Immunomodulators, Atopic Dermatitis
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
abrocitinib (Cibinqo™)*[1]	Pfizer	Treatment of refractory, moderate to severe atopic dermatitis in patients ≥ 12 years of age whose disease is not adequately controlled with other systemic drugs, including biologics, or when use of those therapies is inadvisable
crisaborole (Eucrisa®)[2]	Pfizer	Topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients ≥ 3 months of age
dupilumab (Dupixent®)ł[3]	Sanofi-Aventis	Treatment of patients ≥ 6 months of age with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable; may be used with or without topical corticosteroids
pimecrolimus (Elidel®)[4]	generic, Bausch	Second‑line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children ≥ 2 years of age, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable
ruxolitinib (Opzelura™)‡[5]	Incyte	Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients ≥ 12 years of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
tacrolimus (Protopic®)[6]	generic, Leo	Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable ▪ 0.03% ointment approved for patients 2 years to 15 years old ▪ 0.03% ointment and 0.1% ointment approved for adults
tralokinumab-ldrm (Adbry™)[7]	Leo	Treatment of moderate to severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable; can be used with or without topical corticosteroids
upadacitinib (Rinvoq®)*§[8]	AbbVie	Treatment of refractory, moderate to severe atopic dermatitis in patients ≥ 12 years of age whose disease is not adequately controlled with other systemic drugs, including biologics, or when use of those therapies is inadvisable

* Abrocitinib (Cibinqo) and upadacitinib (Rinvoq) are not recommended for use in combination with other Janus kinase (JAK) inhibitors, immunosuppressants, or biologic immunomodulators.

ł Dupilumab (Dupixent) is also indicated as add-on maintenance treatment in patients with moderate to severe asthma aged ≥ 6 years with an eosinophilic phenotype or with oral corticosteroid dependent asthma, for eosinophilic esophagitis in patients aged ≥ 12 years weighing ≥ 40 kg, for the treatment of adults with prurigo nodularis, and as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis. These indications will not be addressed in this therapeutic class review.

‡ Ruxolitinib (Opzelura) is also indicated for the topical treatment of nonsegmental vitiligo in adult and pediatric patients aged ≥ 12 years. This indication will not be addressed in this therapeutic class review.

§ Upadacitinib (Rinvoq) is also indicated for the treatment of select adult patients with rheumatoid arthritis, active psoriatic arthritis, active ulcerative colitis, active ankylosing spondylitis, and non-radiographic axial spondyloarthritis.

OVERVIEW

Atopic dermatitis (AD) is a chronic, non-contagious, inflammatory disease of the skin resulting from a combination of genetic and environmental factors.[9] Approximately 70% of patients diagnosed with AD have a positive family history of atopic diseases.[10] The odds of developing AD are 2 to 3 times higher in children with one atopic parent and increase to 3 to 5 times higher if both parents are atopic.

Often referred to as "eczema," AD affects up to 15% of children and about 7.3% of adults in the United States (US).[11,12] Although symptoms of AD can develop at any age, it has been estimated that 60% of patients develop symptoms in the first year of life, while 90% develop symptoms before the age of 5 years.[13] The majority of affected patients have resolution of the disease by adulthood, 10% to 30% do not, and a smaller percentage experience initial symptom development in adulthood. There is some evidence to suggest individuals living in cities or with exposure to hard water are at higher risk and those with early exposure to daycare or farm animals are at lower risk of developing AD. [14] AD commonly occurs in patients affected by asthma and other allergic conditions and is associated with elevated serum IgE levels. Evidence suggests that patients with asthma or food allergies have an increased severity of AD.[15] There are also associations between AD and allergic rhinitis, anxiety, depression, heart disease, osteoporosis, and obesity.

AD is characterized by extremely dry, itchy skin on the insides of the elbows, behind the knees, and on the face, hands, and feet caused by epidermal barrier dysfunction.[16,17] As the skin loses moisture from the epidermal layer, it becomes increasingly dry and may begin to crack, weep, crust, and scale. In response to the intense itching, patients may scratch or rub the affected area, which leads to further irritation and inflammation. Damage to the integrity of the skin renders it less protective and more prone to infection. Despite the chronic nature of this dermatologic condition, there may be periods of the disease when the skin improves and periods when the skin worsens.[18] Allergenic foods, irritants such as detergents, wool, and bleach, , and allergens like dust mites, pollen, and animal dander can exacerbate AD or cause disease flares.

The pathogenesis of epidermal barrier dysfunction is multifactorial and, in some cases, may involve reduced production of filaggrin which is a key component in maintaining stratum corneum integrity and hydration. The filaggrin precursor, profilaggrin, is encoded by the *FLG* gene; loss-of-function gene variants are associated with certain AD phenotypes.[19,20] Variations in other genes have also been associated with an increased risk of AD. Tissue damage and/or microorganisms are responsible for igniting an inflammatory cascade involving interleukins, mast cells, basophils, and antigen-specific immunoglobulin E (IgE) molecules. Bacterial proteins function as superantigens that bind to major histocompatibility class II (MHCII) molecules on the surface of antigen-presenting cells and receptors on T cells, resulting in excessive production of T cell cytokines and can elicit an IgE response. Chronic itch in AD is thought to be largely mediated by type 2 cytokines, including interleukin (IL)-4, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP).

The 2023 American Academy of Dermatology (AAD) guidelines for the management of atopic dermatitis in adults with topical therapies strongly recommend moisturizers, topical corticosteroids, topical calcineurin inhibitors, topical phosphodiesterase 4 (PDE-4) inhibitors (e.g., crisaborole [Eucrisa]), and topical JAK inhibitors (e.g., ruxolitinib cream [Opzelura]) for the treatment of AD.[21] Topical corticosteroids are typically used first line for mild to severe dermatitis, and medium potency agents are strongly recommended as twice weekly maintenance therapy. Topical calcineurin inhibitors are a safe anti-inflammatory option, especially when corticosteroid avoidance is warranted. The guidelines note

that tacrolimus might be more clinically effective than pimecrolimus, based on clinical trials; however, it may cause more local irritation and is only formulated as an ointment, which may not be preferable to patients. For mild to moderate disease, crisaborole has a favorable safety profile and may be used as an alternative to topical corticosteroids and calcineurin inhibitors. Topical ruxolitinib cream has demonstrated significant efficacy for short-term, non-continuous treatment of mild to moderate AD, but carries the black box warnings inherent to the JAK inhibitor class. The guidelines note that the strong recommendation for JAK inhibitors in AD is based on moderate certainty, short-term efficacy and safety data and may be updated when longer term data are available. In the AAD guidelines for use of phototherapy and systemic agents in the treatment of AD, phototherapy is recommended as a treatment option after failure of emollients, topical steroids, and topical calcineurin inhibitors.[22] Systemic immunomodulating agents are indicated for patients whose AD is not adequately controlled by topical regimens and/or phototherapy. Dupilumab (Dupixent), tralokinumab-ldrm (Adbry), abrocitinib (Cibinqo), and upadacitinib (Rinvoq) were not available at the time of development of these guidelines.

The American Academy of Allergy, Asthma, and Immunology (AAAAI) 2012 guidelines state that pimecrolimus and tacrolimus are reasonable treatment options for patients as second-line treatment choices.[23] First-line options include hydration (emollients), moisturizers, and topical corticosteroids. Although topical corticosteroids are the standard of care in the treatment of AD, dermatologic effects, such as striae, atrophy, and tachyphylaxis, as well as potential non-dermatologic effects on linear growth rate, bone density, and hypothalamic-pituitary-adrenal (HPA) axis suppression, limit the long-term use of these agents. Crisaborole (Eucrisa), dupilumab (Dupixent), ruxolitinib (Opzelura), tralokinumab-ldrm (Adbry), abrocitinib (Cibinqo), and upadacitinib (Rinvoq) were not available at the time of the development of the AAAAI guidelines.

PHARMACOLOGY[24,25,26,27,28,29,30,31,32,33]

Abrocitinib (Cibinqo) reversibly inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. Janus kinase enzymes are responsible for intracellular cytokine signaling and while the role of inhibition of JAK enzymes in the treatment of AD is not well understood, abrocitinib has been associated with dose-dependent reductions in serum markers of inflammation.

Crisaborole (Eucrisa) is a PDE-4 inhibitor. PDE-4 inhibition leads to increased intracellular cyclic adenosine monophosphate (cAMP) levels; however, the specific therapeutic action of crisaborole for the treatment of atopic dermatitis is not well defined.

Dupilumab (Dupixent), a human monoclonal IgG4 antibody, inhibits IL-4 IL-13 signaling via binding to the IL-4 receptor alpha subunit found on both complexes, resulting in inhibition of cytokine-induced responses (e.g., proinflammatory cytokines, chemokines, IgE).

Pimecrolimus (Elidel) is a derivative of the macrolactam ascomycin. It binds to the intracellular protein macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase calcineurin. Consequently, it inhibits T-cell activation by blocking the transcription of cytokines. Cytokines of both the Th1-type (IL-2 and interferon-gamma) and Th2-type (IL-4 and IL-10) are inhibited in T-cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells after stimulation by antigen/IgE. Pimecrolimus has no effect on the growth of fibroblasts or keratinocytes.

Ruxolitinib (Opzelura) is a JAK inhibitor that targets the JAK and signal transducer and activator of transcription (STAT) pathway, and may mediate itch response, inflammation, and skin barrier dysfunction associated with AD.

Tacrolimus (Protopic) is a topical macrolactam agent. It exerts its pharmacologic activity by binding to FKBP-12. A complex is then formed which includes calcineurin. This complex prevents the phosphatase activity of calcineurin and thus prevents gene transcription for the formation of various lymphokines (IL-2, interferon-gamma). Formation of other lymphokines may be inhibited, including IL-3, IL-4, IL-5, granulocyte macrophage colony stimulating factor, and tumor necrosis factor-alpha (TNF-α).

Tralokinumab-ldrm (Adbry) is a human monoclonal antibody that is an interleukin-13 antagonist and inhibits the inflammatory response of cytokines, chemokines, and IgE.

Upadacitinib (Rinvoq) is a JAK inhibitor that prevents cytokine-induced STAT phosphorylation mediated by JAK1, JAK1/JAK3, and to a lesser extent JAK2/JAK2. STAT phosphorylation is critical to immune cell gene expression. The role of this activity in the therapeutic effectiveness of the drug is not well understood.

PHARMACOKINETICS[34,35,36,37,38,39,40,41]

More than 91% of an oral dose of abrocitinib (Cibinqo) is absorbed and absolute bioavailability is 60%. Peak plasma concentrations are achieved within 1 hour. Abrocitinib is metabolized by cytochrome P450 (CYP) enzymes: CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%), and CYP2B6 (~6%). Circulating abrocitinib and its active metabolites, M1 and M2, are 64%, 37%, and 29% bound to plasma proteins, respectively. The mean elimination half-life of abrocitinib, M1, and M2 is 3 to 5 hours. Metabolites are predominantly excreted in the urine and are substrates of organic anion transporter 3 (OAT3).

Systemic absorption occurs with crisaborole (Eucrisa). Once absorbed, it is highly protein bound (97%) and is metabolized to 2 inactive metabolites, which are primarily eliminated via renal excretion.

Dupilumab (Dupixent) reaches mean peak concentrations approximately 1 week post subcutaneous (SC) administration (C_{max} = 70.1 mcg/mL; SD of ± 24.1); however, trough concentrations were lower in patients with higher body weight in pharmacokinetic studies. Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations. Steady-state is achieved by 16 weeks, bioavailability is estimated to be 64%, and the estimated volume of distribution is 4.8 ± 1.3 L. The metabolic pathway of dupilumab has not been characterized.

Minimal systemic absorption occurs from topical use of pimecrolimus (Elidel) or tacrolimus (Protopic).

The half-life of ruxolitinib (Opzelura) is approximately 116 hours. It is highly protein bound (97%) and is primarily metabolized by cytochrome P450 (CYP) 3A4 and CYP2C9. It is excreted primarily through the urine (74%) and feces (22%).

Tralokinumab-ldrm (Adbry) maximum concentration was reached 5 to 8 days after administration, with a steady-state concentration achieved by week 16. Its mean volume of distribution is estimated to be approximately 4.2 L. Tralokinumab-ldrm is metabolized into small peptides by catabolic pathways with an elimination half-life of 3 weeks. The exposure of tralokinumab-ldrm decreases with increasing body weight, specifically > 100 kg. Its half-life is 3 weeks.

When administered once daily, maximum concentration of upadacitinib (Rinvoq) is achieved in 2 to 4 hours, and steady-state plasma concentrations are achieved within 4 days. Plasma protein binding is 52%. Upadacitinib is predominantly metabolized by CYP3A4, and to a lesser extent CYP2D6, to inactive metabolites. Parent drug is excreted in the urine (24%) and feces (38%), and mean terminal elimination half-life is 8 to 14 hours.

CONTRAINDICATIONS/WARNINGS[42,43,44,45,46,47,48,49,50]

Crisaborole (Eucrisa), dupilumab (Dupixent), pimecrolimus (Elidel), tacrolimus (Protopic), tralokinumab-ldrm (Adbry), and upadacitinib (Rinvoq) are **contraindicated** in those with known hypersensitivity to an active or inactive ingredient.

Hypersensitivity reactions, including contact urticaria, have been reported in patients using crisaborole (Eucrisa).

Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme, have been reported in patients using dupilumab (Dupixent). In addition, conjunctivitis and keratitis were reported more frequently in clinical trials and postmarketing settings with dupilumab compared to placebo. Any new onset or worsening symptoms related to conjunctivitis or keratitis should be reported to a healthcare provider. Safety and efficacy of dupilumab in patients with parasitic (helminth) infections were excluded from clinical trials; thus, the effect of dupilumab in these patients is unknown. Patients with asthma who are taking dupilumab for conditions other than asthma, such as atopic dermatitis, should be instructed not to adjust or stop their asthma treatment without consulting with their provider. Use of live vaccines should be avoided during treatment with dupilumab. Responses to select non-live vaccines were similar in both dupilumab- and placebo-treated patients in clinical trials; however, the full impact of use of non-live vaccines has not been fully evaluated.

The Food and Drug Administration (FDA) in 2006 issued a public health advisory to inform healthcare professionals and patients about the potential cancer risk associated with use of pimecrolimus (Elidel) and tacrolimus (Protopic).[51] Animal studies, case reports in a small number of patients, and knowledge of the mechanism of action of these drugs formed the basis for concern. With the true risk unknown, the FDA advised that these agents be used as second-line treatment options only as labeled for the short-term and intermittent treatment of AD after other prescription treatments have failed or cannot be tolerated. Both pimecrolimus (Elidel) and tacrolimus (Protopic) have a boxed warning regarding the long-term safety of topical calcineurin inhibitors, which has not been established. Rare cases of malignancy have occurred. Continuous long-term use of calcineurin inhibitors should be avoided and application should be limited to areas affected by AD. The safety of these drugs has not been established beyond 1 year of non-continuous use. If signs and symptoms of AD do not resolve within 6 weeks of pimecrolimus or tacrolimus use, patients should have their physician re-examine and confirm the diagnosis.

Bacterial and viral infections of treatment sites must be resolved prior to AD treatment with pimecrolimus and tacrolimus. AD patients should avoid use on malignant or pre-malignant skin conditions. In addition, some malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), may mimic atopic dermatitis. Patients with Netherton's syndrome or other skin diseases that may allow for increased systemic absorption should not use these products. Increased risk of varicella zoster virus infection, herpes simplex virus infection, and eczema herpeticum is associated with use of pimecrolimus and tacrolimus.

During treatment with pimecrolimus or tacrolimus, patients with AD should minimize or avoid natural and artificial sunlight, even if pimecrolimus or tacrolimus is not present on the skin. It is not known if either agent interferes with skin response to ultraviolet damage. Safety of these products under occlusive dressings, which may promote systemic exposure, has not been studied and therefore should not be used by patients.

Patients who develop lymphadenopathy should have the etiology examined to determine its cause. In clinical studies, less than 1% of cases of lymphadenopathy were reported while using pimecrolimus and tacrolimus which resolved upon appropriate antibiotic therapy. The majority of these cases had either a clear etiology or resolved. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, pimecrolimus or tacrolimus should be discontinued.

Abrocitinib (Cibinqo) is **contraindicated** in patients taking antiplatelet medications during the first 3 months of treatment, with the exception of low-dose aspirin. Ruxolitinib (Opzelura) has no contraindications.

Abrocitinib, ruxolitinib, and upadacitinib carry multiple boxed warnings associated with use of oral JAK inhibitors, including the risk of serious infections, a higher rate of all-cause mortality observed in a rheumatoid arthritis trial, the occurrence of lymphoma and other malignancies (current or past smokers at increased risk), non-melanoma skin cancer (skin examinations should be performed during and after treatment), a higher rate of major adverse cardiovascular events (MACE) compared with TNF blockers in rheumatoid arthritis patients, and an increased incidence of thrombosis. Use of abrocitinib, ruxolitinib, or upadacitinib in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended. Thrombocytopenia, lymphopenia, and lipid elevations have also been reported with JAK inhibitors. Complete blood counts (CBC) are recommended at baseline and periodically during abrocitinib and upadacitinib treatment with temporary treatment discontinuation advised based on hematologic abnormalities. Live vaccines should be avoided during, immediately prior to, and immediately after treatment with abrocitinib and upadacitinib.

Upadacitinib is associated with gastrointestinal perforation; patients with a history of diverticulitis or taking non-steroidal anti-inflammatory drugs (NSAIDs) may be at greater risk. Liver enzyme elevations have also been reported with upadacitinib; interruption of treatment is warranted if liver injury is suspected.

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred after tralokinumab-ldrm use. Conjunctivitis and keratitis occurred at an increased incidence in clinical trials in patients receiving tralokinumab-ldrm compared to patients receiving placebo. Patients should be advised to report any new or worsening eye symptoms to their healthcare provider. Helminth infections should be treated and resolved prior to initiation or continuation of tralokinumab-ldrm. Use of live vaccines should be avoided during treatment with tralokinumab-ldrm due to the potential for altered immune response and increased risk of infection; limited data exist for non-live vaccines.

DRUG INTERACTIONS[52,53,54,55,56,57,58,59]

Exposure of abrocitinib and its metabolites is significantly increased when coadministered with drugs that are strong inhibitors of CYP2C19; dose reduction of abrocitinib is recommended. Avoidance of concomitant use of drugs that are moderate to strong inhibitors of both CYP2C19 and CYP2C9 is recommended. Likewise, exposure is reduced with concomitant strong CYP2C19 or CYP2C9 inducers, and avoidance of these agents is recommended. Abrocitinib increases the plasma concentration of P-glycoprotein (P-gp) substrates; monitoring of sensitive substrates, e.g., digoxin, is recommended. The risk of thrombocytopenia and bleeding are increased when abrocitinib is used concomitantly with antiplatelet drugs.

One metabolite of crisaborole (Eucrisa) can weakly inhibit CYP1A2 and CYP2B6, and moderately inhibit CYP21C8 and CYP2C9. The other metabolite and parent drug are not expected to have an effect on CYP450 metabolism. However, no clinically significant drug interactions have been noted to date with crisaborole.

Due to low blood levels of pimecrolimus (Elidel) and tacrolimus (Protopic) detected after topical application, systemic drug interactions are not expected. However, concomitant administration of known CYP3A4 inhibitors (e.g., erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, and cimetidine) with pimecrolimus or tacrolimus in patients with widespread and/or erythrodermic disease should be done with caution.

Strong inhibitors of CYP3A4 should be avoided due to increased exposure of ruxolitinib (Opzelura) and the risk of increased adverse reactions. Inducers of CYP3A4 may decrease exposure of ruxolitinib.

Drug interaction studies with tralokinumab-ldrm (Adbry) and CYP substrates did not identify significant alterations in CYP substrate drug exposure.

Strong CYP3A4 inhibitors increase the exposure of upadacitinib and when used concomitantly the recommended dose of upadacitinib is 15 mg once daily, monitor closely for adverse reactions. Coadministration of upadacitinib 30 mg once daily with strong CYP3A4 inhibitors for atopic dermatitis is not recommended. Due to reduced exposure of upadacitinib with strong CYP3A4 inducers, coadministration is not recommended.

ADVERSE EFFECTS[60,61,62,63,64,65,66,67]

Drug	Skin Burning (%)	Pruritus (%)	Skin Erythema (%)	Rash (%)
crisaborole (Eucrisa) n=1,012 adults and children	4	-	-	reported
vehicle n=499 adults and children	1			nd
pimecrolimus (Elidel) n=328 adults	25.9	5.5	2.1	0
pimecrolimus (Elidel) n=272 children	8.5	1.8	2.2	4 (viral rash in infants)
vehicle n=75 children	6.7	0	0	0
ruxolitinib (Opzelura)[#] n=499 adults and children vehicle n=250 adults and children	-	-	-	1
tacrolimus 0.1% (Protopic) n=209 adults	58	46	28	2
tacrolimus 0.03% (Protopic) n=210 adults	46	46	25	5
vehicle n=212 adults	26	37	20	1
tacrolimus 0.03% (Protopic) n=118 children	43	41	12	2
vehicle n=116 children	29	27	13	4

Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nd = no data.

[#] Other adverse effects reported for ruxolitinib (incidence ≥1%) were nasopharyngitis, bronchitis, ear infection, eosinophil count increased, diarrhea, folliculitis, tonsillitis, and rhinorrhea.

Abrocitinib (Cibinqo) is a systemic drug associated with various adverse effects not seen with topical products. The most common adverse reactions (incidence ≥ 2%) reported in clinical trials of abrocitinib were nasopharyngitis, nausea, headache, herpes simplex, urinary tract infection, dizziness, acne, vomiting, and increased blood creatine phosphokinase (CPK).

As subcutaneous (SC) agents, dupilumab (Dupixent) and tralokinumab-ldrm (Adbry) are associated with differing adverse effects than those listed above. The most common adverse reactions (incidence ≥ 1%) reported in clinical trials for dupilumab for AD were injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, dry eye, and eosinophilia. As with all therapeutic proteins, dupilumab has the potential for immunogenicity. In atopic dermatitis clinical trials evaluating dupilumab 300 mg every 2 weeks and in patients 6 months to 11 years receiving various doses approximately 6% of patients developed antibodies to dupilumab, with approximately 2% having persistent anti-drug antibody (ADA) responses and 1% with neutralizing antibodies. In pediatric patients 12 to 17 years of age with AD, approximately 16% developed antibodies to dupilumab, of which 5% had neutralizing antibodies.

The most common adverse reactions (incidence ≥ 1%) reported in clinical trials for tralokinumab-ldrm were upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia. Like other therapeutic proteins, it also has the potential for immunogenicity. The ADA incidence for tralokinumab-ldrm across all trial periods was 4.6% with 0.9% being persistent and 1% with neutralizing antibodies.

The most common adverse reactions (incidence ≥ 2%) reported in clinical trials of upadacitinib for the treatment of AD were upper respiratory infection, acne, herpes simplex, headache, increased blood CPK, cough, hypersensitivity, folliculitis, nausea, abdominal pain, pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, myalgia, and influenza-like illness.

SPECIAL POPULATIONS[68,69,70,71,72,73,74,75]

Pediatrics

Crisaborole (Eucrisa) is indicated for patients ≥ 3 months of age.

Pimecrolimus (Elidel) and tacrolimus 0.03% (Protopic) are approved for use in patients ≥ 2 years of age.

Dupilumab (Dupixent) is indicated for patients ≥ 6 months of age.

The safety and effectiveness of tacrolimus ointment 0.1% have not been established in pediatric patients.

The safety and efficacy of ruxolitinib (Opzelura), abrocitinib (Cibinqo), and upadacitinib (Rinvoq) in pediatric patients < 12 years of age have not been established.

Safety and efficacy of tralokinumab-ldrm (Adbry) have not been established in pediatric patients (≤ 18 years of age).

Geriatrics

While clinical trials of abrocitinib did not include sufficient numbers of patients ≥ 65 years of age to determine if therapeutic response is different from that of a younger population, it was noted that a higher proportion of patients ≥ 65 years of age discontinued from clinical trials, experienced platelet counts < 75,000/mm^3 or absolute lymphocyte counts < 500/mm^3, and had a higher incidence of herpes zoster.

Likewise, therapeutic differences were not observed between patients ≥ 65 years of age and younger patients in upadacitinib trials, however patients ≥ 65 years of age in the 30 mg dosing group experienced a higher rate of serious infections and malignancies.

Pregnancy

Pimecrolimus (Elidel) is Pregnancy Category C; tacrolimus (Protopic) was previously Category C, but labeling has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). There are no available adequate well-controlled studied in women for the use of pimecrolimus or tacrolimus in pregnant women.

There are no available data regarding use of crisaborole (Eucrisa) in pregnant women to inform of drug-associated risk of miscarriage or fetal harm.

Available data for use of dupilumab (Dupixent) in pregnant women have not identified a drug-associated fetal or maternal risks. However, as IgG antibodies are known to cross the placenta, dupilumab may be transferred to the developing fetus. A pregnancy exposure registry has been established to monitor pregnant women exposed to dupilumab.

Data on abrocitinib (Cibinqo) and ruxolitinib (Opzelura) use in pregnant women are insufficient to inform of a drug-associated maternal or fetal risk. Enrollment in the pregnancy registry is recommended to monitor pregnancy outcomes. Due to the risks for serious adverse events, including infections, thrombocytopenia, anemia, and neutropenia, women should be advised not to breastfeed.

Data for tralokinumab-ldrm (Adbry) in pregnancy are inadequate to advise of maternal or fetal risk; however, no maternal or embryofetal toxicity was observed in animal studies.

Data for upadacitinib (Rinvoq) in pregnancy are inadequate to advise of maternal or fetal risk; however, animal studies suggest upadacitinib has the potential to adversely affect a developing fetus and carries a warning for embryo-fetal toxicity. Effective contraception is recommended during treatment and for 4 weeks following the final dose.

Renal Impairment

Due to increased exposure in renal impairment, abrocitinib (Cibinqo) is not recommended in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min) and end stage renal disease (ESRD), including those on renal replacement therapy. Clinical trials excluded patients with baseline creatinine clearance < 40 mL/min. Dose reduction is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/min).

The maximum recommended dose of upadacitinib (Rinvoq) in patients with severe renal impairment (eGFR 15 to < 30 mL/min) is 15 mg once daily. Use in patients with ESRD (eGFR < 15 mL/min) is not recommended.

Hepatic Impairment

Abrocitinib and upadacitinib were not studied in patients with severe (Child Pugh C) hepatic impairment, and use in this population should be avoided.

Immunocompromised

Neither pimecrolimus (Elidel), ruxolitinib (Opzelura), nor tacrolimus (Protopic) should be used in adult and pediatric patients who are immunocompromised.

DOSAGES[76,77,78,79,80,81,82,83]

Drug	Dosing	Availability
abrocitinib (Cibinqo)	Adults and children ≥ 12 years of age: 100 mg orally once daily; dose may be increased to 200 mg once daily if an adequate response is not achieved in 12 weeks Patients with moderate renal impairment (eGFR 30 to 59 mL/min): 50 mg once daily; maximum dose 100 mg once daily Poor CYP2C19 metabolizers or patients taking strong CYP2C19 inhibitors: 50 mg once daily; maximum dose 100 mg once daily	Tablets: 50 mg, 100 mg, 200 mg
crisaborole 2% (Eucrisa)	Adults and children ≥ 3 months of age: apply a thin layer to affected skin twice daily	Ointment: 60 g, 100 g tubes
dupilumab (Dupixent)	Adults and children 6 to 17 years of age and weighing ≥ 60 kg: 600 mg (2 x 300 mg subcutaneous [SC] injections at different sites) for 1 dose, followed by 300 mg every other week thereafter Children 6 to 17 years of age and weight 30 kg to < 60 kg: 400 mg (2 x 200 mg SC injection at different injection sites) for 1 dose, followed by 200 mg every other week thereafter Children 6 to 17 years of age and weight 15 kg to < 30 kg: 600 mg (2 x 300 mg SC injection at different injection sites) for 1 dose, followed by 300 mg every 4 weeks thereafter Children 6 months to 5 years of age and weight 15 kg to < 30 kg: 300 mg every 4 weeks Children 6 months to 5 years of age and weight 5 kg to < 15 kg: 200 mg every 4 weeks Administer subcutaneously in the thigh, abdomen (excluding area around the navel), or upper arm; rotate the injection site May be used with or without topical corticosteroids May be used with or without topical calcineurin inhibitors, but use of these should be reserved for problem areas only (e.g., face, neck, intertriginous and genital areas) May be administered by the patient or caregiver following proper training; caregivers should administer the dose in patients 6 months to 11 years old Prefilled pens are only for patients ≥ 2 years of age	Single-dose, prefilled syringe for SC injection: 100 mg/0.67 mL, 200 mg/1.14 mL, 300 mg/2 mL Single-dose, prefilled pen for SC injection: 200 mg/1.14 mL, 300 mg/2 mL
pimecrolimus 1% (Elidel)	Adults and children ≥ 2 years of age: apply a thin layer to affected skin twice daily	Cream: 30 g, 60 g, and 100 g tubes
ruxolitinib (Opzelura)	Adults and children ≥ 12 years of age: apply a thin layer twice daily to affected areas of up to 20% body surface area; do not use more than 60 grams per week	Cream: 60 g tube
tacrolimus 0.03% (Protopic)	Adults and children ≥ 2 years of age: apply a thin layer to affected skin twice daily	Ointment: 30 g, 60 g, and 100 g tubes
tacrolimus 0.1% (Protopic)	Adults: Apply a thin layer to affected skin twice daily	Ointment: 30 g, 60 g, and 100 g tubes

Dosages (continued)

Drug	Dosing	Availability
tralokinumab-ldrm (Adbry)	Adults: 600 mg (4 x 150 mg SC injections), followed by 300 mg (2 x 150 mg SC injections at different sites in same area) administered every other week; After 16 weeks of treatment, in patients weighing < 100 kg who achieve clear or almost clear skin, a dosage of 300 mg (2 x 150 mg SC injections at different sites in same area) every 4 weeks may be considered Administer SC in the thigh, abdomen (excluding area around the navel), or upper arm; rotate the injection site; may be self-administered after proper training May be used with or without topical corticosteroids; may be used with or without topical calcineurin inhibitors, but use of these should be reserved for problem areas only (e.g., face, neck, intertriginous and genital areas)	Single-dose, prefilled syringe for SC injection with needle guard: 150 mg/mL
upadacitinib (Rinvoq)	Adults < 65 years of age and pediatric patients ≥ 12 years of age and weighing ≥ 40 kg: 15 mg once daily; maximum dose 30 mg once daily Adults ≥ 65 years of age, patients with severe renal impairment, patients taking strong CYP3A4 inhibitors: 15 mg once daily	Extended-release tablets: 15 mg, 30 mg, 45 mg

Pimecrolimus (Elidel) cream and tacrolimus (Protopic) ointment are not associated with skin atrophy and therefore, can be used on sensitive areas such as the face, neck, and skin folds.[84,85] Avoid contact with eyes or mouth.

Discontinue the use of pimecrolimus (Elidel) cream, ruxolitinib (Opzelura), and tacrolimus (Protopic) ointment when signs and symptoms (e.g., itch, rash, redness) have resolved. If no improvement with pimecrolimus or tacrolimus within 6 weeks or 8 weeks with ruxolitinib, patients should be reexamined by their healthcare provider.

All age-appropriate vaccinations should be completed prior to starting treatment with abrocitinib (Cibinqo), dupilumab (Dupixent), tralokinumab-ldrm (Adbry), and upadacitinib (Rinvoq).

Both dupilumab and tralokinumab-ldrm should be stored in the refrigerator and allowed to reach room temperature before injection. After removal from the refrigeration, both dupilumab and tralokinumab-ldrm should be used within 14 days or discarded.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the

potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Comparative studies of topical treatments that are investigator-blinded have not been included.[86,87,88]

abrocitinib (Cibinqo) versus placebo

JADE MONO-1 (NCT03349060); JADE MONO-2 (NCT03575871): The safety and efficacy of abrocitinib for the treatment of atopic dermatitis were evaluated in 2 multicenter, randomized, placebo-controlled, phase 3 trials.[89,90] Eligible subjects were aged ≥ 12 years with a confirmed diagnosis of moderate-to-severe atopic dermatitis and inadequate response in the previous 6 months to treatment with topical corticosteroids or calcineurin inhibitors for ≥ 4 weeks (or for whom topical treatments were medically inadvisable). Topical therapies for atopic dermatitis other than non-medicated emollients were not permitted during the study. Patients were randomly assigned in each trial 2:2:1 to receive once daily abrocitinib 100 mg (n=156; n=155), abrocitinib 200 mg (n=154; n=155), or matching placebo (n=77; n=77). The coprimary efficacy endpoints were the proportion of patients who achieved an Investigator Global Assessment (IGA) response (score of 0 [clear] or 1 [almost clear] and a ≥ 2 grade improvement from baseline), and the proportion of patients with ≥ 75% improvement from baseline in Eczema Area and Severity Index score (EASI-75) at week 12 of treatment. In JADE MONO-1, 24% of patients in the abrocitinib 100 mg group (difference from placebo, 16%; 95% confidence interval [CI], 6.8 to 24.8; p=0.0037), 44% of patients in the abrocitinib 200 mg group (difference from placebo, 36%; 95% CI, 26.2 to 45.7; p<0.0001), and 8% of placebo patients achieved an IGA response. EASI-75 response at week 12 was achieved by 40% of patients in the abrocitinib 100 mg group (difference from placebo, 27.9%; 95% CI, 17.4 to 38.3; p<0.0001), 63% of patients in the abrocitinib 200 mg group (difference from placebo, 51%; 95% CI, 40.5 to 61.5; p<0.0001), and 12% of patients in the placebo group. In JADE MONO-2, an IGA response at week 12 was achieved by 38.1%, 28.4%, and 9.1% of patients in the abrocitinib 200 mg and 100 mg groups, and placebo group, respectively. Differences from placebo were 19.3% (95% CI, 9.6 to 29; p<0.001) for the 100 mg group and 28.7% (95% CI, 18.6 to 38.8; p<0.001) for the 200 mg group. In the 100 mg group and 200 mg groups, 44.5% and 61% of patients, respectively, achieved an EASI-75, compared with 10.4% of placebo patients. Differences from placebo were 33.9% (95% CI, 23.3 to 44.4; p<0.001) for the 100 mg group and 50.5% (95% CI, 40 to 60.9; p<0.001) for the 200 mg group.

crisaborole (Eucrisa) versus vehicle in adults and pediatrics

Two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials (AD-301 and AD-302) included a total of 1,522 patients with AD affecting a 5% to 95% treatable body surface area (BSA).[91,92] The subjects ranged from 2 to 79 years of age, 86.3% of which were from 2 to 17 years of age. On the Investigator's Static Global Assessment (ISGA) severity scale of 0 to 4, 38.5% of the subjects had a score of 2 (mild), and 61.5% had an ISGA score of 3 (moderate) in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) at baseline. In both trials, subjects were randomized 2:1 to receive crisaborole or vehicle applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at Day 29 who achieved an ISGA grade of clear (score of 0) or almost clear (score of 1) with a 2-grade or greater improvement from baseline. The primary efficacy endpoint was achieved in more crisaborole-treated subjects versus vehicle-treated subjects (AD-301: 32.8% versus 25.4%, p=0.038; AD-302: 31.4% versus 18%; p<0.001). More crisaborole-treated subjects achieved an ISGA score of clear (0) or almost clear (1) versus vehicle-treated subjects at Day 29 (AD-301: 51.7% versus 40.6%, p=0.005; AD-302: 48.5% versus 29.7%, p<0.001). At Day 29, pooled data showed crisaborole improved disease severity versus vehicle-treated patients as evidenced by a reduction in

signs and symptoms of AD including pruritus (p=0.002), erythema (p<0.001), exudation (p=0.001), excoriation (p<0.001), induration/papulation (p=0.002), and lichenification (p<0.001). Crisaborole was well tolerated, with similar incidence of adverse effects as the vehicle.

A 4-week open-label trial studied the safety, efficacy, and pharmacokinetics of crisaborole 2% ointment in 137 patients 3 months to 2 years with mild to moderate AD with ≥ 35% treatable BSA.[93] Crisaborole was well-tolerated in terms of adverse events in this age group.

dupilumab (Dupixent) versus placebo in adults

Two randomized, 16-week, double-blind, placebo-controlled, phase 3 trials established the safety and efficacy of dupilumab for the treatment of AD (SOLO 1, n=671; and SOLO 2, n=708).[94,95] In both trials, adults with moderate to severe AD for which topical treatment provided inadequate control or was medically inadvisable and with chronic AD for ≥ 3 years prior to screening were randomized 1:1:1 to subcutaneous (SC) dupilumab 300 mg or placebo weekly or dupilumab 300 mg every 2 weeks. Concomitant topical corticosteroids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants were prohibited. Rescue treatment for AD was available in select circumstances. Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥ 3 (range, 0 to 4) in the overall assessment of AD lesions, an EASI score ≥ 16 (range, 0 to 72), and a minimum BSA involvement of ≥ 10%. The primary outcome was the proportion of patients with a score of 0 or 1 (clear or almost clear) on the IGA and a reduction of ≥ 2 points from baseline at 16 weeks. In SOLO 1, this primary endpoint occurred in 38% of patients receiving every other week dupilumab, 37% of patients receiving weekly dupilumab, and 10% of patients receiving placebo (p<0.001 for both dupilumab regimens versus placebo). In SOLO 2, this primary endpoint occurred in 36% of patients receiving every other week dupilumab, 36% of patients receiving weekly dupilumab, and 8% of patients receiving placebo (p<0.001 for both dupilumab regimens versus placebo). In both trials, an improvement from baseline to 16 weeks of ≥ 75% on the EASI was also higher in patients receiving dupilumab compared to placebo (p<0.001). Injection-site reactions and conjunctivitis were reported more frequently with dupilumab compared to placebo. Notably, only the dupilumab every other week regimen is FDA-approved.

LIBERTY AD CHRONOS: A third trial with similar methodology compared 52 weeks of dupilumab 300 mg once weekly, once every 2 weeks, or placebo in adults with moderate to severe AD not adequately controlled by topical medications; however, in both groups, patients also received background topical corticosteroids (n=740).[96] Patients were also permitted to receive as needed topical calcineurin inhibitors for problem areas only (e.g., face, neck, intertriginous and genital areas). The primary outcome was the proportion of patients with a score of 0 or 1 (clear or almost clear) on the IGA and a reduction of ≥ 2 points from baseline at 16 weeks. The primary endpoint occurred in 39% of patients receiving dupilumab compared to 12% of patients receiving placebo (p<0.0001). In addition, an improvement from baseline to 16 weeks of ≥ 75% on the EASI was also higher in patients receiving dupilumab compared to placebo (64% or 69% versus 23%, respectively; p<0.0001). Adverse events were reported more often in the dupilumab groups than placebo.

LIBERTY AD SOLO-CONTINUE: A randomized, double-blind, phase 3 clinical trial (NCT02395133) included patients (n=422) with moderate to severe AD who received dupilumab and achieved an IGA score of 0 or 1 or 75% improvement in EASI-75 at week 16 in LIBERTY AD SOLO 1 and 2.[97] Patients were re-randomized 2:1:1:1 in SOLO-CONTINUE to continue their original regimen of dupilumab 300 mg weekly or every 2 weeks, 300 mg every 4 or 8 weeks, or placebo for 36 weeks to determine the safety and

efficacy of various dupilumab regimens. Patients on once weekly or every 2 week treatment achieved minimal change in percent EASI improvement versus placebo (-0.06%; p<0.001) while the other regimens worsened (every 4-week treatment: -3.84%; every 8-week treatment: -6.84%; placebo: -21.67%). EASI-75 was better maintained in the weekly or every 2-week treatment group (116 of 162 [71.6%]; p<0.001 versus placebo) compared to the 4-week (49 of 84 [58.3%]) or 8-week treatment group (45 of 82 [54.9%]) or placebo (24 of 79 [30.4%]). No new treatment-emergent side effects were observed. Every 2-week treatment is recommended for long-term use.

dupilumab (Dupixent) versus placebo in pediatrics

The efficacy and safety of dupilumab monotherapy was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (NCT03054428) in adolescent patients 12 to 17 years of age (n=251) with moderate-to-severe AD and a minimum BSA involvement of ≥ 10% (mean 57%).[98] Patients had previous inadequate response to topical medication. Patients who weighed < 60 were started on dupilumab 400 mg at week 0, followed by 200 mg every 2 weeks for 16 weeks; those weighing ≥ 60 kg were started on dupilumab 600 mg at week 0, followed by 300 mg every 2 weeks for 16 weeks. At week 16, the proportion of patients with IGA 0 or 1 was 24% with dupilumab and 2% with placebo. EASI-75 and EASI-90 were reported in 42% and 23% of dupilumab-treated patients, respectively, compared to 8% and 2% of patients who received placebo, respectively. Peak Pruritus Numeric Rating Scale (NRS) with ≥ 4-point improvement was reported as 37% with dupilumab and 5% with placebo. Patients who received rescue treatment were considered non-responders (59% with dupilumab and 21% with placebo).

The efficacy and safety of dupilumab was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (NCT03345914) in children ages 6 to 11 years (n=367) with AD, an IGA score of 4, and a minimum BSA involvement of ≥ 15% (mean 57%).[99] Included patients had previous inadequate response to topical medication and were stratified by weight. Patients were assigned to dupilumab or placebo, both with background topical corticosteroids and with dupilumab dosed as 200 mg on day 1, then 100 mg every 2 weeks for those < 30 kg 400 mg on day 1, then 200 mg every 2 weeks for those ≥ 30 kg. At week 16, the proportion of patients with IGA 0 or 1 was 30% and 39% with dupilumab and 13% and 10% with placebo for those weighing < 30 kg and ≥ 30 kg, respectively. EASI-75 was reported in 75% of dupilumab-treated patients compared to 28% and 26% with placebo for those weighing < 30 kg and ≥ 30 kg, respectively. EASI-90 was reported in 46% and 36% of dupilumab-treated patients compared to 7% and 8% with placebo for those weighing < 30 kg and ≥ 30 kg, respectively.

The efficacy and safety of dupilumab was evaluated in a randomized, multicenter, double-blind, placebo controlled trial (Liberty AD PRESCHOOL; NCT03346434) in 162 patients aged 6 months to 5 years with moderate-to-severe AD and an inadequate response to topical corticosteroids.[100] Participants were randomized 1:1 to receive dupilumab (n=83) or placebo (n=79); all patients also received a low-potency topical corticosteroid. In patients weighing 5 kg to < 15 kg, the dupilumab dose was 200 mg SC every 4 weeks and in patients weighing 15 kg to < 30 kg, the dupilumab dose was 300 mg SC every 4 weeks. The proportion of patients with IGA score 0 to 1 (clear or almost clear skin) at week 16, the primary endpoint, was greater in the dupilumab group than with placebo (28% versus 4%; difference, 24%; 95% CI, 13 to 34; p<0.0001). The key secondary endpoint, the proportion of patients achieving EASI-75 was also greater in dupilumab-treated patients (53%) versus placebo (11%) with a between-group difference of 42% (95% CI, 29 to 55, p<0.0001). While overall prevalence of adverse events was similar between groups, more patients in the dupilumab group experienced conjunctivitis.

pimecrolimus (Elidel) versus topical corticosteroids in adults

A randomized, double-blind, multicenter European study compared the long-term safety and tolerability of pimecrolimus 1% cream and topical corticosteroid (TCS) in 658 adults with moderate-severe AD.[101] Patients applied either pimecrolimus or TCS (e.g., triamcinolone acetonide 0.1% cream and/or hydrocortisone acetate 1% cream) twice daily to all affected areas until complete clearance or for up to 1 year. A majority of patients treated with either pimecrolimus or TCS used the drug on a continuous basis over 1 year. In patients who had greater than 30% BSA involvement, the incidence rate of all skin infections was significantly lower in the pimecrolimus group than in the TCS group (95% confidence interval [CI] of the treatment difference: -25.3% to -3.4%). The most frequent application site reaction was burning (25.9% pimecrolimus and 10.9% TCS). Three TCS-treated patients reported skin striae. Efficacy was better in patients on continuous TCS therapy, although patients completing the study were similarly well-controlled in both groups. About 42% of the pimecrolimus-treated patients were maintained for 1 year without TCS.

abrocitinib (Cibinqo) versus dupilumab (Dupixent) in adults

A randomized, double-blind, active-controlled, phase 3 trial compared the safety and efficacy of abrocitinib with dupilumab in adults to moderate-to-severe atopic dermatitis.[102] Eligible participants had an affected surface area ≥ 10% and had required systemic therapies for disease control within the past year or had an inadequate response to ≥ 4 consecutive weeks of medicated topical therapy within the past 6 months. Except for rescue therapy, only low- or medium-potency topical corticosteroids and non-medicated topical therapy were permitted during the study. Participants were randomized 1:1 to receive abrocitinib 200 mg once daily plus dupilumab matching placebo (n=362) or dupilumab 300 mg SC every 2 weeks and abrocitinib matching placebo (n=365). Response in Peak Pruritus Numerical Rating Scale (PP-NRS4) at week 2 and 90% improvement in EASI (EASI-90) at week 4 were the primary endpoints. More patients in the abrocitinib group achieved a PP-NRS4 response than in the dupilumab group (48% versus 26%; difference, 22.6%; 95% CI, 15.8 to 29.5; p<0.0001). Achievement of EASI-90 was also higher in the abrocitinib group (29%) than in the dupilumab group (15%) with a between-group difference of 14.1% (95% CI, 8.2 to 20; p<0.0001) and statistical significance was maintained at week 16. More patients in the abrocitinib group (74%) experienced adverse events than in the dupilumab group (65%), however the proportion of patients experiencing serious adverse events or adverse events leading to study discontinuation were similar between groups.

pimecrolimus (Elidel) versus vehicle in pediatrics

A double-blind, randomized study assessed the time of onset of pruritus improvement in 174 children and adolescents (aged 2 to 17 years) with mild to moderate AD with moderate to severe pruritus.[103] In the 8-day study, patients applied twice daily pimecrolimus 1% cream or vehicle control. Pruritus was assessed by subjects using a 4-point pruritus severity scale (0 to 3). The primary outcome parameter, the time to a 1-point or more improvement from baseline for the pruritus score, was 48 hours in the pimecrolimus group and 72 hours for the vehicle group (p=0.038). From day 3 onward, significantly more patients receiving pimecrolimus had complete pruritus resolution compared to those receiving vehicle (p=0.023). At the end of the seven-day treatment, significantly more patients in the pimecrolimus group had improved or completed resolution of pruritus compared to the group assigned to the vehicle control (p=0.008).

A randomized, double-blind, multicenter study compared twice daily pimecrolimus cream 1% to vehicle cream in 521 patients aged 2 to 17 years, with a history of mild or moderate AD.[104] These patients were clear or almost clear of disease prior to randomization. Treatment was initiated at the first signs and/or symptoms of recurring AD. A moderately potent TCS was allowed in both groups if AD worsened (as confirmed by the investigator) despite the application of study medication for at least 3 days. The primary efficacy endpoint was the number of days on study without TCS use for a flare. The mean number of TCS-free days was significantly higher ($p<0.0001$) in the pimecrolimus group compared to the vehicle group (160.2 versus 137.7 days, respectively). Patients treated with pimecrolimus cream 1% experienced 50% fewer flares requiring topical corticosteroids than patients who received vehicle cream (mean number of flares 0.84 versus 1.68, respectively; $p<0.0001$).

A randomized, double-blind study of less than or equal to 6 weeks, followed by a 6-week, open-label phase compared pimecrolimus cream 1% to vehicle twice daily in 200 children aged 2 to 11 years with mild to moderate facial AD dependent on or intolerant of topical corticosteroids.[105] Patients were treated with the pimecrolimus cream or vehicle twice daily until clearance of facial AD or for a maximum of 6 weeks. Significantly more patients on pimecrolimus compared to vehicle patients were cleared/almost cleared of facial AD (IGA 0/1) on day 22 (57.1% versus 36.0%; $p=0.004$) and day 43 (74.5% versus 51%; $p<0.001$). Median time to clearance was 22 days compared to 43 days for the pimecrolimus group versus the vehicle group, respectively. Statistically significant differences for pimecrolimus compared with vehicle were also seen on head and neck EASI, overall EASI, and head and neck pruritus scores. There were no differences in adverse events between treatment groups.

pimecrolimus (Elidel) versus hydrocortisone in pediatrics

In the 1-year, controlled, double-blind study, 713 AD patients ages 2 to 17 years were randomized 2:1 to a pimecrolimus-based or conventional AD regimen consisting of vehicle and topical corticosteroids.[106] The proportion of patients who completed 6 or 12 months with no flares was approximately twice as high in the pimecrolimus group compared with control (61% versus 34.2% at 6 months; 50.8% versus 28.3% at 12 months). Fewer flares were observed in the pimecrolimus group regardless of baseline disease severity. There were no appreciable differences between treatment groups in the overall incidence of adverse events. The authors concluded that pimecrolimus ointment appears to be safe and effective in children with atopic dermatitis.

ruxolitinib (Opzelura) versus vehicle in patients ≥ 12 years of age

Efficacy and safety of ruxolitinib cream were evaluated in 2 identical, double-blind, randomized, vehicle-controlled, phase 3 trials (TRuE-AD1: NCT03745638 and TRuE-AD1: NCT03745651).[107] Patients aged ≥ 12 years with AD for ≥ 2 years with 3% to 20% affected BSA (excluding scalp) and an IIGA score of 2 (mild) to 3 (moderate) were randomized 2:2:1 to 0.75% ruxolitinib cream (n=500), 1.5% ruxolitinib cream (n=498), or vehicle cream (n=250) twice daily for 8 weeks. The primary efficacy endpoint was IGA treatment success (IGA-TS) at week 8, defined as IGA score of 0 (clear) or 1 (almost clear) and ≥ 2-grade improvement from baseline. More patients in both trials achieved the primary endpoint with 0.75% ruxolitinib cream (50% and 39%, TRuE-AD1 and TRuE-AD2, respectively) and 1.5% ruxolitinib cream (53.8% and 51.3%, respectively) compared to the vehicle cream (15.1% and 7.6%, respectively; all $p<0.0001$). During the 8-week study period, ruxolitinib cream was well tolerated. The ruxolitinib 0.75% strength is not FDA approved at this time.

tacrolimus (Protopic) versus topical corticosteroids in adults

A randomized, double-blind study compared the efficacy and safety of twice daily tacrolimus ointment 0.1% to a corticosteroid ointment regimen in 972 adults with moderate to severe AD, for a maximum of 6 months.[108] Tacrolimus ointment was applied to all affected areas over the whole body. For the corticosteroid group, hydrocortisone butyrate ointment 0.1% was applied to affected areas on the trunk and extremities, and hydrocortisone acetate ointment 1% was applied to affected areas on the face and neck. The study primary endpoint was the response rate defined as the proportion of patients with at least 60% improvement in the modified Eczema Area and Severity Index (mEASI) between baseline and month 3. More patients in the tacrolimus group responded to treatment by the third month compared to the corticosteroid group, 72.6% versus 52.3%, respectively ($p<0.001$). The tacrolimus patients also showed greater improvement in mEASI, EASI, affected BSA, and physician and patient assessments of global response. More patients in the tacrolimus group experienced skin burning compared to the corticosteroid group, 52.4% versus 13.8%, respectively ($p<0.001$). Skin burning was mild to moderate in severity and decreased rapidly after the first week of treatment in the majority of patients. There was no increase in the incidence of infections or malignancies over time in either treatment group.

A 3-week randomized, double-blind, parallel-group, multicenter study compared twice daily tacrolimus 0.03% and 0.1% ointment with hydrocortisone 17-butyrate 0.1% ointment in the treatment of 570 adults with moderate to severe AD.[109] Patients applied ointment twice daily to all affected areas for 3 weeks. The primary outcome of median mEASI mean area under the curve as a percentage of baseline was 47%, 36.5%, and 36.1% for patients who received 0.03% tacrolimus, 0.1% tacrolimus, and 0.1% hydrocortisone butyrate, respectively. There was no statistically significant difference between 0.1% tacrolimus and 0.1% hydrocortisone butyrate. The lower improvement in mEASI for 0.03% tacrolimus was statistically significant when compared with 0.1% tacrolimus ($p<0.001$) or hydrocortisone butyrate ($p=0.002$). The tacrolimus groups had more skin burning and pruritus at the application site compared to the hydrocortisone butyrate group ($p<0.05$).

tacrolimus (Protopic) versus vehicle in pediatrics

The safety and efficacy of tacrolimus 0.03% and 0.1% ointment for the treatment of AD were evaluated in a 12-week, randomized, double-blind, vehicle-controlled study of 351 children 2 to 15 years of age with moderate to severe AD.[110] The mean percentage of BSA affected was 47.7%. Significantly more patients ($p<0.001$) achieved clinical improvement of 90% or better with tacrolimus 0.03% or 0.1% ointment compared with vehicle. Significant improvements in the signs and symptoms of AD, percent BSA affected, and the patient's/caregiver's assessment of pruritus were also observed early in treatment and were maintained throughout the study. Adverse events with a statistically significantly greater incidence in the tacrolimus 0.03% ointment treatment group compared with vehicle were limited to the sensation of skin burning, pruritus, varicella, and vesiculobullous rash ("blisters"). No adverse event occurred at a statistically higher incidence in the tacrolimus 0.1% ointment-treated group compared with vehicle. Both tacrolimus ointment concentrations were safe and significantly more effective than vehicle for the treatment of AD in children.

In the randomized, double-blind, vehicle-controlled multicenter trial, children ages 7 to 16 years were treated with tacrolimus 0.03%, 0.1%, or 0.3% ointment twice daily or vehicle for up to 22 days with a 2-week follow-up period.[111] The Physician's Global Evaluation of clinical response showed that 69% of patients in the 0.03% tacrolimus group, 67% in the 0.1% tacrolimus group, and 70% in the 0.3% tacrolimus group, compared with 38% in the vehicle group, had a marked to excellent (>75%)

improvement or clearing of their AD (p=0.005, p=0.007, and p=0.004, respectively, for the 3 tacrolimus groups compared with the vehicle group). The mean percent improvement for the modified EASI at end of treatment for each of the tacrolimus groups (0.03%, 72%; 0.1%, 77%; and 0.3%, 81%) was significantly greater than that of the vehicle group (26%, p<0.001). The median percentage reduction in pruritus was significantly greater for tacrolimus-treated patients (74% to 89%) than for vehicle-treated patients (51%, p=0.027).

tacrolimus (Protopic) versus hydrocortisone in pediatrics

The efficacy and safety of tacrolimus 0.03% ointment applied once or twice daily over a 3-week period were compared with the twice daily application of hydrocortisone acetate 1% ointment in children with moderate to severe AD.[112] The primary study endpoint was the percentage change in the modified EASI between baseline and treatment end. Patients ages 2 years to 15 years were randomized in the double-blinded study to tacrolimus 0.03% ointment once daily (n=207) or twice daily (n=210) or hydrocortisone acetate 1% twice daily (n=207). By the end of treatment, application of tacrolimus 0.03% ointment both once or twice daily resulted in significantly greater median percentage decreases in modified EASI (66.7% and 76.7%, respectively) compared with hydrocortisone acetate 1% (47.6%; p<0.001). Furthermore, the median percentage decrease in modified EASI was significantly greater for patients applying 0.03% tacrolimus twice daily compared with once daily (p=0.007). Patients with severe AD benefited especially from twice daily application of 0.03% tacrolimus ointment compared with once daily application (p=0.001). Transient mild to moderate skin burning occurred significantly more often in the tacrolimus groups but resolved in most cases within 3 to 4 days (p=0.028).

tacrolimus (Protopic) versus fluticasone in pediatrics

A randomized, double-blind, non-inferiority trial compared tacrolimus 0.03% ointment to fluticasone 0.005% ointment in 479 children ages 2 to 15 years old with moderate to severe AD who had not responded sufficiently to conventional therapies.[113] Ointments were applied twice daily until clearance or for a maximum of 3 weeks and, if lesions remained, once daily for up to 3 weeks further. Primary endpoint was week 3 response rate (improvement of ≥ 60% in mEASI and not withdrawn for lack of efficacy). Response rates were 86.3% and 91.5% with tacrolimus and fluticasone, respectively. Lower limit of the 95% CI was -11.8%, which exceeded the non-inferiority limit of -15% and met the primary endpoint. Moderate or better improvement on secondary endpoints of the physicians' global assessment occurred in 93.6% and 92.4% of patients in the tacrolimus and fluticasone groups, respectively, while median pruritus scores improved by 84% and 91.5%, respectively. Sleep quality improved by approximately 92% in both treatment groups. After day 21, new flare-up occurred in 5.5% and 11.3% of patients receiving tacrolimus and fluticasone, respectively. Mean times to new flares were 6.5 ± 5 days and 8.6 ± 5.2 days. Adverse events were similar between the 2 arms but burning at application-site was higher in the tacrolimus arm.

tralokinumab (Adbry) versus placebo in adults

The safety and efficacy of tralokinumab was assessed in 3controlled trials, ECZTRA 1 (n=802), ECZTRA 2 (n=794), and ECZTRA 3. ECZTRA 1 and ECZTRA 2 were identically designed 52-week, randomized, double-blind, placebo-controlled, phase 3 trials that evaluated tralokinumab-ldrm monotherapy in adult patients with moderate-to-severe AD with an inadequate response to topical treatments.[114] Eligible patients were randomized 3:1 to SC tralokinumab 600 mg loading dose followed by 300 mg every other week or placebo for 16 weeks. The primary endpoints were IGA score of 0 (clear) or 1 (almost clear) at

week 16 and ≥ 75% improvement in EASI-75 at week 16. After the initial treatment period, tralokinumab-treated patients who achieved an IGA score of 0 or 1, or EASI-75 were rerandomized 2:2:1 to tralokinumab 300 mg every 2 weeks, tralokinumab 300 mg every 4 weeks, or placebo for maintenance for the duration of the study. Maintenance endpoints were maintenance of IGA score of 0 or 1 and EASI-75 at week 52. At 16 weeks, the primary endpoints occurred at a higher rate in the tralokinumab-treated patients compared to the placebo, respectively. In ECZTRA 1, IGA 0 or 1 was achieved by 15.8% versus 7.1% (difference, 8.6%; 95% CI, 4.1 to 13.1; p=0.002) and in ECZTRA 2, by 22.2% versus 10.9% (difference, 11.1%; 95% CI, 5.8 to 16.4; p<0.001). In ECZTRA 1, EASI-75 was achieved by 25% versus 12.7% (difference, 12.1%; 95% CI, 6.5 to 17.7; p<0.001) and in ECZTRA 2, by 33.2% versus 11.4% (difference, 21.6%; 95% CI, 15.8 to 27.3; p<0.001). At week 52, a majority of tralokinumab 16-week responders maintained clinical response with continued tralokinumab treatment without any rescue medication (including TCS). In ECZTRA 1 AND ECZTRA 2, 51% and 59%, respectively, of patients who continued tralokinumab every other week, and 39% and 45%, respectively, of those who changed to tralokinumab every 4 weeks maintained IGA response at 52 weeks without any use of rescue medication. In addition, 47% and 25% who switched from every other week tralokinumab to placebo maintained IGA response without rescue medication at week 52 in ECZTRA 1 and ECZTRA 2, respectively. Likewise, in ECZTRA 1 AND ECZTRA 2, 60% and 56%, respectively, of patients who continued tralokinumab every other week, and 49% and 51%, respectively, of those who changed to tralokinumab every 4 weeks maintained EASI-75 response at 52 weeks without any use of rescue medication, compared to 33% and 21%, respectively who switched from every other week tralokinumab.

ECZTRA 3 was a 32-week double-blind, placebo-controlled phase 3 trial that evaluated tralokinumab in combination with TCS in adult patients with moderate-to-severe AD who were candidates for systemic therapy.[115] Eligible patients were randomized 2:1 to SC tralokinumab 600 mg loading dose followed by 300 mg every other week or placebo for 16 weeks. Patients in both groups received TCS as needed, once daily. The primary endpoints were IGA score of 0 or 1 at week 16 and EASI-75 at week 16. After the initial treatment period, tralokinumab-treated patients who achieved an IGA score of 0 or 1, or EASI-75 on tralokinumab were rerandomized 1:1 to tralokinumab 300 mg every 2 weeks or tralokinumab 300 mg every 4 weeks for maintenance for the duration of the study. Patients who achieved an IGA score of 0 or 1, or EASI-75 with placebo continued to receive placebo. Maintenance endpoints were maintenance of IGA score of 0 or 1 and EASI-75 at week 32. At 16 weeks, the primary endpoints occurred at a higher rate in the tralokinumab-treated patients compared to the placebo, respectively. At week 16, IGA 0 or 1 was achieved by 38.9% versus 26.2% (difference, 12.4%; 95% CI, 2.9 to 21.9; p=0.015) and EASI-75 was achieved by 56% versus 35.7% (difference, 20.2%; 95% CI, 9.8 to 30.6; p<0.001). At week 32, among the 16-week responders, an IGA response of 0 or 1 was maintained without rescue therapy (topical and systemic medications) with tralokinumab every 2 weeks and every 4 weeks in 89.6% (95% CI, 77.8 to 95.5) and 77.6% (95% CI, 64.1 to 87), respectively, and EASI-75 was maintained in 92.5% (95% CI, 83.7 to 96.8) and 90.5% (95% CI, 81.3 to 95.7), respectively.

upadacitinib (Rinvoq) versus placebo

The safety and efficacy of upadacitinib were established in three phase 3, multicenter, randomized, double-blind trials (AD-1 [Measure Up 1], AD-2 [Measure Up 2], AD-3 [AD Up]; NCT03569293, NCT03607422, and NCT03568318, respectively) in 2,584 patients with moderate to severe atopic dermatitis not controlled by topical medications and who were ages 12 years and older.[116,117,118] Included patients had a validated Investigator's Global Assessment (vIGA-AD) score ≥ 3 in the overall assessment (range, 0 to 4), an Eczema Area and Severity Index (EASI) score ≥ 16, a minimum involvement

of ≥ 10% BSA, and weekly average Worst Pruritus Numerical Rating Scale (NRS) score ≥ 4. In all trials, patients were randomized to upadacitinib 15 mg or 30 mg or placebo for 16 weeks. The AD-1 and AD-2 trials were monotherapy trials, while patients in AD-3 also received concomitant topical corticosteroids. The co-primary endpoints were the proportion of patients with a vIGA-AD score of 0 (clear) or 1 (almost clear) with a ≥ 2-point improvement and the proportion of patients with improvement of ≥ 75% in EASI score from baseline (EASI-75) at 16 weeks. Baseline characteristics across all 3 trials were 57% male, 69% White, and a mean age of 34 years (range, 12 to 75 years; 13% were < 18 years). At baseline, 49% had a vIGA-AD score of 3 (moderate), 51% had a vIGA-AD score of 4 (severe), a baseline mean EASI score of 29, a baseline weekly Worst Pruritus NRS score of 7, and 52% had a prior exposure to systemic AD treatment. At week 16, the placebo subtracted difference in patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 40% (95% CI, 33 to 46) in AD-1 and 34% (95% CI, 28 to 40) in AD-2.[119,120,121] The placebo subtracted difference in those treated with 30 mg was 54% (95% CI, 47 to 60) in AD-1 and 47% (95% CI, 41 to 54) in AD-2. At week 16, the placebo subtracted difference in patients achieving EASI-75 in patients treated with upadacitinib 15 mg was 53% (95% CI, 46 to 60) in AD-1 and 47% (95% CI, 40 to 54) in AD-2. The placebo subtracted difference in those treated with 30 mg was 63% (95% CI, 57 to 70) in AD-1 and 60% (95% CI, 53 to 66) in AD-2. In AD-3 at week 16, the placebo subtracted difference in patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 29% (95% CI, 22 to 35) and was 48% (95% CI, 41 to 54) in those treated with upadacitinib 30 mg. The placebo subtracted difference in patients achieving EASI-75 treated with upadacitinib 15 mg was 38% (95% CI, 31 to 45) and 51% (95% CI, 44 to 57) in those treated with upadacitinib 30 mg.

When evaluating the pediatric patient population alone at week 16, the placebo subtracted difference in patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 31% (95% CI, 14 to 47) in AD-1 and 40% (95% CI, 22 to 57) in AD-2.[122,123,124] The placebo subtracted difference in those treated with 30 mg was 62% (95% CI, 45 to 78) in AD-1 and 60% (95% CI, 42 to 77) in AD-2. At week 16, the placebo subtracted difference in patients achieving EASI-75 in patients treated with upadacitinib 15 mg was 63% (95% CI, 47 to 79) in AD-1 and 53% (95% CI, 33 to 72) in AD-2. The placebo subtracted difference in those treated with 30 mg was 75% (95% CI, 61 to 89) in AD-1 and 61% (95% CI, 42 to 79) in AD-2. In AD-3 at week 16, the placebo subtracted difference in pediatric patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 23% (95% CI, 7 to 40) and was 57% (95% CI, 40 to 75) in those treated with upadacitinib 30 mg. The placebo subtracted difference in patients achieving EASI-75 treated with upadacitinib 15 mg was 26% (95% CI, 5 to 47) and 46% (95% CI, 26 to 65) in those treated with upadacitinib 30 mg.

upadacitinib (Rinvoq) versus dupilumab (Dupixent)

The efficacy and safety of upadacitinib versus dupilumab in the treatment of adults with AD were assessed in a randomized, double-blind, active-controlled trial.[125] Eligible subjects were 18 to 75 years of age with moderate-to-severe AD and documented use of systemic treatment or an inadequate response to topical treatments (or for whom topical treatments are not advised). Participants were randomized 1:1 to receive upadacitinib 30 mg once daily (n=348) or dupilumab 300 mg SC every 2 weeks following a 600 mg loading dose (n=344). Improvement in EASI-75 at week 16, the primary endpoint, was observed in significantly more patients receiving upadacitinib than those receiving dupilumab (71% versus 61.1%; adjusted difference 10%; 95% CI, 2.9% to 17%; p=0.006). This difference was observed as early as week 2 of treatment. Additionally, significantly more patients in the upadacitinib group achieved EASI-90 and EASI-100 as well as greater improvement in Worst Pruritus NRS. Treatment-emergent adverse events were observed in 71.6% of upadacitinib-treated patients and 62.8% of dupilumab-

treated patients. While rates of serious infection were low overall, they were numerically higher in the upadacitinib group compared with the dupilumab group.

SUMMARY

Liberal use of moisturizers is recommended by the 2023 American Academy of Dermatology (AAD) and the American Academy of Allergy, Asthma, and Immunology (AAAAI) 2012 guidelines; as emollients or moisturizing agents may reduce atopic dermatitis (AD) disease severity and the need for pharmacologic intervention. Both guidelines consider topical corticosteroids first-line agents effective in a majority of patients with AD, though skin atrophy is a risk.

Other agents approved for the treatment of atopic dermatitis differ in mechanism of action offering alternative treatment options for individualized care. The calcineurin inhibitors are indicated to be used second-line for the short-term and non-continuous chronic treatment of AD; pimecrolimus (Elidel) is indicated for mild to moderate disease, and tacrolimus (Protopic) is indicated for moderate to severe disease. Crisaborole (Eucrisa) is a topical product administered twice daily and may be used in pediatric patients ≥ 3 months of age. Ruxolitinib (Opzelura) is a topical Janus kinase (JAK) inhibitor indicated for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients ≥ 12 years of age following trial of other topical therapies. The 2023 AAD guidelines for the management of AD in adults with topical therapies strongly recommend moisturizers, topical corticosteroids, topical calcineurin inhibitors, crisaborole, and ruxolitinib as potential topical treatment options.

Dupilumab (Dupixent) and tralokinumab-ldrm (Adbry) are indicated for moderate to severe AD following trials of topical therapies; both are administered subcutaneously. Dupilumab is administered every 2 to 4 weeks and is approved in patients ≥ 6 months of age. Its use has been studied in combination with topical corticosteroids as well as topical calcineurin inhibitors applied to select areas. Tralokinumab-ldrm is also administered every 2 to 4 weeks and is approved in adults; it can be used with or without topical corticosteroids.

Abrocitinib (Cibinqo) and upadacitinib (Rinvoq) are oral JAK inhibitors approved for AD treatment. They are indicated only for refractory, moderate to severe AD in patients who have already tried other systemic treatments, including biologics, or in patients for whom other systemic treatments are not advisable.

Rare cases of malignancies have been reported with the use of the calcineurin inhibitors, pimecrolimus and tacrolimus, although a causal relationship has not been established. Therefore, the Food and Drug Administration (FDA) has recommended that these agents be used for the short-term and intermittent treatment of AD. In addition, as therapeutic proteins, there is a risk of antibody development with dupilumab and tralokinumab-ldrm. The JAK inhibitors, abrocitinib, ruxolitinib, and upadacitinib carry boxed warnings for serious infections, increased risk of all-cause mortality, malignancy, thrombosis, and major cardiovascular events (MACE).

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