Atopic dermatitis is a chronic relapsing condition that can have a substantial impact on quality of life. The goal of therapy is to treat to no or minimal disease and symptoms. Most patients can obtain safe and effective relief with nonpharmacologic and prescription topical treatment. Bathing, moisturizing, preventing skin infections, and topical corticosteroids and topical calcineurin inhibitors remain important components of therapy. In those cases which such measures do not provide adequate control over the disease, new and investigational therapies may offer additional options.

Abstract
Recently a new class of topical medications for mild to moderate atopic dermatitis has been introduced with US Food and Drug Administration (FDA) approval of the first new prescription medication for this condition in more than a decade. Crisaborole, the newly approved medication, has relieved pruritus in more than one-third of patients within as little as 48 hours. It also has demonstrated efficacy in patients with skin of color. Topical therapies representing other new approaches to atopic dermatitis, with novel mechanisms of action, have shown promise in clinical development.

Keywords
Atopic dermatitis; crisaborole; INCB018424; MM36; pruritus; skin of color; tapinarof

PDE-4 Inhibitors: Mechanisms of Action
Phosphodiesterase (PDE)-4 mediates the conversion of cyclic adenosine monophosphate (cAMP) into AMP, thereby reducing intracellular cAMP levels (Figure 1). In normal physiology, high intracellular concentrations of cAMP in T cells and other immune system cells suppresses production of proinflammatory mediators. Leukocytes and monocytes in patients with atopic dermatitis demonstrate low cAMP and abnormally high PDE activity. Increased PDE activity is associated with inflammatory hyperreactivity. Inhibiting PDE, including PDE-4, reduces the release of proinflammatory cytokine mediators. PDE in the leukocytes of atopic patients has displayed a high sensitivity to PDE inhibitors, compared with PDE in the leukocytes of non-atopic individuals.

Crisaborole: A New Therapy for Atopic Dermatitis
Crisaborole is first topical PDE-4 inhibitor to receive US Food and Drug Administration (FDA) approval for use in atopic dermatitis in patients age 2 and older. A boron-based compound, crisaborole selectively inhibits PDE-4. The use of boron chemistry enables synthesis of a low molecular weight entity, facilitating skin penetration.

Crisaborole demonstrated efficacy in 2 identically designed, randomized, double-blind, vehicle-controlled phase 3 studies (crisaborole n=1,016; vehicle n=506). Patients with mild to moderate atopic dermatitis applied treatment twice daily for 28 days. Most participants (≥85%) were children. The vehicle was not inactive but instead was an emollient substance expected to offer some benefit.

Significantly more patients using crisaborole achieved the primary outcome at day 29, defined as clear/almost clear (0 or 1, Investigator’s Static Global Assessment [ISGA]) score,
Crisaborole was associated with earlier relief of itch compared with vehicle in a post-hoc, pooled analysis of phase 3 data (Figure 2).11 Pruritus is the hallmark of atopic dermatitis and the symptom often cited as most bothersome to patients.12 Roughly one-third of patients receiving crisaborole reported relief of itch at 48 hours; more than half experienced itch relief at 6 days.11

Crisaborole also has shown efficacy in skin of color.13 Significantly higher proportions of Hispanic as well as white patients reached the primary outcome (clear/almost clear; or 1 on IGSA plus a ≥2-grade improvement from baseline) with crisaborole compared with vehicle. Furthermore, significantly higher proportions of black, white, and Hispanic patients attained clear/almost clear with crisaborole compared with vehicle, irrespective of improvement from baseline.13 This is noteworthy because the frequency of atopic dermatitis is higher among children who are black or multiracial than it is among those who are white only (16%, 15%, and 10%, respectively).14

Long-term safety data for crisaborole are encouraging. Participants from the phase 3 trials who entered a 48-week-long, open-label follow-up study (N=517) were evaluated every 4 weeks. Those with at least mild disease (≥2 on the ISGA scale) were prescribed 4 weeks of twice-daily crisaborole therapy. Others received no treatment. During the phase 3 and long-term studies combined, treatment-related adverse events (TEAEs) were reported in 10.3% of patients. Most of these (85.9%) were mild or moderate in severity. The most common events were worsening or flaring of atopic dermatitis (3.1%), and burning or stinging (2.3%) or infection (1.2%) at the application site.15

### MM36: PDE-4 Subtype B Inhibitor

MM36 (formerly OPA-15406), a highly selective compound targeted to PDE-4 subtype B, has demonstrated efficacy in children and adults with atopic dermatitis.16,17 In a proof-of-concept study (n=90, ≥18 years old), nearly 60% of adults achieved treatment success (ie, clear/almost clear [0 or 1, Investigator’s Global Assessment plus ≥2-grade IGA improvement]) at 4 weeks with MM36 1%, Figure 3. More than a third of participants (36.4%) reached this milestone at week 2 with the 1% concentration. The rate of treatment success at 4 weeks was significantly higher with MM36 1% (59.1%) than with vehicle (20%; P=0.04); the rate of success was numerically though not statistically significantly higher than that observed with the active comparator tacrolimus.17

A phase 2, double-blind, 8-week study also demonstrated benefit, in adults (n=97) and children (n=24). As in the proof-of-concept study findings, a significantly higher proportion of patients randomized to MM36 1% twice daily achieved treatment success (clear/almost clear plus ≥2-grade IGA improvement) at 4 weeks, compared with vehicle (20.9% vs 2.7%; P=0.0165). Nearly one-third (30.2%) of patients achieved clear/almost clear (irrespective of change from baseline) with MM36 1% at 4 weeks, compared with 10.0% for vehicle (P=0.0354 for difference).16 The proof-of-concept study included patients with more body surface area (BSA) affected by atopic dermatitis (range, 5% to 66% in proof-of-concept study, 5% to 40% in phase 2 study).16,17

Significant benefit compared with baseline occurred after 1 week of therapy with MM36 (Eczema Area andSeverity Index [EASI] score improvement, 31.4% with MM36 vs 6.0% for vehicle (P=0.0005 for between-group difference). EASI score improvement from baseline rose to 39.0% at week 2 with MM36 1%, and was maintained at that level through week 8. The difference from vehicle remained significant at all time points. Itch, as measured by change in Visual Analog Scale (VAS) scores, improved by a mean of 36.4% at week 1 compared with from baseline with MM36 1%.16
The rate of adverse events (AEs) considered potentially related to treatment was 9% among study participants overall and was lowest in the MM36 group (2%, 12%, and 14% in the MM36 1%, MM36 0.3%, and vehicle groups, respectively). All treatment-related AEs were mild to moderate in intensity.16

Comparing Nonsteroidal Topical Therapies
Topical calcineurin inhibitors (TCIs) and PDE-4 inhibitors have not been compared in head-to-head trials. Study designs and patient populations differ. For the clinician attempting to assess relative efficacy, one metric is the rate of clear/almost clear (IGA/IGSA 0 or 1) at 4 weeks in randomized, double-blind, vehicle-controlled trials:

- **20%** higher rates of clear/almost clear with pimecrolimus 1% than with vehicle (32% and 12%, respectively), among 403 children with mild or moderate atopic dermatitis (IGA 2 or 3 at baseline)18
- **19%** and **11%** higher rates of clear/almost clear with crisaborole than with vehicle (49% and 52% with crisaborole, 30% and 41% with vehicle), in 2 phase 3 trials (n=1,522, ≥85% children with mild or moderate atopic dermatitis at baseline)10
- **20%** higher rates of clear/almost clear with MM36, phase 2 randomized, double-blind study (30% with MM36, 10% with vehicle).16

Topical Small Molecules in Phase 2 Development
Tapinarof (GSK2894512, formerly WBI-1001) activates the aryl hydrocarbon receptor (AhR) in skin and other cells. The AhR affects the balance of T17 and regulatory T cells and contributes substantially to the development and maintenance of the skin barrier. Tapinarof moderates the expression of proinflammatory cytokines in stimulated peripheral blood CD4+ T cells and in skin cells.19

An older formulation of tapinarof cream, applied twice daily, significantly reduced disease severity compared with baseline in a dose-ranging, randomized, double-blind, 4-week-long study in adults with mild or moderate atopic dermatitis (n=37; baseline IGA 2 or 3). Specifically, IGA score improved by 38.9% and 45.8% at week 4 with the lower (0.5%) and higher (1%) tapinarof concentrations, respectively, and by 5.6% with vehicle (P=0.003; **Figure 4**).20

Half (50%) of the participants assigned to either concentration of tapinarof attained clear/almost clear (IGA 0 or 1) at week 4, compared with 8.3% for vehicle. EASI scores improved by 59.3% and 54.9% at 4 weeks with the lower and higher concentrations of active therapy, compared with 7.1% for vehicle (P=0.03). Pruritus scores (VAS) improved as well. Affected BSA fell by more than half to nearly two-thirds at 4 weeks (64.4% and 57.7%, lower and higher concentrations, respectively, compared with 10.8% for vehicle; P=0.03).20

Preliminary findings of a small (n=11) open-label, study with the new formulation indicated that EASI scores improved by at least 50% in those who completed the study (to day 21). Adults with moderate to severe atopic dermatitis at baseline (IGA ≥3) applied tapinarof cream 1% or 2% strength twice daily for 21 days. Efficacy was similar with both concentrations but tolerability was superior with the 1% concentration. Among participants receiving 2% tapinarof, 3 of the 5 experienced headache, diarrhea, nausea, and/or vomiting, leading to discontinuation after 1 treatment application. These effects did not appear related to tapinarof plasma levels or participants’ baseline atopic dermatitis.21

A phase 2 trial of the new formulation in 1% and 0.5% strengths has been completed but data have not been reported at this writing (ClinicalTrials.gov Identifier: NCT02564055).

A Janus kinase (JAK) 1/2 inhibitor known as INCB018424, which blocks signal transduction of proinflammatory cytokines, was evaluated in a 4-week phase 2 study in adults with mild to moderate atopic dermatitis (IGA score of 2 or 3). The trial compared twice-daily INCB018424 1.5% cream with an active treatment (triamicinolone 0.1% cream twice daily) and vehicle (ClinicalTrials.gov Identifier: NCT03011892). Results are pending. INCB018424 demonstrated activity (eg, improved lesion scores) in an earlier 4-week study of plaque psoriasis.22

Summary
After more than a decade without a new prescription therapy for atopic dermatitis, a new topical treatment has been introduced and others are on the horizon. Crisaborole was approved by the FDA in December 2016. MM36, another topical PDE-4 inhibitor, demonstrated efficacy in phase 2 trials. The AhR receptor agonist tapinarof has shown promise in a phase 2 trial. A JAK1/JAK2 inhibitor is undergoing phase 2 study. Good skin care, including bathing and moisturizing as well as topical corticosteroids and topical calcineurin inhibitors, remain important components of therapy for atopic dermatitis.

References


