

The role of phosphodiesterase 4 in the pathophysiology of atopic dermatitis and the perspective for its inhibition

Emma Guttman-Yassky¹, Jon M. Hanifin², Mark Boguniewicz³, Andreas Wollenberg⁴, Robert Bissonnette⁵, Vivek Purohit⁶, Iain Kilty⁷, Anna M. Tallman⁸, Michael A. Zielinski⁹

¹Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

²Department of Dermatology, Oregon Health and Science University, Portland, OR, USA

³Department of Pediatrics, National Jewish Health, Denver, CO, USA

⁴Department of Dermatology and Allergy, Ludwig Maximilian University, Munich, Germany

⁵Innovaderm Research Inc., Montreal, Quebec, Canada

⁶Pfizer Inc., Groton, CT, USA

⁷Pfizer Inc., Cambridge, MA, USA

⁸Former Pfizer Inc., employee, New York, NY, USA

⁹Pfizer Inc., Collegeville, PA, USA

Running title: Inhibition of PDE4 in atopic dermatitis

Corresponding author:

Emma Guttman-Yassky, MD, PhD

Department of Dermatology, Icahn School of Medicine at Mount Sinai

5 E 98th St, 5th Floor, New York, NY 10029.

E-mail: Emma.Guttman@mountsinai.org

ABSTRACT

Atopic dermatitis (AD) is a highly prevalent, chronic inflammatory skin disease that affects children and adults. The pathophysiology of AD is complex and involves skin barrier and immune dysfunction. Many immune cytokine pathways are amplified in AD, including T helper (Th) 2, Th22, Th17 and Th1. Current treatment guidelines recommend topical medications as initial therapy; however, until recently, only two drug classes were available: topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs). Several limitations are associated with these agents. TCSs can cause a wide range of adverse effects, including skin atrophy, telangiectasia, rosacea and acne. TCIs can cause burning and stinging, and the prescribing information lists a boxed warning for a theoretical risk for malignancy. Novel medications with new mechanisms of action are necessary to provide better long-term control

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/exd.13808

This article is protected by copyright. All rights reserved.

of AD. Phosphodiesterase 4 (PDE4) regulates cyclic adenosine monophosphate in cells and has been shown to be involved in the pathophysiology of AD, making it an attractive therapeutic target. Several PDE4 inhibitors are in clinical development for use in the treatment of AD, including crisaborole, which recently became the first topical PDE4 inhibitor approved for treatment of mild to moderate AD. This review will further describe the pathophysiology of AD, explain the possible role of PDE4 in AD and review PDE4 inhibitors currently approved or being investigated for use in AD.

Keywords: eczema, crisaborole, corticosteroids, calcineurin inhibitor, cytokines

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin disease that affects between 15% and 30% of children and 2% and 10% of adults worldwide.^[1-3] Although multiple therapeutic options are available for the management of AD,^[4-7] until crisaborole was approved in the United States in December 2016, no topical medications with novel mechanisms of action had been approved for approximately 15 years.^[8]

Use of topical corticosteroids (TCSs), the mainstay of AD therapy, decreases acute and chronic signs of AD and pruritus and is effective in treating active inflammatory disease.^[4, 6, 7, 9, 10] However, use of TCSs is associated with adverse events (AEs) such as telangiectasia, striae, rosacea and acne, whereas prolonged application of moderate to potent TCSs is associated with skin atrophy.^[11, 12] Some TCSs, like mometasone furoate, have been reported to have lower atrophogenic potential.^[13]

Topical calcineurin inhibitors (TCIs) became an alternate treatment option when tacrolimus and pimecrolimus were first approved for use in AD.^[11] Although TCIs have demonstrated effectiveness in treating AD, they can induce local skin burning and stinging.^[11, 14] Prescribing information for TCIs include a boxed warning in the United States for a theoretical risk for malignancy, although after years of use, no evidence that topical application can cause malignancy has emerged.^[11, 14-16]

Proactive use of TCIs after AD is controlled can result in long-lasting flare-free periods and decrease the need for TCSs, leading to improvement in skin lesions and quality of life.^[17] Proactive use of the medium-potency TCS fluticasone propionate (acute phase: twice daily; maintenance phase: 4 weeks of once-daily dosing 4 days/week, followed by 16 weeks of once-daily dosing 2 days/week) did not result in skin atrophy, which might otherwise occur as a result of improper reactive use, suggesting that maintenance use for prevention of flares could mitigate some of the limitations of these agents.^[17, 18]

Other treatment methods include phototherapy, commonly with narrow-band ultraviolet B (UVB) light, which is used primarily as add-on therapy to TCSs. Systemic treatments include immune suppressants such as cyclosporine, azathioprine, methotrexate and mycophenolate mofetil, which are sometimes used in severe or refractory AD.^[5-7, 19, 20] Recently the anti-interleukin 4 receptor (IL-4R α) monoclonal antibody dupilumab was approved in the United States and Europe for use in adults with moderate to severe AD.^[21, 22] Combinations of topical and systemic treatments may also be useful in treating moderate to severe AD, for example, topical therapies combined with cyclosporine have been shown to reduce duration and dose of cyclosporine while achieving positive clinical results and prolonged disease remission.^[23]

Phosphodiesterase 4 (PDE4) inhibition may be an alternative for long-term treatment of AD.^[24] The enzyme PDE4 is found in a variety of immune cells and breaks down cyclic adenosine monophosphate (cAMP).^[25, 26] Increases in cAMP levels as a result of PDE4 inhibition in cellular studies of atopic leukocytes have been associated with the suppression of proinflammatory molecules such as IL-4 and prostaglandin E₂, suggesting that inhibition of PDE4 may decrease the inflammatory processes associated with AD.^[24, 27, 28]

PATHOPHYSIOLOGY OF AD

AD is characterized by skin inflammation, acute and chronic eczematous lesions and intense pruritus.^[29-31] Major advances in the past 10 years have shown that skin barrier dysfunction and immune activation participate in the complex pathophysiology of AD.^[32-35] AD is believed to result primarily from overexpression of the T helper (Th) 2 cytokine axis; however, Th22, Th17 and Th1 cytokine pathways may also play a role (Figure 1).^[33, 35] This overexpression leads to an accumulation of dendritic cells, particularly inflammatory dendritic epidermal cells (IDECs) in skin lesions.^[36-39] Increased Th17 activation has also been observed in Asian patients,^[40] and reduced counter-regulation by Th1 T cells has been observed in children.^[41]

Increased levels of Th2 cytokines such as IL-4, IL-5, IL-13, IL-25, IL-31 and IL-33 and chemokines CCL17, CCL18, CCL22 and CCL26, as well as Th22 responses (via IL-22 and S100A proteins), have been observed in AD lesions.^[31, 33, 42-44] Some Th2 and Th22 cytokines have been shown to decrease expression of terminal differentiation genes (i.e. filaggrin), which contributes to skin barrier defects.^[33, 44-46] Increased IL-31 is associated with itch and elongation and branching of IL-31 receptor A-positive sensory nerve fibers, and administration of the anti-IL-31 receptor A monoclonal antibody nemolizumab to patients with AD resulted in significant reduction in the severity of pruritus compared with placebo.^[33, 47, 48] Conversely, IL-22 mediates epidermal hyperplasia.^[33, 49] The Th2 cytokines IL-4 and IL-13 are thought to have a pathogenic role in AD.^[33] Single-nucleotide polymorphisms have been observed in the genes for IL-4 and IL-13 and their receptors in patients with AD.^[33, 50-53] IL-4 and IL-13 have been linked to inhibition of production of antimicrobial peptides and have been observed to override other skin immune defense mechanisms in patients with AD.^[33, 54, 55] This is of special importance because of the susceptibility of AD patients to eczema

herpeticum.^[56] Skin barrier dysfunction and decreased expression of antibacterial peptides can lead to subsequent infection and allergen sensitivity in AD.^[33] IL-4 and IL-13 are targeted by dupilumab, which can reverse clinical and molecular tissue characteristics of AD.^[57-59]

Upregulation of Th17 and Th1 cytokines and chemokines is also detected in AD lesions. Components of the Th17 pathway such as IL-17, IL-17A, CXCL1, elafin (PI3) and CCL20 are upregulated in acute and chronic AD.^[31, 33] They also contribute to skin barrier dysfunction by downregulating filaggrin or by upregulating inflammatory molecules such as S100A proteins.^[33, 49, 60] In chronic AD, Th2 and Th22 remain upregulated with the addition of activated Th1 response, which includes interferon gamma (IFN γ) and CXCL9 and CXCL10.^[31, 33]

In addition to changes in immune cells, AD is associated with skin barrier dysfunction characterized by increased stratum corneum pH, increased transepidermal water loss, and decreased stratum corneum hydration.^[61] Epidermal abnormalities include defects in terminal differentiation of keratinocytes, as well as epidermal hyperplasia and induction of S100As.^[33, 62, 63] In addition to dysfunction in the synthesis of ceramides, reduced skin hydration in AD has also been associated with decreased sebum production suggesting that this contributes to skin barrier dysfunction.^[61]

The skin microbiome can also play a role in the pathophysiology of AD. Human skin is regularly colonized by microbes such as *Staphylococcus* spp. and *Corynebacterium* and *Propionibacterium* (now known as *Cutibacterium*) genera.^[64] Dominant presence of *Staphylococcus epidermidis* in healthy skin inhibits growth of *Staphylococcus aureus* which is found in ~90% of patients with AD and, of which, 50% are toxin producing.^[65] Secretion of metabolites from skin microbes can result in crosstalk with the patient's immune system and regulate immune responses.^[65] *S aureus*, in particular, has been associated with the production of extracellular vesicles that induce increased production of pro-inflammatory mediators in the skin resulting in AD-like inflammation.^[66] Dysbiosis of skin microflora has been associated with AD pathogenesis. For example, increased colonization of *S aureus* has been characteristic in lesional skin and is associated with disease flares.^[64] However, the complex role the microbiome in the skin is still being elucidated.

ROLE OF PDE4 IN AD

cAMP has been shown to play a role in the regulation of inflammatory and immune responses, and increased levels of cAMP have been associated with effects such as suppression of T cells and monocytes.^[67] PDEs are enzymes that break down cAMP or cyclic guanosine monophosphate (cGMP), and they demonstrate activity in all cells in the body.^[68-70] However, certain isoenzymes are expressed only in select tissue. For example, PDE3 is preferentially expressed in the heart, lungs, liver, platelets, adipose tissue and inflammatory cells, whereas PDE7 is preferentially expressed in the heart, skeletal muscle, kidney, brain, pancreas and T lymphocytes.^[69]

The role of PDE4 in a broad group of immune-related diseases has been reviewed previously.^[71] There are 20 variants among the PDE4 gene families of *PDE4A*, *PDE4B*, *PDE4C* and *PDE4D*.^[72] With regard to AD, PDE4 is found in immune and inflammatory cells such as basophils, mast cells, eosinophils, B and T lymphocytes, monocytes, macrophages, neutrophils and endothelial cells.^[73-75] Increased cAMP-PDE activity has been reported in freshly isolated mononuclear lymphocyte (MNL) preparations from patients with AD and in three patients with documented AD whose disease had been in remission for 2 to 20 years, despite lack of visual evidence of cutaneous inflammation.^[76] Using immunohistochemistry staining, PDE4 isoforms PDE4A, PDE4B, PDE4C and PDE4D have also been observed to be increased in dermal fibroblasts of skin samples of patients with AD relative to dermal fibroblasts from healthy skin; however, the clinical significance of each isoform is not fully understood in AD.^[77] Adenylate cyclase, which catalyzes adenosine triphosphate to cAMP, was found to be upregulated in MNLS in AD, thus increasing cAMP generation, which in turn is believed to drive increased PDE activity in an effort to establish a homeostatic steady state in unstimulated cells.^[78] When these leukocytes are then stimulated, a further increase in cAMP production would normally dampen the cell response, however, due to the already increased levels of PDE, adequate cAMP levels cannot be maintained.^[78] In addition, increased PDE activity in atopic monocytes was associated with increased prostaglandin E₂ production, resulting in increased IL-6 and increased IL-10, with both contributing to Th1/Th2 imbalance.^[28] While IL-10 is typically considered a global suppressor cytokine of immune responses, increased IL-10 in AD monocytes is attributed to decreased IFN γ production by Th1 cells, shifting the balance of the Th1/Th2 ratio towards Th2 response.^[28] Experiments in atopic MNL cultures showed that PDE4 inhibitors significantly reduced levels of prostaglandin E₂, IL-10 and IL-4, as measured by immunoassay.^[24] However, in some cases, PDE4 inhibitors have been observed to increase proinflammatory molecules such as IL-8 in human umbilical vein endothelial cells and in mouse lung neutrophils.^[79] Based on this potential to reverse broad imbalances in immune responses in AD without the use of corticosteroids, inhibition of PDE4 was considered a desirable target to pursue in further studies (Figure 1).

Although the effects of PDE4 in AD are still being studied, selective PDE4 inhibition has provided additional insight regarding affected cytokines and immune markers. PDE4 inhibitors have been shown to be associated with reductions in various cytokines similarly to TCIs and TCS (Table 1).^[9, 10, 14, 24, 80-90] In human cellular models, the PDE4 inhibitor apremilast inhibited production of inflammatory mediators such as: tumor necrosis factor (TNF) in T cells, natural killer (NK) cells, and dendritic cells; IL-12 in monocytes; IL-2 in T cells; IFN γ in NK and T cells; IL-5 in T cells; IL-8, leukotriene B4 (LTB4) and the adhesion molecule CD18/CD11b (Mac-1) in neutrophils; and augmented the inflammatory suppressor IL-10 in monocytes.^[80] In a pharmacodynamics study of oral apremilast in patients with psoriatic arthritis, the biomarkers IL-8, TNF α and IL-6 were reduced at 24 weeks of treatment, and IL-17, IL-23 and IL-6 were reduced at 40 weeks.^[83] Similarly, in psoriasis patients treated with oral apremilast, clinical efficacy (improvement in Psoriasis Area and Severity Index) was linked to reduction of IL-17F, IL-17A and IL-22 cytokines at week 16 of treatment.^[84]

To date, there is a lack of published research examining the effect of PDE4 inhibition on microbiome dysbiosis associated with AD.

PDE4 INHIBITORS CURRENTLY AVAILABLE AND IN DEVELOPMENT FOR AD

Crisaborole

Crisaborole is a nonsteroidal boron-based molecule (Figure 2) that selectively inhibits PDE4. The boron moiety in the crisaborole molecule is important for its inhibitory activity, serving as a phosphate isostere in the PDE4 active site. In fact, replacement of the boron moiety with carbon (bound to either oxygen or a hydroxyl group) results in loss of effective enzymatic inhibition and subsequent reduction in cytokine concentrations in peripheral blood mononuclear cells (PBMCs).^[26, 91] In addition, the incorporation of boron into crisaborole's structure allows for a low molecular weight (251 Daltons) and thus easier penetration into the skin.^[26] In available maximal-use and long-term studies with crisaborole, AEs were primarily mild to moderate application site reactions.^[92, 93]

When tested across the spectrum of PDE isoforms PDE1 through PDE11, crisaborole exhibited greater affinity for PDE4 isoforms than for other PDE families (particularly in members of isoforms PDE4A, PDE4B and PDE4D), although it did show some inhibitory activity against PDE1A, PDE3A and PDE7A.^[82] Its use resulted in reduced concentration of cytokines such as TNF α , IFN γ , IL-2 and, to a lesser extent, IL-5 and IL-10 in cell studies of PBMCs stimulated by lipopolysaccharide or phytohemagglutinin.^[81, 82]

Crisaborole ointment, 2%, is currently the only PDE4 inhibitor approved for treatment of mild to moderate AD.^[94, 95] Approval was based on the results of two identically designed multicenter, randomized (2:1), double-blind, phase 3 clinical studies that included 1522 patients (clinicaltrials.gov identifier, AD-301: NCT02118766; AD-302: NCT02118792).^[8] In both studies, patients aged ≥ 2 years with mild to moderate AD (according to Hanifin and Rajka criteria^[96]) and $\geq 5\%$ treatable body surface area (BSA) involvement were randomly assigned to receive crisaborole or vehicle. The primary efficacy end point was success in Investigator's Static Global Assessment (ISGA) score (which was defined as clear [0] or almost clear [1] with at least a two-grade improvement from baseline) at day 29. Crisaborole significantly reduced the severity of skin manifestations in this population of children and adults compared with vehicle, as evidenced by significantly more patients achieving the primary end point of success in ISGA (AD-301: 32.8% vs 25.4%, $P = 0.038$; AD-302: 31.4% vs 18.0%, $P < 0.001$), significantly more patients achieving an ISGA score of clear or almost clear (51.7% vs 40.6%, $P = 0.005$; 48.5% vs 29.7%, $P < 0.001$) and more patients experiencing reduction in the severity of signs and symptoms of AD and early and sustained relief from pruritus.^[8]

Treatment with crisaborole was well tolerated over the 4-week treatment period. Most treatment-emergent AEs were mild or moderate, and the most common treatment-related AE was application site pain (crisaborole: 4.4%, vehicle: 1.2%).^[8] Because AD often necessitates prolonged treatment, longer term safety of crisaborole was explored in an open-label extension study of patients (N = 517) who completed these two phase 3 studies, revealing a similar safety profile after being treated for an additional 48-week period, with no serious treatment-related AEs.^[93] Clinical testing of crisaborole in patients aged ≥ 2 years under maximal-use conditions demonstrated a mean maximum plasma concentration ($C_{\max}$) of 127 ng/mL after 8 days of treatment.^[92] Topical application minimizes the risk for systemic pharmacologic effects associated with oral PDE4 inhibition. The current prescribing information for crisaborole ointment does not include a boxed warning and there are no restrictions on duration of use, though adverse effects such as application site pain may be a concern for patients.

Other topical PDE4 inhibitors

Other topical PDE4 inhibitors that have been or that are currently in development for treatment of AD include E6005/RVT-501, LEO 29102, OPA-15406/MM36 and DRM02.^[97] Unlike crisaborole, none of these investigational drugs contains boron; however, like crisaborole, they generally fall under the 500-Dalton rule in terms of molecular weight, allowing for skin penetration (Figure 2).^[98] In addition, although promising results have been published for some of these agents,^[99-102] none has been evaluated in phase 3 studies.

E6005/RVT-501 is a topical PDE4 inhibitor that has been evaluated in several phase 1/2 studies. Results have been promising in children and adults in Japan.^[100-102] For example, at 0.03% and 0.2% strengths, a significant reduction in Scoring of Atopic Dermatitis (SCORAD) index^[103] score was observed in adults aged 20 to 60 years.^[100] In children aged 2 to 15 years with mild to moderate clinical symptoms, the 0.2% strength demonstrated numerically greater reduction in severity per the Eczema Area and Severity Index (EASI) than did vehicle (−45.94% vs −32.26%), though it did not reach statistical significance.^[101] In addition, pharmacokinetic studies have shown systemic absorption to be minimal.^[104] An additional phase 2 study was recently conducted to evaluate 0.2% and 0.5% strengths in patients with AD in the United States and Canada (clinicaltrials.gov identifier, NCT02950922), with results expected in 2018. E6005 was more selective for PDE4 when tested against PDE isoforms PDE1 through PDE5, and it has shown modest activity in reducing IFN γ , TNF α , IL-2, IL-4 and IL-12 in PBMCs.^[105]

OPA-15406/MM36 was evaluated in a recent randomized, double-blind, vehicle-controlled phase 2 study in patients aged 10 to 70 years with mild to moderate AD.^[99] OPA-15406, 1%, had a significantly higher rate of treatment success than did vehicle at 4 weeks (20.9% vs 2.7%; $P = 0.0165$), where success was defined as a score of 0 (clear) or 1 (almost clear), with at least a two-grade reduction from the baseline score of 2 (mild) or 3 (moderate) on the ISGA.^[99] A maximal-use phase 2 study in pediatric patients (aged 2 to <18 years) with AD (clinicaltrials.gov identifier, NCT02945657) was completed in June 2017, but results are not yet published. OPA-15406 has

exhibited highly selective inhibitory activity against PDE4 subtypes, particularly subtype B; however, the evidence has not been published.^[99]

LEO 29102 is another selective topical PDE4 inhibitor.^[106] A dose-escalation study showed that systemic exposure was minimal, with a C_{max} of 5.07 ng/mL at 53% BSA exposure.^[106] Although a phase 2 dose-ranging study that compared several different dose strengths of LEO 29102 with pimecrolimus cream in adult patients with AD (aged 18-65 years) has been completed (ClinicalTrials.gov identifier, NCT01037881), results have not been published, and current development status is unknown.^[107] LEO 29102 has been shown to selectively inhibit isoform PDE4D and exhibit some inhibitory activity toward $TNF\alpha$ ^[106]; however, data on activity toward other PDE isoforms and other immune cytokines are unpublished.

DRM02 was evaluated in a double-blind, vehicle-controlled, phase 2 proof-of-concept study in adult patients (aged 18-70 years) with stable AD (clinicaltrials.gov identifier, NCT01993420). The study was completed in 2014; however, results were not published.^[108] Development of DRM02 was discontinued by late 2015.^[109] Data on PDE isoform and cytokine inhibitory activity are unpublished.

Oral apremilast

Apremilast is an oral PDE4 inhibitor approved for use in adult patients with active psoriatic arthritis and patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.^[110] When tested for inhibitory activity against PDE isoforms PDE1 through PDE11, apremilast had activity against PDE4 isoforms of all sub-families and it did not significantly inhibit any other PDE enzymes.^[111] In PBMCs, apremilast inhibited production of $TNF\alpha$, IFN γ , IL-2, IL-5, IL-10, IL-13, IL-17 and granulocyte-macrophage colony-stimulating factor (GM-CSF).^[111] An open-label investigator-initiated study was conducted to evaluate apremilast (20 mg or 30 mg twice daily) in 16 patients with AD, with results showing significant improvement from baseline in disease severity (30 mg dose), pruritus (20 mg dose) and quality of life (20 mg and 30 mg doses) at 3 months.^[80] However, a high incidence of nausea was reported as an AE, with an incidence of 33% in the 20 mg cohort and 90% in the 30 mg cohort.^[80] This study also conducted ontologic analyses of peripheral blood samples showing significant differential expression of the cAMP response element binding pathway ($P < 0.001$), bcl-2 antagonist of cell death phosphorylation pathway ($P < 0.05$), chemokine-mediated signaling ($P < 0.0001$), IL-12 signaling ($P < 0.05$), cytoskeleton remodeling ($P < 0.05$), and regulation of immune complex clearing by monocytes and macrophages ($P < 0.0001$) compared with baseline in the 20 mg cohort.^[80] In the 30 mg cohort, there was significant differential expression of CCR3 signalling in eosinophils ($P = 0.05$).^[80] A phase 2 study consisting of 185 patients was conducted to evaluate apremilast 30 mg twice daily and 40 mg twice daily against placebo in patients with moderate to severe AD (clinicaltrials.gov identifier, NCT02087943).^[112] Patients who received apremilast 40 mg twice daily had significantly greater percentage change reduction in EASI score at week 12 (primary end point) than those who received placebo; however, this was not observed with the 30 mg twice-daily dose. Neither treatment group was significantly better than the placebo group on all secondary end points. Diarrhea and nausea were more common in the 30 mg and 40 mg arms

(diarrhea: 17% and 24%; nausea: 16% and 11%, respectively) than in the placebo arm (diarrhea: 2%; nausea: 2%) over 12 weeks.^[112] These gastrointestinal AEs are not typically seen in studies of topical formulations of PDE4 inhibitors, which may be because of the limited systemic exposure. Cellulitis was reported in the 40 mg arm, with an incidence of 5% over 12 weeks of treatment.

CONCLUSIONS/INTERPRETATION

AD is a complex disease caused by skin barrier dysfunction and immune dysregulation that involves many inflammatory cytokines. The limited topical treatments for patients with AD have led to development of novel non-steroidal targeted therapies. PDE4 plays a role in the regulation of the inflammatory cascade associated with AD inflammation, making it a desirable target of drug therapy. PDE4 inhibitors have a unique mechanism that differs from the mechanisms of TCSs and TCIs, and they affect a broad range of cytokines involved in AD. One topical PDE4 inhibitor, crisaborole, has been approved in the United States for the treatment of AD, while several other agents are currently in clinical development. The mechanism of action of crisaborole will be further characterized in a study that is underway to evaluate the efficacy and changes in key skin biomarkers in patients with mild to moderate AD (clinicaltrials.gov identifier, NCT03233529). Overall, evidence suggests that targeting of PDE4 may be a safe and effective approach to the management of AD. A recent review provides practical recommendations to help clinicians incorporate crisaborole into the treatment armamentarium for AD.^[113]

ACKNOWLEDGMENTS

Editorial/medical writing support under the guidance of the authors was provided by Corey Mandel, PhD, and Robert Schoen, PharmD (ApotheCom, San Francisco, CA), and was funded by Pfizer Inc., New York, NY, U.S.A., in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015; **163**:461–4).

CONFLICTS OF INTEREST

EG-Y is an employee of Mount Sinai and has received research funds (grants paid to her institution) from AbbVie, Celgene, Eli Lilly, Janssen Pharmaceuticals, MedImmune/AstraZeneca, Novartis, Pfizer, Regeneron, Vitae, Glenmark, Galderma, Asana BioSciences, Innovaderm, Dermira, and UCB; she is also a consultant for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor Pharmaceuticals, a wholly owned subsidiary of Pfizer Inc., AnaptysBio, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, LEO Pharma, AbbVie, Eli Lilly, Kyowa, Mitsubishi Tanabe, Asana BioSciences, and Promius. JH has provided consulting services for Menlo Therapeutics, AbbVie, GlaxoSmithKline, Anacor Pharmaceuticals, a wholly owned subsidiary of Pfizer Inc., Otsuka Pharmaceutical, Dermira, F. Hoffman-La Roche., and Chugai Pharmaceutical; he has also received study support from GlaxoSmithKline, Otsuka Pharmaceutical, and Merck. MB has received a research grant from Anacor Pharmaceuticals, a wholly owned subsidiary of Pfizer Inc. AW has been an advisor

for Anacor Pharmaceuticals, a wholly owned subsidiary of Pfizer Inc. and Pfizer, and has received honoraria for consultancy and lectures in the field of atopic dermatitis from Almirall, Anacor, Astellas, Celgene, Chugai, Galderma, LEO Pharma, L'Oreal, MEDA, MedImmune, Novartis, Pierre Fabre, Pfizer, Regeneron, and Sanofi. RB was an investigator, consultant, advisory board member, speaker for, and/or received honoraria from Antibiotox, Aquinox, Asana BioSciences, Astellas, Brickell, Dermavant, Dermira, Dignity Sciences, Galderma, Glenmark, Stiefel/GlaxoSmithKline, F. Hoffman-La Roche, LEO Pharma, NeoKera, Pfizer, Regeneron, and Vitae. VP, IK, and MAZ are shareholders and employees of Pfizer Inc. AMT is a former employee and former shareholder of Pfizer Inc.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing and revising for intellectual content of the manuscript and approved the final version for submission.

REFERENCES

- 1 J.I. Silverberg. *Dermatologic clinics*. 2017, 35, 283.
- 2 J.A. Odhiambo, H.C. Williams, T.O. Clayton, C.F. Robertson, M.I. Asher; ISAAC Phase Three Study Group. *The Journal of allergy and clinical immunology*. 2009, 124, 1251.
- 3 T.E. Shaw, G.P. Currie, C.W. Koudelka, E.L. Simpson. *The Journal of investigative dermatology*. 2011, 131, 67.
- 4 L.F. Eichenfield, W.L. Tom, T.G. Berger, A. Krol, A.S. Paller, K. Schwarzenberger, J.N. Bergman, S.L. Chamlin, D.E. Cohen, K.D. Cooper, K.M. Cordoro, D.M. Davis, S.R. Feldman, J.M. Hanifin, D.J. Margolis, R.A. Silverman, E.L. Simpson, H.C. Williams, C.A. Elmetts, J. Block, C.G. Harrod, W. Smith Begolka, R. Sidbury. *Journal of the American Academy of Dermatology*. 2014, 71, 116.
- 5 R. Sidbury, D.M. Davis, D.E. Cohen, K.M. Cordoro, T.G. Berger, J.N. Bergman, S.L. Chamlin, K.D. Cooper, S.R. Feldman, J.M. Hanifin, A. Krol, D.J. Margolis, A.S. Paller, K. Schwarzenberger, R.A. Silverman, E.L. Simpson, W.L. Tom, H.C. Williams, C.A. Elmetts, J. Block, C.G. Harrod, W.S. Begolka, L.F. Eichenfield; American Academy of Dermatology. *Journal of the American Academy of Dermatology*. 2014, 71, 327.
- 6 L. Schneider, S. Tilles, P. Lio, M. Boguniewicz, L. Beck, J. LeBovidge, N. Novak, D. Bernstein, J. Blessing-Moore, D. Khan, D. Lang, R. Nicklas, J. Oppenheimer, J. Portnoy, C. Randolph, D. Schuller, S. Spector, S. Tilles, D. Wallace. *The Journal of allergy and clinical immunology*. 2013, 131, 295.
- 7 A. Wollenberg, A. Oranje, M. Deleuran, D. Simon, Z. Szalai, B. Kunz, A. Svensson, S. Barbarot, L. von Kobyletzki, A. Taieb, M. de Bruin-Weller, T. Werfel, M. Trzeciak, C. Vestergard, J. Ring, U. Darsow; European Task Force on Atopic Dermatitis/EADV Eczema Task Force. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2016, 30, 729.
- 8 A.S. Paller, W.L. Tom, M.G. Lebwohl, R.L. Blumenthal, M. Boguniewicz, R.S. Call, L.F. Eichenfield, D.W. Forsha, W.C. Rees, E.L. Simpson, M.C. Spellman, L.F. Stein Gold, A.L. Zaenglein, M.H. Hughes, L.T. Zane, A.A. Hebert. *Journal of the American Academy of*

- Dermatology. 2016, 75, 494.
- 9 P.M. Brunner, S. Khattri, S. Garcet, R. Finney, M. Oliva, R. Dutt, J. Fuentes-Duculan, X. Zheng, X. Li, K.M. Bonifacio, N. Kunjraiva, I. Coats, I. Cueto, P. Gilleaudeau, M. Sullivan-Whalen, M. Suarez-Farinas, J.G. Krueger, E. Guttman-Yassky. The Journal of allergy and clinical immunology. 2016, 138, 169.
 - 10 E. Guttman-Yassky, B. Ungar, K. Malik, D. Dickstein, M. Suprun, Y.D. Estrada, H. Xu, X. Peng, M. Oliva, D. Todd, T. Labuda, M. Suarez-Farinas, R. Bissonnette. The Journal of allergy and clinical immunology. 2017, 140, 1032.
 - 11 W.W. Carr. Paediatric drugs. 2013, 15, 303.
 - 12 U.R. Hengge, T. Ruzicka, R.A. Schwartz, M.J. Cork. Journal of the American Academy of Dermatology. 2006, 54, 1.
 - 13 T. Ruzicka, C. Willers, W. Wigger-Alberti. Skin pharmacology and physiology. 2012, 25, 305.
 - 14 J.M. Spergel. American journal of clinical dermatology. 2008, 9, 233.
 - 15 J.M. Hanifin. JAMA dermatology. 2015, 151, 587.
 - 16 D.J. Margolis, K. Abuabara, O.J. Hoffstad, J. Wan, D. Raimondo, W.B. Bilker. JAMA dermatology. 2015, 151, 594.
 - 17 A. Wollenberg, L.M. Ehmman. Annals of dermatology. 2012, 24, 253.
 - 18 J. Hanifin, A.K. Gupta, R. Rajagopalan. The British journal of dermatology. 2002, 147, 528.
 - 19 S. Tintle, A. Shemer, M. Suarez-Farinas, H. Fujita, P. Gilleaudeau, M. Sullivan-Whalen, L. Johnson-Huang, A. Chiricozzi, I. Cardinale, S. Duan, A. Bowcock, J.G. Krueger, E. Guttman-Yassky. The Journal of allergy and clinical immunology. 2011, 128, 583.
 - 20 S. Khattri, A. Shemer, M. Rozenblit, N. Dhingra, T. Czarnowicki, R. Finney, P. Gilleaudeau, M. Sullivan-Whalen, X. Zheng, H. Xu, I. Cardinale, C. de Guzman Strong, J. Gonzalez, M. Suarez-Farinas, J.G. Krueger, E. Guttman-Yassky. The Journal of allergy and clinical immunology. 2014, 133, 1626.
 - 21 US Food and Drug Administration. FDA approves new eczema drug Dupixent [press release]. Silver Spring, MD: US Food and Drug Administration: March 28, 2017. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm549078.htm> (accessed: April 20, 2018).
 - 22 Dupixent (dupilumab) [summary of opinion. initial authorization]. London, UK: European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). July 20, 2017.
 - 23 M. Megna, M. Napolitano, C. Patrino, A. Villani, A. Balato, G. Monfrecola, F. Ayala, N. Balato. Dermatology and therapy. 2017, 7, 1.
 - 24 J.M. Hanifin, S.C. Chan, J.B. Cheng, S.J. Tofte, Henderson WR Jr, D.S. Kirby, E.S. Weiner. The Journal of investigative dermatology. 1996, 107, 51.
 - 25 M. Wittmann, P.S. Helliwell. Dermatology and therapy. 2013, 3, 1.
 - 26 K. Jarnagin, S. Chanda, D. Coronado, V. Ciaravino, L.T. Zane, E. Guttman-Yassky, M.G. Lebwohl. Journal of drugs in dermatology : JDD. 2016, 15, 390.
 - 27 S.C. Chan, S.H. Li, J.M. Hanifin. The Journal of investigative dermatology. 1993, 100, 681.
 - 28 J.M. Hanifin, S.C. Chan. The Journal of investigative dermatology. 1995, 105, 845.
 - 29 S. Weidinger, N. Novak. Lancet (London, England). 2016, 387, 1109.
 - 30 M. Boguniewicz, D.Y. Leung. Immunological reviews. 2011, 242, 233.
 - 31 J.K. Gittler, A. Shemer, M. Suarez-Farinas, J. Fuentes-Duculan, K.J. Gulewicz, C.Q. Wang, H. Mitsui, I. Cardinale, C. de Guzman Strong, J.G. Krueger, E. Guttman-Yassky. The Journal of allergy and clinical immunology. 2012, 130, 1344.

- 32 S. Noda, J.G. Krueger, E. Guttman-Yassky. *The Journal of allergy and clinical immunology*. 2015, 135, 324.
- 33 P.M. Brunner, E. Guttman-Yassky, D.Y. Leung. *The Journal of allergy and clinical immunology*. 2017, 139, S65.
- 34 D. Malajian, E. Guttman-Yassky. *Cytokine*. 2015, 73, 311.
- 35 T. Czarnowicki, J.G. Krueger, E. Guttman-Yassky. *The Journal of allergy and clinical immunology*. 2017, 139, 1723.
- 36 A. Wollenberg, S. Kraft, D. Hanau, T. Bieber. *The Journal of investigative dermatology*. 1996, 106, 446.
- 37 A. Wollenberg, M. Wagner, S. Gunther, A. Towarowski, E. Tuma, M. Moderer, S. Rothenfusser, S. Wetzel, S. Endres, G. Hartmann. *The Journal of investigative dermatology*. 2002, 119, 1096.
- 38 E. Guttman-Yassky, M.A. Lowes, J. Fuentes-Duculan, J. Whynot, I. Novitskaya, I. Cardinale, A. Haider, A. Khatcherian, J.A. Carucci, R. Bergman, J.G. Krueger. *The Journal of allergy and clinical immunology*. 2007, 119, 1210.
- 39 H. Fujita, A. Shemer, M. Suarez-Farinas, L.M. Johnson-Huang, S. Tintle, I. Cardinale, J. Fuentes-Duculan, I. Novitskaya, J.A. Carucci, J.G. Krueger, E. Guttman-Yassky. *The Journal of allergy and clinical immunology*. 2011, 128, 574.
- 40 S. Noda, M. Suarez-Farinas, B. Ungar, S.J. Kim, C. de Guzman Strong, H. Xu, X. Peng, Y.D. Estrada, S. Nakajima, T. Honda, J.U. Shin, H. Lee, J.G. Krueger, K.H. Lee, K. Kabashima, E. Guttman-Yassky. *The Journal of allergy and clinical immunology*. 2015, 136, 1254.
- 41 T. Werfel, J.P. Allam, T. Biedermann, K. Eyerich, S. Gilles, E. Guttman-Yassky, W. Hoetzenecker, E. Knol, H.U. Simon, A. Wollenberg, T. Bieber, R. Lauener, P. Schmid-Grendelmeier, C. Traidl-Hoffmann, C.A. Akdis. *The Journal of allergy and clinical immunology*. 2016, 138, 336.
- 42 T. Savinko, S. Matikainen, U. Saarialho-Kere, M. Lehto, G. Wang, S. Lehtimäki, P. Karisola, T. Reunala, H. Wolff, A. Lauerma, H. Alenius. *The Journal of investigative dermatology*. 2012, 132, 1392.
- 43 M.K. Aktar, M. Kido-Nakahara, M. Furue, T. Nakahara. *Allergy*. 2015, 70, 846.
- 44 M. Suarez-Farinas, B. Ungar, J. Correa da Rosa, D.A. Ewald, M. Rozenblit, J. Gonzalez, H. Xu, X. Zheng, X. Peng, Y.D. Estrada, S.R. Dillon, J.G. Krueger, E. Guttman-Yassky. *The Journal of allergy and clinical immunology*. 2015, 135, 1218.
- 45 M.D. Howell, B.E. Kim, P. Gao, A.V. Grant, M. Boguniewicz, A. De Benedetto, L. Schneider, L.A. Beck, K.C. Barnes, D.Y. Leung. *The Journal of allergy and clinical immunology*. 2007, 120, 150.
- 46 D.A. Ewald, D. Malajian, J.G. Krueger, C.T. Workman, T. Wang, S. Tian, T. Litman, E. Guttman-Yassky, M. Suarez-Farinas. *BMC medical genomics*. 2015, 8, 60.
- 47 T. Ruzicka, J.M. Hanifin, M. Furue, G. Pulka, I. Młynarczyk, A. Wollenberg, R. Galus, T. Etoh, R. Mihara, H. Yoshida, J. Stewart, K. Kabashima; XCIMA Study Group. *The New England journal of medicine*. 2017, 376, 826.
- 48 M. Furue, K. Yamamura, M. Kido-Nakahara, T. Nakahara, Y. Fukui. *Allergy*. 2018, 73, 29.
- 49 K.E. Nogales, L.C. Zaba, E. Guttman-Yassky, J. Fuentes-Duculan, M. Suarez-Farinas, I. Cardinale, A. Khatcherian, J. Gonzalez, K.C. Pierson, T.R. White, C. Pensabene, I. Coats, I. Novitskaya, M.A. Lowes, J.G. Krueger. *The British journal of dermatology*. 2008, 159, 1092.
- 50 N. Novak, S. Kruse, S. Kraft, E. Geiger, H. Kluken, R. Fimmers, K.A. Deichmann, T. Bieber. *The Journal of investigative dermatology*. 2002, 119, 870.
- 51 J.Q. He, M. Chan-Yeung, A.B. Becker, H. Dimich-Ward, A.C. Ferguson, J. Manfreda, W.T. Watson, A.J. Sandford. *Genes and immunity*. 2003, 4, 385.

- 52 A. Lesiak, P. Kuna, M. Zakrzewski, M. van Geel, R.S. Bladergroen, K. Przybylowska, I. Stelmach, P. Majak, T. Hawro, A. Sysa-Jedrzejowska, J. Narbutt. *Experimental dermatology*. 2011, 20, 491.
- 53 J.H. Namkung, J.E. Lee, E. Kim, H.J. Kim, E.Y. Seo, H.Y. Jang, E.S. Shin, E.Y. Cho, J.M. Yang. *Experimental dermatology*. 2011, 20, 915.
- 54 J.I. Silverberg, R. Kantor. *Dermatologic clinics*. 2017, 35, 327.
- 55 P.Y. Ong, T. Ohtake, C. Brandt, I. Strickland, M. Boguniewicz, T. Ganz, R.L. Gallo, D.Y. Leung. *The New England journal of medicine*. 2002, 347, 1151.
- 56 M.D. Howell, A. Wollenberg, R.L. Gallo, M. Flaig, J.E. Streib, C. Wong, T. Pavicic, M. Boguniewicz, D.Y. Leung. *The Journal of allergy and clinical immunology*. 2006, 117, 836.
- 57 J.D. Hamilton, M. Suarez-Farinas, N. Dhingra, I. Cardinale, X. Li, A. Kostic, J.E. Ming, A.R. Radin, J.G. Krueger, N. Graham, G.D. Yancopoulos, G. Pirozzi, E. Guttman-Yassky. *The Journal of allergy and clinical immunology*. 2014, 134, 1293.
- 58 L.A. Beck, D. Thaci, J.D. Hamilton, N.M. Graham, T. Bieber, R. Rocklin, J.E. Ming, H. Ren, R. Kao, E. Simpson, M. Ardeleanu, S.P. Weinstein, G. Pirozzi, E. Guttman-Yassky, M. Suarez-Farinas, M.D. Hager, N. Stahl, G.D. Yancopoulos, A.R. Radin. *The New England journal of medicine*. 2014, 371, 130.
- 59 E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork, J.I. Silverberg, M. Deleuran, Y. Kataoka, J.P. Lacour, K. Kingo, M. Worm, Y. Poulin, A. Wollenberg, Y. Soo, N.M. Graham, G. Pirozzi, B. Akinlade, H. Staudinger, V. Mastey, L. Eckert, A. Gadkari, N. Stahl, G.D. Yancopoulos, M. Ardeleanu; SOLO 1 and SOLO 2 Investigators. *The New England journal of medicine*. 2016, 375, 2335.
- 60 D. Gutowska-Owsiak, A.L. Schaupp, M. Salimi, T.A. Selvakumar, T. McPherson, S. Taylor, G.S. Ogg. *Experimental dermatology*. 2012, 21, 104.
- 61 V.Y. Shi, M. Leo, L. Hassoun, D.S. Chahal, H.I. Maibach, R.K. Sivamani. *Journal of the American Academy of Dermatology*. 2015, 73, 856.
- 62 E. Guttman-Yassky, J.G. Krueger, M.G. Lebwohl. *Experimental dermatology*. 2018, 27, 409.
- 63 P.M. Brunner, D.Y.M. Leung, E. Guttman-Yassky. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2018, 120, 34.
- 64 Y. Yamazaki, Y. Nakamura, G. Nunez. *Allergology international : official journal of the Japanese Society of Allergology*. 2017, 66, 539.
- 65 U. Wollina. *Clinical, cosmetic and investigational dermatology*. 2017, 10, 51.
- 66 S.W. Hong, M.R. Kim, E.Y. Lee, J.H. Kim, Y.S. Kim, S.G. Jeon, J.M. Yang, B.J. Lee, B.Y. Pyun, Y.S. Gho, Y.K. Kim. *Allergy*. 2011, 66, 351.
- 67 V.K. Raker, C. Becker, K. Steinbrink. *Frontiers in immunology*. 2016, 7, 123.
- 68 S.G. Dastidar, D. Rajagopal, A. Ray. *Current opinion in investigational drugs (London, England : 2000)*. 2007, 8, 364.
- 69 V. Boswell-Smith, D. Spina, C.P. Page. *British journal of pharmacology*. 2006, 147 Suppl 1, S252.
- 70 S.P. Alexander, D. Fabbro, E. Kelly, N.V. Marrion, J.A. Peters, E. Faccenda, S.D. Harding, A.J. Pawson, J.L. Sharman, C. Southan, J.A. Davies; CGTP Collaborators. *British journal of pharmacology*. 2017, 174 Suppl 1, S272.
- 71 L.I. Sakkas, A. Mavropoulos, D.P. Bogdanos. *Current medicinal chemistry*. 2017, 24, 3054.
- 72 V.C. Manganiello, T. Murata, M. Taira, P. Belfrage, E. Degerman. *Arch Biochem Biophys*. 1995, 322, 1.

- 73 A.R. Moore, D.A. Willoughby. *Clinical and experimental immunology*. 1995, 101, 387.
- 74 W. Baumer, J. Hoppmann, C. Rundfeldt, M. Kietzmann. *Inflammation & allergy drug targets*. 2007, 6, 17.
- 75 D.M. Essayan. *The Journal of allergy and clinical immunology*. 2001, 108, 671.
- 76 S.R. Grewe, S.C. Chan, J.M. Hanifin. *The Journal of allergy and clinical immunology*. 1982, 70, 452.
- 77 P.H. Schafer, F. Truzzi, A. Parton, L. Wu, J. Kosek, L.H. Zhang, G. Horan, A. Saltari, M. Quadri, R. Lotti, A. Marconi, C. Pincelli. *Cellular signalling*. 2016, 28, 753.
- 78 J.M. Hanifin, R. Lloyd, K. Okubo, L.L. Guerin, L. Fancher, S.C. Chan. *The Journal of investigative dermatology*. 1992, 98, 100S.
- 79 K. McCluskie, U. Klein, C. Linnevers, Y.H. Ji, A. Yang, C. Husfeld, G.R. Thomas. *The Journal of pharmacology and experimental therapeutics*. 2006, 319, 468.
- 80 A. Samrao, T.M. Berry, R. Goreshi, E.L. Simpson. *Archives of dermatology*. 2012, 148, 890.
- 81 T. Akama, S.J. Baker, Y.K. Zhang, V. Hernandez, H. Zhou, V. Sanders, Y. Freund, R. Kimura, K.R. Maples, J.J. Plattner. *Bioorganic & medicinal chemistry letters*. 2009, 19, 2129.
- 82 Y.R. Freund, T. Akama, M.R. Alley, J. Antunes, C. Dong, K. Jarnagin, R. Kimura, J.A. Nieman, K.R. Maples, J.J. Plattner, F. Rock, R. Sharma, R. Singh, V. Sanders, Y. Zhou. *FEBS Lett*. 2012, 586, 3410.
- 83 P.H. Schafer, P. Chen, L. Fang, A. Wang, R. Chopra. *Journal of immunology research*. 2015, 2015, 906349.
- 84 J.G. Krueger. *Journal of the American Academy of Dermatology*. 2017, 76, AB47. Abstract 5413.
- 85 M. Grassberger, T. Baumruker, A. Enz, P. Hiestand, T. Hultsch, F. Kalthoff, W. Schuler, M. Schulz, F.J. Werner, A. Winiski, B. Wolff, G. Zenke. *The British journal of dermatology*. 1999, 141, 264.
- 86 K. Gutfreund, W. Bienias, A. Szewczyk, A. Kaszuba. *Postepy dermatologii i alergologii*. 2013, 30, 165.
- 87 P. Gisondi, C.N. Ellis, G. Girolomoni. *International journal of clinical practice*. 2005, 59, 969.
- 88 D. Simon, E. Vassina, S. Yousefi, L.R. Braathen, H.U. Simon. *Allergy*. 2005, 60, 944.
- 89 D.A. Norris. *Journal of the American Academy of Dermatology*. 2005, 53, S17.
- 90 R. Brattsand, M. Linden. *Alimentary pharmacology & therapeutics*. 1996, 10 Suppl 2, 81.
- 91 R. Nazarian, J.M. Weinberg. *Current opinion in investigational drugs (London, England : 2000)*. 2009, 10, 1236.
- 92 L.T. Zane, L. Kircik, R. Call, E. Tschen, Z.D. Draelos, S. Chanda, M. Van Syoc, A.A. Hebert. *Pediatric dermatology*. 2016, 33, 380.
- 93 L.F. Eichenfield, R.S. Call, D.W. Forsha, Fowler J Jr, A.A. Hebert, M. Spellman, L.F. Stein Gold, M. Van Syoc, L.T. Zane, E. Tschen. *Journal of the American Academy of Dermatology*. 2017, 77, 641.
- 94 EUCRISA- crisaborole ointment [package insert]. New York, NY: Pfizer Labs. 2017.
- 95 US Food and Drug Administration. FDA Approves Eucrisa for eczema [press release]. Silver Spring, MD: US Food and Drug Administration: December 16, 2016.
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533371.htm>
(accessed: April 20, 2018).
- 96 J.M. Hanifin, G. Rajka. *Acta Derm Venereol*. 1980, 60, 44.
- 97 J.I. Silverberg, D.B. Nelson, G. Yosipovitch. *The Journal of dermatological treatment*. 2016, 27, 568.

- 98 J.D. Bos, M.M. Meinardi. *Experimental dermatology*. 2000, 9, 165.
- 99 J.M. Hanifin, C.N. Ellis, I.J. Frieden, R. Folster-Holst, L.F. Stein Gold, A. Secci, A.J. Smith, C. Zhao, E. Kornyeveva, L.F. Eichenfield. *Journal of the American Academy of Dermatology*. 2016, 75, 297.
- 100 F. Ohba, S. Matsuki, S. Imayama, K. Matsuguma, S. Hojo, M. Nomoto, H. Akama. *The Journal of dermatological treatment*. 2016, 27, 467.
- 101 O. Nemoto, N. Hayashi, Y. Kitahara, M. Furue, S. Hojo, M. Nomoto, S. Shima; Japanese E6005 Study Investigators. *The Journal of dermatology*. 2016, 43, 881.
- 102 M. Furue, Y. Kitahara, H. Akama, S. Hojo, N. Hayashi, H. Nakagawa; JAPANESE E6005 Study Investigators. *The Journal of dermatology*. 2014, 41, 577.
- 103 European Task Force on Atopic Dermatitis. *Dermatology (Basel, Switzerland)*. 1993, 186, 23.
- 104 F. Ohba, M. Nomoto, S. Hojo, H. Akama. *The Journal of dermatological treatment*. 2016, 27, 241.
- 105 N. Ishii, M. Shirato, H. Wakita, K. Miyazaki, Y. Takase, O. Asano, K. Kusano, E. Yamamoto, C. Inoue, I. Hishinuma. *The Journal of pharmacology and experimental therapeutics*. 2013, 346, 105.
- 106 J. Felding, M.D. Sorensen, T.D. Poulsen, J. Larsen, C. Andersson, P. Refer, K. Engell, L.G. Ladefoged, T. Thormann, A.M. Vinggaard, P. Hegardt, A. Sohoel, S.F. Nielsen. *Journal of medicinal chemistry*. 2014, 57, 5893.
- 107 LEO 29102 Cream in the Treatment of Atopic Dermatitis [Clinicaltrials.gov web site, https://clinicaltrials.gov/ct2/show/NCT01037881](https://clinicaltrials.gov/ct2/show/NCT01037881) (accessed: August 9, 2018).
- 108 A Safety and Efficacy of DRM02 in Subjects With Atopic Dermatitis [Clinicaltrials.gov web site, https://clinicaltrials.gov/ct2/show/NCT01993420](https://clinicaltrials.gov/ct2/show/NCT01993420) (accessed: August 9, 2018).
- 109 Dermira Inc. Dermira Reports Fourth Quarter and Full Year 2015 Financial Results and Provides Corporate Update [press release]. Menlo Park, CA: Globe Newswire: March 3, 2016. <http://investor.dermira.com/phoenix.zhtml?c=253686&p=irol-newsArticle&ID=2145560> (accessed: August 9, 2018).
- 110 OTEZLA® (apremilast) tablets, for oral use Summit, NJ: Celgene Corporation. 06/2017.
- 111 P.H. Schafer, A. Parton, L. Capone, D. Cedzik, H. Brady, J.F. Evans, H.W. Man, G.W. Muller, D.I. Stirling, R. Chopra. *Cellular signalling*. 2014, 26, 2016.
- 112 Efficacy and Safety Study of Apremilast in Subjects With Moderate to Severe Atopic Dermatitis [Clinicaltrials.gov web site, https://clinicaltrials.gov/ct2/show/NCT02087943](https://clinicaltrials.gov/ct2/show/NCT02087943) (accessed: August 9, 2018).
- 113 M. Boguniewicz, L. Fonacier, E. Guttman-Yassky, P.Y. Ong, J. Silverberg, J.R. Farrar. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2018, 120, 10.

TABLE 1 Possible effects on cytokines by topical drug classes used to treat AD^a

Producing cell	PDE4 inhibitors ^{b,[24, 80-84]}	TCI ^[85-88]	TCS ^[9, 10, 14, 87, 89, 90]
Th1	↓IFN γ , IL-2 , TNF α , IL-8, GM-CSF	↓IFN γ , IL-2, IL-3, TNF α	↓IFN γ , IL-2, TNF α , IL-8, GM-CSF
Th2	↓IL-4, IL-5 , IL-6, IL-10 , IL-13	↓IL-4, IL-5, IL-10, IL-13	↓IL-4, IL-5, IL-6, IL-10, IL-13
Th17	↓ IL-17 , IL-22		↓IL-17A, IL-22
Th22	↓IL-22		↓IL-22
Monocytes	↓IL-6, IL-10	↓IL-10	↓IL-6, IL-10
Dendritic cells or macrophages	↓IL-12, IL-23		↓IL-1, IL-12, IL-23
Neutrophils	↓IL-8		↓IL-8

GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN γ , interferon gamma; IL, interleukin; PDE4, phosphodiesterase 4; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TNF α , tumour necrosis factor alpha.

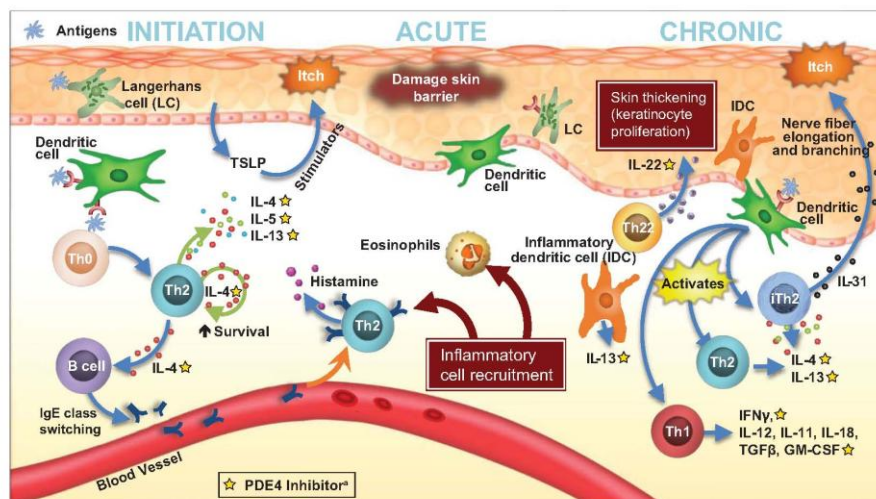
^aActual effect on cytokine may vary with specific agent and potency.

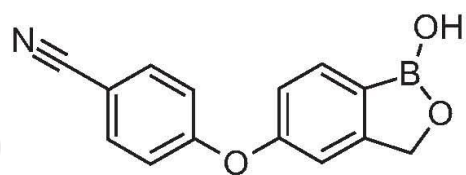
^bBolded cytokines indicate those that have been shown to be affected by crisaborole.

FIGURE LEGENDS

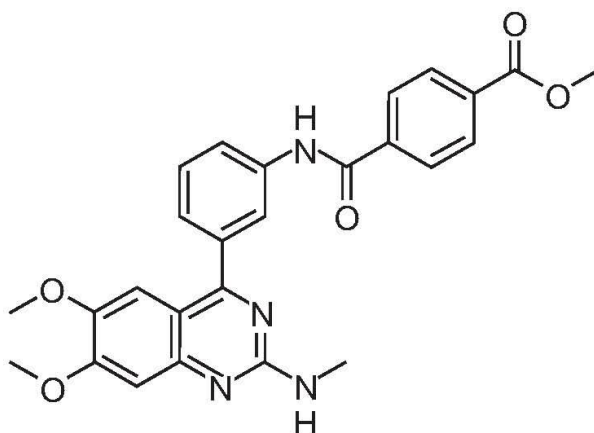
FIGURE 1 Immune pathways associated with AD. ^aA star has been placed to the right of cytokines or molecules that are known to be affected by PDE4 inhibition. Actual effect on cytokines may vary with specific agent and potency. AD, atopic dermatitis; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN γ , interferon gamma; IgE, immunoglobulin E; IL, interleukin; TGF, transforming growth factor; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

FIGURE 2 PDE4 inhibitor chemical structures and molecular weights. PDE4, phosphodiesterase 4.

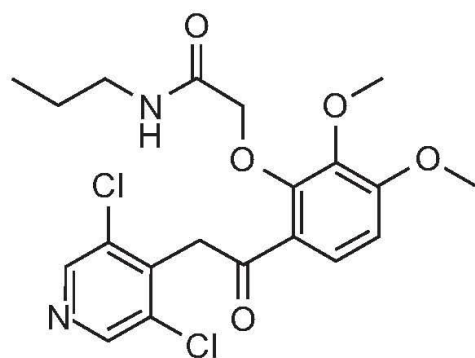




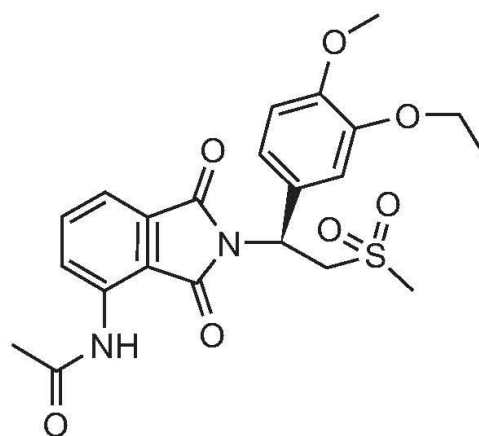
Crisaborole
 $M_r = 251$ D



E6005/RVT-501
 $M_r = 472$ D



LEO 29102
 $M_r = 441$ D



Apremilast
 $M_r = 461$ D