ORIGINAL ARTICLE

OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-controlled study

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Background: Peripheral leukocytes in patients with atopic dermatitis (AD) have elevated phosphodiesterase-4 activity, which is associated with production of proinflammatory mediators. OPA-15406 is a phosphodiesterase-4 inhibitor with high selectivity for phosphodiesterase-4-B.

Objectives: We sought to assess effectiveness and tolerability of topical OPA-15406 in patients with AD.

Methods: This was a randomized, double-blind, vehicle-controlled, phase-II study. Patients 10 to 70 years of age with mild or moderate AD received topical OPA-15406 0.3% (n = 41), OPA-15406 1% (n = 43), or vehicle (n = 37) twice daily for 8 weeks.

Results: The primary end point, Investigator Global Assessment of Disease Severity score of 0 or 1 with greater than or equal to 2-grade reduction, was met at week 4 in the OPA-15406 1% group (P = .0165 vs vehicle). Mean percentage improvement from baseline Eczema Area and Severity Index score for OPA-15406 1% was notable in week 1 (31.4% vs 6.0% for vehicle; P = .0005), even larger in week 2 (39.0% vs 3.0%; P = .0001), and persisted for 8 weeks. Visual analog scale pruritus scores improved from moderate to mild within the first week in the OPA-15406 1% group (36.4% mean change; P = .0011). OPA-15406 levels in blood were negligible. Incidence of adverse events was low, with most events mild in intensity.

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Disclosure: Dr Hanifin served as a consultant to Anacor Pharmaceutical, Dermira, Leo Pharma, and Otsuka Pharmaceuticals and participated in studies in recent years for Pfizer, Merck, Chugai Pharmaceutical, and Anacor Pharmaceuticals. Dr Ellis served as a consultant to Celgene Corporation, Ferndale Healthcare, Johnson & Johnson, and Otsuka Pharmaceutical. Dr Frieden serves as the chair of the data and safety monitoring board for this OPA-15406 phase-II study, is an advisor for Galderma SA and Anacor Pharmaceuticals, and is a consultant with Laboratoires Pierre Fabre. Dr Fölster-Holst participated in studies in recent years for Novartis International AG, Astellas Pharma, Laboratoires Pierre Fabre, Regeneron Pharmaceuticals, and Pharmanet AG; delivered presentations for La Roche–Posay, ALK, Abbott Laboratories, and Neubourg GmbH; served on an advisory board for Johnson & Johnson; and is a member of the data and safety monitoring board for this OPA-15406 phase-II study. Dr Stein Gold is a member of the data and safety monitoring board for this OPA-15406 phase-II study and is an advisor and investigator for Anacor Pharmaceuticals and an investigator for GSK. Drs Secci, Zhao, and Kornyeyeva and Ms Smith are employees of Otsuka Pharmaceutical Development and Commercialization Inc. Dr Eichenfield served as a consultant and investigator for Anacor Pharmaceuticals and Otsuka Pharmaceutical.

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Limitations: Further confirmatory phase-III studies are required.

Conclusion: OPA-15406 ointment may provide an effective therapeutic modality for patients with mild to moderate AD. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.04.001.)

Key words: atopic dermatitis; atopic eczema; OPA-15406; phosphodiesterase type 4 inhibitor; topical agents; topical calcineurin inhibitor.

CAPSULE SUMMARY

- Peripheral leukocytes of patients with atopic dermatitis have increased phosphodiesterase activity.
- OPA-15406, a new topical inhibitor of phosphodiesterase-4, provided rapid and sustained relief of patient-reported pruritus and significant overall improvement of atopic dermatitis.
- OPA-15406-mediated selective phosphodiesterase-4 inhibition may provide an effective treatment modality for patients with atopic dermatitis.

This study was conducted in compliance with International Conference on Harmonization good clinical practice guidelines for conducting, recording, and reporting clinical trials, and for archiving essential documents.[1] Consistent with ethical principles for the protection of human research subjects,[2] no trial procedures were performed on trial candidates until written consent had been obtained. The informed consent form, protocol, and amendments for the study were submitted to and approved by the institutional review board or independent ethics committee for each respective trial site or country.

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritic erythematous skin lesions and associated cutaneous dysfunction (eg, barrier-disrupted skin).[3] The onset of AD occurs most commonly between 3 and 6 months of age, with approximately 60% of patients developing the condition in the first year of life and 90% by 5 years of age.[4-6] The majority of affected individuals have resolution of disease during childhood, although 10% to 30% of patients maintain the condition throughout their lives, and a small number of others develop first symptoms as adults.[4,7] It has been estimated that approximately 18 million people are living with AD in the United States, many with undiagnosed disease.[8]

AD cannot be cured, but prompt and effective management can greatly improve both the symptoms and quality of life of affected individuals. According to guidelines from the American Academy of Dermatology,[4] when emollient use and good skin care are insufficient to control AD, pharmacologic treatment should start with mild- to moderate-potency topical corticosteroids. If this approach is unsuccessful, treatment with calcineurin inhibitors can be considered. For severe AD that remains refractory to topical agents, treatment may be intensified to ultraviolet phototherapy and systemic immunomodulators. Although current pharmacotherapeutic approaches have proven to be efficacious in clinical trials,[4,9-13] each has limitations. Extended use of topical corticosteroids is associated with cutaneous atrophy[3] and can sometimes have systemic side effects, such as suppression of the hypothalamic-pituitary-adrenal axis, especially in children.[14] Available topical calcineurin inhibitors carry boxed warnings posing some limitations on their long-term use, based on possible associations with lymphomas and skin malignancies in animal studies.[15,16] However, clinical studies in human beings have failed to identify an association between topical calcineurin inhibitor use and malignancies,[17] with the possible exception of a very slightly increased risk of skin lymphomas in patients with severe AD.[18]

Peripheral blood leukocytes in patients with AD have increased phosphodiesterase-4 (PDE4) activity,[19-21] which has been associated with higher production of the proinflammatory mediators tumor necrosis factor-alfa, interleukin (IL)-17, IL-22, and interferon-γ and lower production of the anti-inflammatory mediator IL-10.[21] In pharmacologic analyses, the new chemical entity OPA-15406 exhibited highly selective inhibitory activity against PDE4 subtypes, particularly subtype B (IC_{50} = 11.2 nmol/L), and improved skin condition in relevant animal models of AD (unpublished data). This report evaluates the clinical activity, pharmacokinetics, and tolerability of 2 concentrations of OPA-15406 ointment in adult and adolescent patients with mild or moderate AD.

METHODS

Study design

This was a phase-II, randomized, double-blind, vehicle-controlled, parallel-group study. Eligible