deaths occurred. Similar to previous studies, the most common adverse events (incidence ≥ 5% in any treatment group) included: acne (mostly mild to moderate severity), nasopharyngitis, headache, URTI, increased plasma/blood creatine phosphokinase (CPK), and worsening of AD disease (most frequent in the placebo group).[81,82] Oral herpes commonly occurred in the topical combination trial.[81] No long-term efficacy and safety results were identified.

Table 4 outlines the primary and selected key secondary endpoints, and pertinent safety information from the identified placebo-controlled upadacitinib trials.

Table 4. Randomized Placebo-Controlled Trials of Upadacitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
Multicenter, randomized, double-blind, placebo controlled (Guttman-Yassky, 2021, **Measure Up 1**)[82]	Adolescents (12 to 17 with BW ≥ 40 kg) and adults (18 to 75) with moderate-to-severe AD[a] ≥ 3 years, uncontrolled by TCI or TCS therapies or previously receiving systemic AD treatment within prior 6 months	**UPA 15 mg** po daily (N=281) **vs** **UPA 30 mg** po daily (N=285) **vs** **PBO** po daily (N=281) Duration: 16W Patients continued topical emollients	Co-primary endpoints: vIGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline at 16W in ITT population • ***UPA 15 mg vs PBO:*** 135 patients (48%) vs 24 patients (8%); adj. difference = 39.8% (95% CI 33.2 to 46.4%); p<0.0001 • ***UPA 30 mg vs PBO:*** 177 patients (62%) vs 24 patients (8%); treatment difference = 53.6%; (95% CI 47.2% to 60.0%); p<0.0001 EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline in ITT population • ***UPA 15 mg vs PBO:*** 196 patients (70%) vs 46 patients (16%); adj. difference = 53.3% (95% CI 46.4 to 60.2%); p<0.0001 • ***UPA 30 mg vs PBO:*** 227 patients (80%) vs 46 patients (16%); adj. difference = 63.4% (95% CI 57.1% to 69.8%); p<0.0001 Selected key secondary endpoint(s) WP-NRS Response: (≥4 point improvement from baseline in score) at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 40.5% (95% CI 33.5 to 47.5%); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. difference = 48.2% (95% CI 41.3% to 55.0%); p<0.0001 EASI-90 Response: ≥90% improvement in EASI score at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 45.1% (95% CI 38.6 to 51.7%); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. difference = 57.8% (95% CI 51.5 to 64.1%); p<0.0001	Most frequently reported TEAEs (≥5% in any treatment group) • Acne UPA 15 (7%) vs UPA 30 (17%) vs PBO (2%) • Nasopharyngitis UPA 15 (8%) vs UPA 30 (12%) vs PBO (6%) • Headache UPA 15 (5%) vs UPA 30 (7%) vs PBO (4%) • URTI UPA 15 (9%) vs UPA 30 (13%) vs PBO (7%) • Increased plasma CPK UPA 15 (6%) vs UPA 30 (6%) vs PBO (3%) • AD worsening UPA 15 (3%) vs UPA 30 (1%) vs PBO (9%) Discontinued treatment due to AEs UPA 15 (1%) vs UPA 30 (4%) vs PBO (4%) SAEs UPA 15 (2%) vs UPA 30 (3%) vs PBO (3%) Deaths: none Reported infections: • Serious infection UPA 15 (1%) vs UPA 30 (1%) vs PBO (0%) • Eczema herpecitum UPA 15 (0%) vs UPA 30 (1%) vs PBO (1%) • Herpes zoster UPA 15 (2%) vs UPA 30 (2%) vs PBO (0%) Selected other AEs of interest: • Non-NMSC malignancy UPA 15 (0%) vs UPA 30 (1%) vs PBO (0%) • Neutropenia UPA 15 (1%) vs UPA 30 (5%) vs PBO (1%)

Table 4. Randomized Placebo-Controlled Trials of Upadacitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			EASI-100 Response: 100% improvement in EASI score at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 15.0% (95% CI 10.4 to 19.6%); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. difference = 25.3% (95% CI 20.0 to 30.6%); p<0.0001 LSM change in EASI score: from baseline to week 16 • ***UPA 15 mg vs PBO:*** adj. LSM difference = – 39.5 (95% CI – 44.9 to – 34.2); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. LSM difference = – 47.0 (95% CI – 52.4 to – 41.7); p<0.0001 LSM change in (weekly average) WP-NRS score: from baseline to week 16 • ***UPA 15 mg vs PBO:*** adj. LSM difference = – 36.7 (95% CI – 49.7 to – 23.8); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. LSM difference = – 46.0 (95% CI – 58.8 to – 33.1); p<0.0001	
Multicenter, randomized, double-blind, placebo controlled (Guttman-Yassky, 2021, **Measure Up 2**)[82]	Adolescents (12 to 17 with BW ≥ 40 kg) and adults (18 to 75) with moderate-to-severe AD[a] ≥ 3 years, uncontrolled by TCI or TCS therapies or previously	**UPA 15 mg** po daily (N=276) **vs** **UPA 30 mg** po daily (N=282) **vs** **PBO** po daily (N=278) Duration: 16W Patients continued topical emollients	Co-primary endpoints: vIGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline at 16W in ITT population • ***UPA 15 mg vs PBO:*** 107 patients (39%) vs 13 patients (5%); adj. difference = 34.0% (95% CI 27.8 to 40.2%); p<0.0001 • ***UPA 30 mg vs PBO:*** *147* patients (52%) vs 13 patients (5%); adj. difference = 47.4%; (95% CI 41.0 to 53.7%); p<0.0001 EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline in ITT population • ***UPA 15 mg vs PBO:*** 166 patients (60%) vs 37 patients (13%); adj. difference = 46.9% (95% CI 39.9 to 53.9%); p<0.0001	Most frequently reported TEAEs (≥5% in any treatment group) • Acne UPA 15 (13%) vs UPA 30 (15%) vs PBO (2%) • Nasopharyngitis UPA 15 (6%) vs UPA 30 (6%) vs PBO (5%) • Headache UPA 15 (7%) vs UPA 30 (7%) vs PBO (4%) • URTI UPA 15 (7%) vs UPA 30 (6%) vs PBO (4%) • Increased plasma CPK UPA 15 (3%) vs UPA 30 (4%) vs PBO (2%) • AD worsening UPA 15 (3%) vs UPA 30 (1%) vs PBO (9%) Discontinued treatment due to AEs

Table 4. Randomized Placebo-Controlled Trials of Upadacitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
	receiving systemic AD treatment within prior 6 months		• ***UPA 30 mg vs PBO:*** 206 patients (73%) vs 37 patients (13%); adj. difference = 59.6% (95% CI 53.1% to 66.2%); p<0.0001 Selected key secondary endpoint(s) WP-NRS Response: (≥4 point improvement from baseline in score) at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 32.6% (95% CI 25.8 to 39.4%); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. difference = 50.4% (95% CI 43.8 to 57.1%); p<0.0001 EASI-90 Response: ≥90% improvement in EASI score at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 36.9% (95% CI 30.6 to 43.3%); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. difference = 53.1% (95% CI 46.7 to 59.4%); p<0.0001 EASI-100 Response: 100% improvement in EASI score at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 13.4% (95% CI 9.2 to 17.6%); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. difference = 18.1% (95% CI 13.5 to 22.7%); p<0.0001 LSM change in EASI score: from baseline to week 16 • ***UPA 15 mg vs PBO:*** adj. LSM difference = – 39.6 (95% CI – 45.8 to – 33.5); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. LSM difference = – 50.5 (95% CI – 56.3 to – 44.0); p<0.0001 LSM change in (weekly average) WP-NRS score: from baseline to week 16 • ***UPA 15 mg vs PBO:*** adj. LSM difference = – 34.2 (95% CI – 40.8 to – 27.5); p<0.0001	UPA 15 (4%) vs UPA 30 (3%) vs PBO (4%) SAEs UPA 15 (2%) vs UPA 30 (3%) vs PBO (3%) Deaths: none Reported infections: • Serious infection UPA 15 (<1%) vs UPA 30 (1%) vs PBO (1%) • Eczema herpecitum UPA 15 (1%) vs UPA 30 (0%) vs PBO (0%) • Herpes zoster UPA 15 (2%) vs UPA 30 (1%) vs PBO (1%) Selected other AEs of interest: • Non-NMSC malignancy UPA 15 (0%) vs UPA 30 (<1%) vs PBO (0%) • Neutropenia UPA 15 (1%) vs UPA 30 (2%) vs PBO (<1%)

Table 4. Randomized Placebo-Controlled Trials of Upadacitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***UPA 30 mg vs PBO:*** adj. LSM difference = – 49.4 (95% CI – 56.1 to – 42.8); p<0.0001	
Multicenter, randomized, double-blind, placebo controlled (Reich, 2021, **AD Up**)[81]	Adolescents (12 to 17 with BW ≥ 40 kg) and adults (18 to 75) with moderate-to-severe AD[a] for ≥3 years, uncontrolled by TCI or TCS therapies or previously receiving systemic AD treatment within prior 6 months	*Combination treatment with TCS ± TCI per a standardized step-down protocol:* **UPA 15 mg** po daily + TCS (N=300) **vs** **UPA 30 mg** po daily + TCS (N=297) **vs** **PBO** po daily + TCS (N=304) Duration: 16W Patients continued topical emollients	Co-primary endpoints: vIGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline at 16W in ITT population • ***UPA 15 mg vs PBO:*** 119 patients (39.6%) vs 33 patients (10.9%); adj. difference = 28.5% (95% CI 22.1 to 34.9%); p<0.0001 • ***UPA 30 mg vs PBO:*** 174 patients (58.6%) vs 33 patients (10.9%); treatment difference = 47.6%; (95% CI 41.1 to 54.0%); p<0.0001 EASI-75 Response: ≥75% improvement in EASI score at week 16 from baseline in ITT population • ***UPA 15 mg vs PBO:*** 194 patients (64.6%) vs 80 patients (26.4%); adj. difference = 38.1% (95% CI 30.8 to 45.4%); p<0.0001 • ***UPA 30 mg vs PBO:*** 229 patients (77.1%) vs 80 patients (26.4%); adj. difference = 50.6% (95% CI 43.8 to 57.4%); p<0.0001 Selected key secondary endpoint(s) WP-NRS Response: (≥4 point improvement from baseline in score) at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 36.8% (95% CI 29.7 to 43.8%); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. difference = 48.8% (95% CI 41.9 to 55.7%); p<0.0001 EASI-90 Response: ≥90% improvement in EASI score at week 16 • ***UPA 15 mg vs PBO:*** adj. difference = 29.5% (95% CI 22.8 to 36.3%); p<0.0001	Most frequently reported TEAEs (≥5% in any treatment group) • Acne UPA 15 (10%) vs UPA 30 (14%) vs PBO (2%) • Nasopharyngitis UPA 15 (12%) vs UPA 30 (13%) vs PBO (11%) • Headache UPA 15 (5%) vs UPA 30 (5%) vs PBO (5%) • URTI UPA 15 (7%) vs UPA 30 (8%) vs PBO (7%) • Increased blood CPK UPA 15 (4%) vs UPA 30 (6%) vs PBO (2%) • Oral herpes UPA 15 (3%) vs UPA 30 (8%) vs PBO (2%) • AD worsening UPA 15 (4%) vs UPA 30 (1%) vs PBO (7%) Discontinued treatment due to AEs: UPA 15 (1%) vs UPD 30 (1%) vs PBO (2%) SAEs UPA 15 (2%) vs UPA 30 (1%) vs PBO (3%) Deaths: none Reported infections: • Serious infection UPA 15 (1%) vs UPA 30 (0%) vs PBO (1%) • Eczema herpecitum UPA 15 (1%) vs UPA 30 (1%) vs PBO (0%) • Herpes zoster UPA 15 (1%) vs UPA 30 (2%) vs PBO (1%) Selected other AEs of interest: • Non-NMSC malignancy

Table 4. Randomized Placebo-Controlled Trials of Upadacitinib

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
			• ***UPA 30 mg vs PBO:*** adj. difference = 49.9% (95% CI 43.3 to 56.4%); p<0.0001 EASI-100 Response: 100% improvement in EASI score at week 16 • ***UPA 15 mg vs PBO:*** not a secondary end pt • ***UPA 30 mg vs PBO:*** adj. difference = 21.2% (95% CI 16.3 to 26.1%); p<0.0001 LSM change in EASI score: from baseline to week 16 • ***UPA 15 mg vs PBO:*** adj. LSM difference = – 32.1 (95% CI – 26.9 to – 37.4); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. LSM difference = – 41.5 (95% CI – 36.2 to – 46.7); p<0.0001 LSM change in (weekly average) WP-NRS score: from baseline to week 16 • ***UPA 15 mg vs PBO:*** adj. LSM difference = – 33.1 (95% CI – 24.2 to – 41.7); p<0.0001 • ***UPA 30 mg vs PBO:*** adj. LSM difference = – 41.8 (95% CI – 33.1 to – 50.5); p<0.0001	UPA 15 (0%) vs UPA 30 (<1%) vs PBO (0%) • Neutropenia UPA 15 (1%) vs UPA 30 (1%) vs PBO (0%)

Abbreviations: AD, atopic dermatitis; Adj, adjusted; BW, bodyweight; CI, confidence interval; CPK, creatine phosphokinase; EASI, Eczema Area and Severity Index; ITT, intention-to-treat; LSM, least squares mean; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; pt, point; SAEs, serious adverse events; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; TEE, thromboembolic event; UPA, upadacitinib; URTI, upper respiratory tract infection; vIGA-AD, validated Investigator's Global Assessment for Atopic Dermatitis; W, weeks; WP-NRS, Worst Pruritis Numerical Rating Scale.

[a] Diagnosis of AD per the Hanifin and Rajka criteria. Must be "candidates for systemic therapy" based on lack of sufficient response to or intolerance/inappropriateness for topical treatments. Moderate-to-severe AD criteria: ≥ 10% BSA with AD *and* EASI score ≥ 16 *and* vIGA-AD ≥ 3 *and* WP-NRS ≥ 4.

Italicized bold comparator names signifies statistically significant results

Comparative Evidence of Tralokinumab vs. Placebo

Two SRs conducted by **Atlas et al (2021)** and **Nusbaum et al (2021)** containing pooled analyses of phase III, randomized, placebo-controlled trials (ECZTRA 1, ECZTRA 2, and ECZTRA 3) were identified.[2,42] Trial patients were adults (18 years of age and older) diagnosed with moderate-to-severe AD for at least 1 year that either, failed to have an adequate response to or had an intolerance to topical therapies.[83,84] The use of as needed TCS therapy was permitted in ECZTRA 3.[84] Tralokinumab administered at 300 mg every 2 weeks improved AD symptoms and the QoL for patients by reducing itch intensity and positively impacting DLQI scores.[42] A third SR by ICER, also found that tralokinumab significantly improved AD symptoms compared to placebo, based on IGA score improvement (reaching a score of 0 or 1) and EASI-75 response.[2] Details from these placebo-controlled tralokinumab RCTs are included below.

In two, double-blinded RCTs (ECZTRA 1 and ECZTRA 2), patients were randomized to tralokinumab 300 mg (after a 600 mg loading dose) or placebo every 2 weeks for 16 weeks.[83] After the initial 16 week treatment period, patients who responded to treatment (ie, achieved an IGA score of 0 or 1 or EASI-75) were rerandomized to tralokinumab 300 mg every 2 weeks or every 4 weeks, or placebo for an additional 36 weeks.[83] Patients were adults (18 years of age and older) diagnosed with moderate-to-severe AD for at least 1 year with a prior failure or intolerance to topical therapies.[83] Tralokinumab was superior to placebo at improving IGA and EASI-75 response among adults during the initial 16 week treatment period. Additionally, tralokinumab improved QoL outcomes such as DLQI compared to placebo.[83] Of patients that achieved an IGA score of 0 or 1 or EASI-75 response at week 16 with tralokinumab administered every 2 weeks, approximately 50% maintained that response when receiving the same administration frequency at week 52 without the need for rescue medication.[83] Additionally, "39-51% of patients maintained that response when receiving tralokinumab every 4 weeks."[83] A sustained IGA and EASI response was observed at week 52 in patients that received tralokinumab every 2 weeks during the initial 16 week period that were rerandomized to placebo.[83] Across both trials, the most commonly reported adverse events among both treatment groups were worsening AD, URTI, and conjunctivitis.[83] Antidrug antibodies were detected among 3 patients in ECZTRA 1 and 8 patients in ECZTRA 2, but were evaluated to have no impact on the efficacy and safety of tralokinumab.[83]

A third RCT, ECZTRA 3, initially randomized patients to tralokinumab (300 mg subcutaneously after a 600 mg loading dose) or placebo, both in combination with TCS therapy as needed, every 2 weeks for 16 weeks: responders (defined as an IGA score of 0 or 1 or EASI-75 at 16 weeks) were rerandomized to tralokinumab 300 mg at two different frequencies, either every 2 weeks or every 4 weeks, for 16 additional weeks.[84] Included patients were adults (18 years of age and older) diagnosed with moderate-to-severe AD for at least 1 year that either had an inadequate response or intolerance to topical therapies.[84] Treatment with tralokinumab every 2 weeks significantly improved AD symptoms based on IGA response and EASI reduction compared to placebo at 16 weeks. At 32 weeks, a sustained response was observed with tralokinumab administered every 2 weeks and every 4 weeks, without an increased need for TCS use.[84] In addition, tralokinumab treated patients had improvements in DLQI scores compared to placebo that were maintained at week 32.[84] The most commonly reported adverse events were viral and non-viral URTI, conjunctivitis, headache, and injection-site reactions. During the maintenance period, the overall frequency of reported adverse events remained stable among patients treated with tralokinumab every 2 weeks; however, adverse events were numerically more frequent

among patients receiving tralokinumab every 2 weeks compared to those receiving tralokinumab every 4 weeks.[84]

An additional placebo-controlled trial (ECZTRA 7) included adult (≥ 18 years) patients with severe AD for ≥ 1 year with an inadequate response to topical or documented systemic therapies in the prior 12 months, and uncontrolled or intolerance to oral cyclosporine A (CSA).[88] Tralokinumab was more effective than placebo at achieving the primary efficacy endpoint of EASI-75 (64% vs 51%, respectively) at 16 weeks.[88] In addition, patient reported outcomes such as DLQI and itch response were improved with tralokinumab use compared to placebo.[88] A sustained response in EASI-75 was observed at week 26 in tralokinumab-treated patients compared to patients receiving placebo (69% vs 55%, respectively).[88] Similar to previous trials, the most frequently reported adverse events among both treatment groups were viral and non-viral URTI, headache, conjunctivitis, and worsening AD.[88]

Regarding safety, the most frequent treatment-emergent adverse events included viral and non-viral URTI, worsening AD, and conjunctivitis, which were similar among each ECZTRA trial. The majority of the conjunctivitis cases were mild or moderate and typically resolved by the end of the study. In addition, eosinophilia occurred more frequently in tralokinumab-treated patients compared to the placebo arm.

Table 5 outlines the primary and selected key secondary endpoints, and pertinent safety information from the identified placebo-controlled tralokinumab trials. Selected key secondary endpoints were chosen based on consistency with reported outcomes of other pivotal phase III trials, and clinical relevance.

Table 5. Randomized Placebo Controlled Trials of Tralokinumab

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
Multicenter, randomized, double-blind, placebo controlled (Wollenberg, 2021, **ECZTRA 1**)[83]	Adults (≥ 18 years of age) diagnosed with moderate-to-severe AD[a] ≥ 1 year, uncontrolled by TCI or TCS therapies	**TRA 300 mg** subQ Q2W (after a LD of 600 mg) (N=603) **vs** **PBO** (N=199) Duration: 52 weeks Patients continued topical emollients	Co-primary endpoints: IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline at 16 weeks • ***TRA 300 mg vs PBO:*** 95 patients (16%) vs 14 patients (7%); adj. difference = 8.6%; (95% CI 4.1% to 13.1%); p=0.002 EASI-75 Response: ≥75% improvement in EASI score at week 16 • ***TRA 300 mg vs PBO:*** 150 patients (25%) vs 25 patients (13%); adj. difference = 12.1%; (95% CI 6.5% to 17.7%); p=<0.001 Key secondary endpoint(s) WP-NRS Response (weekly average): (≥4 point improvement from baseline in score) at week 16 • ***TRA 300 mg vs PBO:*** adj. difference = 9.7% (95% CI 4.4% to 15.0%); p=0.002 Adjusted mean change in SCORAD score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 10.4 (95% CI – 14.4 to – 6.5); p=<0.001 Adjusted mean change in DLQI score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 2.1 (95% CI – 3.4 to – 0.8); p=0.002	Most frequently reported TEAEs (≥5% in any treatment group) • AD worsening TRA 300 (25.9%) vs PBO (38.3%) • Viral URTI TRA 300 (23.1%) vs PBO (20.9%) • Conjunctivitis[b] TRA 300 (10.0%) vs PBO (3.6%) • Pruritus TRA 300 (5.3%) vs PBO (5.1%) • Headache TRA 300 (4.7%) vs PBO (5.1%) Discontinued treatment due to AEs TRA 300 (3.3%) vs PBO (4.1%) SAEs (≥1) TRA 300 (3.8%) vs PBO (4.1%) Selected other AEs of interest: • Skin infection TRA 300 (1.0%) vs PBO (1.5%) • Skin infection requiring systemic treatment TRA 300 (2.2%) vs PBO (2.0%) • Eczema herpeticum TRA 300 (0.5%) vs PBO (1.0%) • Malignancies None
Multicenter, randomized, double-blind, placebo controlled (Wollenberg, 2021, **ECZTRA 2**)[83]	Adults (≥ 18 years of age) diagnosed with moderate-	**TRA 300 mg** subQ Q2W (after a LD of 600 mg) (N=591)	Co-primary endpoints: IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline at 16 weeks	Most frequently reported TEAEs (≥5% in any treatment group) • AD worsening TRA 300 (16.6%) vs PBO (33.5%) • Viral URTI

Table 5. Randomized Placebo Controlled Trials of Tralokinumab

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
	to-severe AD[a] ≥ 1 year, uncontrolled by TCI or TCS therapies	**vs** **PBO** (N=201) Duration: 52 weeks Patients continued topical emollients	• ***TRA 300 mg vs PBO:*** 131 patients (22%) vs 22 patients (11%); adj. difference = 11.1%; (95% CI 5.8% to 16.4%); p=<0.001 EASI-75 Response: ≥75% improvement in EASI score at week 16 • ***TRA 300 mg vs PBO:*** 196 patients (33%) vs 23 patients (11%); adj. difference = 21.6%; (95% CI 15.8% to 27.3%); p=<0.001 Key secondary endpoint(s) WP-NRS Response (weekly average): (≥4 point improvement from baseline in score) at week 16 • ***TRA 300 mg vs PBO:*** adj. difference = 15.6% (95% CI 10.3% to 20.9%); p=<0.001 Adjusted mean change in SCORAD score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 14.0 (95% CI – 18.0 to – 10.1); p=<0.001 Adjusted mean change in DLQI score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 3.9 (95% CI – 5.2 to – 2.6); p=<0.001	TRA 300 (8.3%) vs PBO (8.5%) • Conjunctivitis[b] TRA 300 (5.2%) vs PBO (2.5%) • Pruritus TRA 300 (2.0%) vs PBO (2.5%) • Headache TRA 300 (2.7%) vs PBO (3.0%) Discontinued treatment due to AEs TRA 300 (1.5%) vs PBO (1.5%) SAEs (≥1) TRA 300 (1.7%) vs PBO (2.5%) Selected other AEs of interest: • Skin infection TRA 300 (2.0%) vs PBO (5.5%) • Skin infection requiring systemic treatment TRA 300 (3.5%) vs PBO (11.0%) • Eczema herpeticum TRA 300 (0.3%) vs PBO (2.5%) • Malignancies TRA 300 (0.2%) vs PBO (0%)
Multicenter, randomized, double-blind, placebo controlled (Silverberg, 2021, **ECZTRA 3**)[84]	Adults (≥ 18 years of age) diagnosed with moderate-to-severe AD[a] ≥ 1 year, uncontrolled by TCI or	**TRA 300 mg** subQ Q2W (after a LD of 600 mg) (N=252) **vs** **PBO** (N=126) Duration: 32 weeks	Co-primary endpoints: IGA Response: score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline at 16 weeks • ***TRA 300 mg vs PBO:*** 98 patients (39%) vs 33 patients (26%); adj. difference = 12.4%; (95% CI 2.9% to 21.9%); p=0.015 EASI-75 Response: ≥75% improvement in EASI score at week 16	Most frequently reported TEAEs (≥5% in any treatment group) • Viral URTI TRA 300 (19.4%) vs PBO (11.1%) • Conjunctivitis[c] TRA 300 (13.1%) vs PBO (5.6%) • Headache TRA 300 (8.7%) vs PBO (4.8%) • Non-viral URTI TRA 300 (7.5%) vs PBO (4.8%)

Table 5. Randomized Placebo Controlled Trials of Tralokinumab

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
	TCS therapies	Patients continued topical emollients and the use of TCSs as needed	• ***TRA 300 mg vs PBO:*** 141 patients (56%) vs 45 patients (36%); adj. difference = 20.2%; (95% CI 9.8% to 30.6%); p=<0.001 Key secondary endpoint(s) WP-NRS Response (weekly average): (≥4 point improvement from baseline in score) at week 16 • ***TRA 300 mg vs PBO:*** adj. difference = 11.3% (95% CI 0.9% to 21.6%); p=0.037 Adjusted mean change in SCORAD score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 10.9 (95% CI – 15.2 to – 6.6); p=<0.001 Adjusted mean change in DLQI score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 2.9 (95% CI – 4.3 to – 1.6); p=<0.001	• Injection-site reaction TRA 300 (6.7%) vs PBO (0%) • AD worsening TRA 300 (2.4%) vs PBO (7.9%) Discontinued treatment due to AEs TRA 300 (2.4%) vs PBO (0.8%) SAEs (≥1) TRA 300 (0.8%) vs PBO (3.2%) Selected other AEs of interest: • Skin infection requiring systemic treatment TRA 300 (1.6%) vs PBO (5.6%) • Eczema herpeticum TRA 300 (0.4%) vs PBO (0.8%) • Malignancies None
Multicenter, randomized, double-blind, placebo controlled (Gutermuth, 2021, **ECZTRA 7**)[88]	Adults (≥ 18 years of age) diagnosed with severe AD[d]≥ 1 year, with an inadequate response to topical or systemic therapies in the prior 12 months, and uncontrolled by oral CSA	**TRA 300 mg** subQ Q2W (after a LD of 600 mg) (N=138) **vs** **PBO** (N=137) Duration: 26 weeks Patients continued topical emollients and the use of TCSs	Primary endpoint: EASI-75 Response: ≥75% improvement in EASI score at week 16 • ***TRA 300 mg vs PBO:*** 88 patients (64%) vs 69 patients (51%); adj. difference = 14.1%; (95% CI 2.5% to 25.7%); p=0.018 Selected key secondary endpoint(s) WP-NRS Response (weekly average): (≥4 point improvement from baseline in score) at week 16 • TRA 300 mg vs PBO: adj. difference = 9.7% (95% CI – 2.0% to 21.4%); p=0.106 Adjusted mean change in SCORAD score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 8.6 (95% CI – 13.0 to – 4.2); nominal p=<0.001	Most frequently reported TEAEs (≥5% in any treatment group) • Viral URTI TRA 300 (26.8%) vs PBO (25.5%) • Headache TRA 300 (15.2%) vs PBO (9.5%) • AD worsening TRA 300 (5.1%) vs PBO (11.7%) • Conjunctivitis[e] TRA 300 (9.4%) vs PBO (4.4%) • Non-viral URTI TRA 300 (7.2%) vs PBO (7.3%) • Asthma TRA 300 (2.9%) vs PBO (5.8%) • Cough

Table 5. Randomized Placebo Controlled Trials of Tralokinumab

RCT Design (author, year, trial name)	*Population*	*Intervention*	*Efficacy Results (% of patients)*	*Safety Results*
		(any potency) as needed	Adjusted mean change in DLQI score: from baseline to week 16 • ***TRA 300 mg vs PBO:*** adj. difference = – 1.5 (95% CI – 2.6 to – 0.4); nominal p=0.009	TRA 300 (2.9%) vs PBO (5.1%) • HTN TRA 300 (2.2%) vs PBO (5.1%) • Oropharyngeal pain TRA 300 (0.7%) vs PBO (5.8%) Discontinued treatment due to AEs TRA 300 (0.7%) vs PBO (2.2%) SAEs TRA 300 (0.7%) vs PBO (3.6%) Selected other AEs of interest: • Skin infection requiring systemic treatment TRA 300 (0.7%) vs PBO (5.8%) • Eczema herpeticum TRA 300 (0.7%) vs PBO (0%) • Malignancies None

Abbreviations: AD, atopic dermatitis; Adj, adjusted; CI, confidence interval; CSA, cyclosporine A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HTN, hypertension; IGA, Investigator's Global Assessment; LD, loading dose; PBO, placebo; Q2W, every two weeks; SAEs, serious adverse events; SCORAD, Scoring Atopic Dermatitis; subQ, subcutaneously; TCI, topical calicineurin inhibitor; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; WP-NRS, Worst Pruritis Numerical Rating Scale.

[a] Diagnosis of AD per the Hanifin and Rajka criteria. Must be "candidates for systemic therapy" based on lack of sufficient response to or intolerance/inappropriateness for topical treatments. Moderate-to-severe AD criteria: ≥ 10% BSA with AD *and* EASI score ≥ 12 at screening and 16 at baseline *and* IGA ≥ 3 *and* WP-NRS ≥ 4 during the week prior to baseline.
[b] Includes conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and allergic conjunctivitis
[c] Includes conjunctivitis, allergic conjunctivitis, and viral conjunctivitis
[d] Diagnosis of AD per the Hanifin and Rajka criteria. Must have a lack of sufficient response (after ≥ 12 weeks) to or intolerance to oral cyclosporine A. Severe AD criteria: ≥ 10% BSA with AD *and* EASI score ≥ 20 *and* IGA ≥ 3 *and* WP-NRS ≥ 4 during the week prior to baseline.
[e] Includes bacterial conjunctivitis, viral conjunctivitis, and allergic conjunctivitis
Italicized bold comparator names signifies statistically significant results

Appendix D: Supplementary Guideline Tables

Table 1. Summary of Clinical Practice Guidelines for the Treatment of AD [3]

Guideline (Sponsoring Organization; Year)	Recommendations
	United States Guidelines

Guidelines of Care for the Management of Atopic Dermatitis: Part 2: Management and Treatment of Atopic Dermatitis with Topical Therapies **(AAD; 2014)**[6]	• All patients with AD, regardless of disease severity, should use moisturizers to prevent disease progression and pharmacologic intervention (**Level I, Strength A**)
	  ○ To improve skin hydration, application should occur soon after bathing (**Level II, Strength B**)
	• Non-pharmacological interventions:
	  ○ Topical moisturizers with emollient, occlusive, and/or humectant ingredients
	  ○ Bathing practices, including additives (**Level III, C**)
	  ○ Wet wrap therapy (**Level II, B**)
	• TCS are recommended for children and adults who have not responded to good skin care and routine use of emollients alone (**Level I, Strength A**)
	• For *children and adults*, TCIs (tacrolimus and pimecrolimus) are recommended for acute and chronic treatment, in addition to maintenance (2-3 times per week). (**Level I, Strength A**) These agents are preferred to topical steroids in the following situations:
	  ○ Refractory to steroids
	  ○ Application to sensitive areas (eg, face, anogenital, skin folds)
	  ○ Presence of steroid-induced atrophy
	  ○ Long-term uninterrupted topical steroid use
	• TCIs are recommended in "actively affected areas as a steroid-sparing agent" (**Level I, Strength A**)
	• "The concomitant use of a TCS with a TCI may be recommended for the treatment of AD" (**Level II, Strength B**)
	• Bleach baths and intranasal mupirocin are recommended to reduce disease severity in patients with moderate-to-severe AD *and* evidence of a secondary bacterial infection (**Level II, Strength B**)
	• Topical antihistamines are not recommended (**Level II, Strength B**)

Guidelines of Care for the Management of Atopic Dermatitis: Part 3: Management and Treatment with	• Phototherapy is recommended as a second-line option, after failure of non-pharmacologic interventions (eg, moisturizers) and topical therapies (TCS and TCIs) in children and adults (**Level II, Strength B**) • Systemic immunomodulatory agents (eg, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil) are recommended in refractory AD among adult and pediatric patients, or when QoL is significantly affected. Systemic agents are used when inadequate control is not achieved with topical therapies and/or phototherapy (**Level I-III, Strength B-C**)

Table 1. Summary of Clinical Practice Guidelines for the Treatment of AD [3]

Guideline (Sponsoring Organization; Year)	Recommendations
Phototherapy and Systemic Agents **(AAD; 2014)[7]**	• Systemic steroids should be reserved exclusively for acute, severe exacerbations, and short-term use (**Level II, Strength B**) • Systemic antibiotics are recommended in patients with evidence of a bacterial infection (**Level II, Strength A**)
The Joint Task Force on Practice Parameters on Atopic Dermatitis **(AAAAI, ACAAI, and the JCAAI; 2012)[5]**	<u>First-line Management and Treatment:</u> • Recommend warm soaking baths for at least 10 minutes followed by moisturizer application to improve skin hydration (**Strength D**) • TCS are recommended if AD is not controlled by the use of moisturizers (**Strength A**) • Topical antihistamines are generally not recommended due to the potential for cutaneous sensitization, but some patients may benefit from the relief of pruritus (**Strength C**) • To reduce the severity of AD, dilute bleach baths (twice per week) should be considered, specifically in patients with recurrent infections (**Strength A**) • Supplementation with vitamin D may be beneficial, especially in patients with low vitamin D consumption or low concentrations (**Strength B**) <u>Refractory AD</u> • Wet-wrap dressings in combination with TCS should be recommended (**Strength A**) • For the treatment of AD, TCIs (pimecrolimus and tacrolimus) may be considered (**Strength A**) ○ Topical tacrolimus ointment, "unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids" (**Strength A**) • Topical pimecrolimus cream, "safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus" (**Strength A**) • Systemic immunologic or anti-inflammatory therapies (eg, cyclosporine, mycophenolate mofetil, azathioprine, corticosteroids) provide benefit to patients with severe refractory AD, but potential serious adverse effects should be considered (**Strength A**) • Phototherapy, UVB is the most effective option available and may be useful for the treatment of recalcitrant AD (**Strength A**)
European Guidelines	
Consensus-based European guidelines for treatment of atopic eczema (atopic	<u>Adults</u> • Baseline (Basic therapy): "Educational programs, emollients, bath oils, avoidance of clinically relevant allergens" • Mild (SCORAD <25 or transient eczema): "Reactive therapy with topical glucocorticosteroids class II or depending on local cofactors; topical calcineurin inhibitors, antiseptics including silver, silver coated textiles"

Table 1. Summary of Clinical Practice Guidelines for the Treatment of AD [3]

Guideline (Sponsoring Organization; Year)	Recommendations
dermatitis) in adults and children: part 1 **(EDF, EADV, EAACI, ETFAD, EFA, ESPD. GA2LEN, UEMS; 2018)[17]**	• Moderate (SCORAD 25-50/ or recurrent eczema): "Proactive therapy with topical tacrolimus or class II or III topical glucocorticosteroids, wet wrap therapy, UV therapy (UVB 311 nm), psychosomatic counseling, climate therapy • Severe (SCORAD >50/ or persistent eczema): "Hospitalization; systemic immunosuppression: cyclosporine A, short course of oral glucocorticosteroids, dupilumab, methotrexate, azathioprine, mycophenolate mofetil; PUVA; alitretinoin" <u>Children:</u> • Baseline (Basic therapy): same as adults • Mild (SCORAD <25 or transient eczema): same as adults • Moderate (SCORAD 25-50/ or recurrent eczema): same as adults • Severe (SCORAD >50/ or persistent eczema): "Hospitalization, systemic immunosuppression: cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil" <u>Recommendations:</u> • Treatment with TCS should be considered for treating acute exacerbations before switching to a TCI (**Level -, Strength D**) • TCIs are indicated in sensitive skin area(s) (eg, face, intertriginous sites, anogenital) (**Level 1b, Strength A**) • Bi-weekly application of tacrolimus ointment may reduce relapses (**Level 1b, Strength A**)

Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part 2 **(EDF, EADV, EAACI, ETFAD, EFA, ESPD. GA2LEN, UEMS; 2018)[23]**	• Dupilumab is recommended in adults with moderate-to-severe AD, in which disease control is not achieved with topical treatment and a contraindication exists or it is not advisable to use other systemic treatment (**Level 1, Strength A**)
	  ○ Should be used with emollients daily and may be used with topical anti-inflammatory agents as needed (eg, TCS) (**Level 2, Strength B**)
	  ○ ***Note*** that the pediatric AD indication approval for dupilumab may have occurred after this guidelines was published.
	• Long-term use of topical antibiotics are not recommended due to concern of increasing resistance (**Level 2, Strength D**)
	  ○ If evidence of a bacterial infection exists, topical antiseptic agents, including antiseptic baths (eg, diluted sodium hypochlorite) are recommended (**Level 4, Strength C**)

Guideline on Atopic Dermatitis; **(NICE; 2013)[1]**	<u>Mild AD:</u> Emollients, mild-potency TCS <u>Moderate AD:</u> Emollients, moderate-potency TCS, TCI, bandages <u>Severe AD:</u> Emollients, potent TCS, TCI, bandages, phototherapy, systemic therapy • TCIs (tacrolimus and pimecrolimus) are not recommended as first-line agents for AD, and should be initiated after a failed response to TCS

Table 1. Summary of Clinical Practice Guidelines for the Treatment of AD [3]

Guideline (Sponsoring Organization; Year)	Recommendations
	○ TCIs should not be used for mild AD • As second-line agents (TCIs), use is recommended when there is concern for serious adverse events from continued TCS use (eg, irreversible skin atrophy)
Dupilumab for treating moderate to severe atopic dermatitis; **(NICE; 2018)[22]** • A technology appraisal guidance	• Dupilumab is recommended for moderate-to-severe AD in adults that have an inadequate response to at least one other systemic therapy (eg, ciclosporin, methotrexate, azathioprine, mycophenolate mofetil) or a contraindication exists • Dupilumab should be stopped at 16 weeks if at least a 50% reduction in EASI and at least a 4-point reduction in the DLQI has not occurred from treatment initiation • Dupilumab may be used with or without TCS • TCIs may be used with dupilumab, but TCI use should be reserved to sensitive areas (eg, face, neck, anogenital, skin folds)
Baricitinib for treating moderate to severe atopic dermatitis; **(NICE; 2021)[21]** • A technology appraisal guidance	• Baricitinib is recommended for moderate-to-severe AD in adults that have an inadequate response to at least one other systemic therapy (eg, ciclosporin, methotrexate, azathioprine, mycophenolate mofetil) or a contraindication exists • Response should be assessed from 8 weeks and stopped at 16 weeks if at least a 50% reduction in EASI and at least a 4-point reduction in the DLQI has not occurred from treatment initiation

Abbreviations: AAAAI, American Academy of Allergy, Asthma & Immunology; AAD, American Academy of Dermatology; ACAAI, American College of Allergy, Asthma & Immunology; AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EAACI, European Academy of Allergy and Clinical Immunology; EADV, European Academy of Dermatology and Venereology; EDF, European Dermatology Forum; EFA, European Federation of Allergy and Airways Diseases Patients' Associations; ESPD, European Society of Pediatric Dermatology; ETFAD, European Task Force on Atopic Dermatitis; GA2LEN, Global Allergy and Asthma European Network; JCAAI, Joint Council of Allergy, Asthma, and Immunology; NICE, National Institute for Health and Care Excellence; PUVA, psoralen and ultraviolet; QoL, quality of life; SCORAD, Scoring Atopic Dermatitis; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; UEMS, European Union of Medical Specialists; UVB, ultraviolet B

Table 2. Guideline Level of Evidence and Strength of Recommendation Definitions

	AAD[4,6,7]
Level I	"Good-quality patient-oriented evidence"
Level II	"Limited-quality patient-oriented evidence"
Level III	"Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence"
Strength A	"Recommendation based on consistent and good-quality patient-oriented evidence"
Strength B	"Recommendation based on inconsistent or limited-quality patient-oriented evidence"
Strength C	"Recommendation based on consensus, opinion, case studies, or disease-oriented evidence"
	AAAAI, ACAAI, and JCAAI[5]
Level Ia	"Evidence from meta-analysis of randomized controlled trials"
Level Ib	"Evidence from at least 1 randomized controlled trial"
Level IIa	"Evidence from at least 1 controlled study without randomization"
Level IIb	Evidence from at least 1 other type of quasiexperimental study"
Level III	"Evidence from nonexperimental descriptive studies, such as comparative studies"
Level IV	"Evidence from expert committee reports, opinions, or clinical experience of respected authorities or both"
Strength A	"Directly based on category I evidence"
Strength B	"Directly based on category II evidence or extrapolated recommendation from category I evidence"
Strength C	"Directly based on category III evidence or extrapolated recommendation from category I or II evidence
Strength D	"Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
	EDF, EADV, EAACI, ETFAD, EFA, ESPD. GA2LEN, and UEMS[23]
Level 1a	"Meta-analysis of RCTs
Level 1b	"Single RCTs"
Level 2a	"Systematic review of cohort studies"
Level 2b	"Single cohort studies and RCTs of limited quality"
Level 3a	"Systematic review of case-control studies"
Level 3b	"Single case-control study"
Level 4	"Case series, case cohort studies or cohort studies of limited quality"
Strength A	Based on 1a or 1b evidence
Strength B	Based on 2a, 2b, 3a, or 3b evidence
Strength C	Based on 4 evidence
Strength D	Expert opinion

Expert Opinion

In 2015, **Eichenfield et al** published an article proposing an AD treatment management plan for pediatricians and other primary care providers based on the US guidelines (AAD [2014] and (AAAI/ACAAI [2012] practice parameter), and the 2012 European Dermatology Forum (EDF) guideline (**Table 6**).[3,37]

The selection of using TCIs over TCSs varies on patient/ provider preference, medication access (including cost), location of lesions (use of TCSs on sensitive skin area(s) should be restricted), and the effectiveness and tolerability with a specific agent.[3,37] In addition, the lowest potency TCS should be used for long-term use to minimize the risk of experiencing adverse reactions (eg, skin atrophy, glaucoma, adrenocortical suppression).[37]

Table 3. Management Plan of Atopic Dermatitis for Primary Care Providers[3,37]

Mild Disease	Moderate-to-Severe Disease
Basic Management[a]: • **Appropriate skin care:** warm baths or showers (using mild soaps or non-soap cleansers) daily followed by moisturizer use • **Antiseptic measures:** dilute bleach baths (at least twice per week), particularly with recurrent skin infections • **Trigger avoidance:** avoid irritants (eg, soaps), extreme temperatures, and allergens Maintenance Therapy: moisturizers	Basic Management **PLUS:** **Maintenance TCI:** Tacrolimus or pimecrolimus (2-3 times per week) ***AND/OR*** ***OR (if unresponsive)*** 1-2 times per day **Maintenance TCS:** • Medium potency TCS (except for face and eyes) 1-2 times per week ***AND/OR*** • Low potency TCS (face and eyes included) 1-2 times per day
Acute treatment for flares[b]: low potency TCS applied twice per day for up to 3 days beyond flare resolution; sometimes medium potency TCS may be used	Relapsing AD ("frequent/ persistent flares"): "topical anti-inflammatory agents at first signs/symptoms or to flare-prone area(s)" Acute treatment for flares[b]: medium potency TCS applied twice per day for up to 3 days beyond flare resolution. For flares not resolved within 7 days, consider nonadherence, infection, misdiagnosis, or referral

Abbreviations: TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

[a] Recommended for all patients, regardless of disease severity. Maintenance and/or acute treatment should be added as needed

[b] A flare is defined as an "acute worsening of symptoms necessitating escalation in treatment"

Appendix E: Included and Excluded References

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