ORIGINAL ARTICLE

Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2)

Phoebe Rich, MD,[a] Melinda Gooderham, MD,[b] Hervé Bachelez, MD, PhD,[c] Joana Goncalves, MD,[d] Robert M. Day, PhD,[d] Rongdean Chen, PhD,[d] and Jeffrey Crowley, MD[e]
Portland, Oregon; Peterborough, Ontario, Canada; Paris, France; Warren, New Jersey; and Bakersfield, California

Background: In the phase III double-blind Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) 1 and 2, apremilast, an oral phosphodiesterase 4 inhibitor, demonstrated efficacy in moderate to severe psoriasis.

Objective: We sought to evaluate efficacy of apremilast in nail/scalp psoriasis in ESTEEM 1 and 2.

Methods: A total of 1255 patients were randomized (2:1) to apremilast 30 mg twice daily or placebo. At week 16, placebo patients switched to apremilast through week 32, followed by a randomized withdrawal phase to week 52. A priori efficacy analyses included patients with nail (target nail Nail Psoriasis Severity Index score ≥1) and moderate to very severe scalp (Scalp Physician Global Assessment score ≥3) psoriasis at baseline.

Results: At baseline, 66.1% and 64.7% of patients had nail psoriasis; 66.7% and 65.5% had moderate to very severe scalp psoriasis in ESTEEM 1 and 2. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index score versus placebo; mean percent change: −22.5% versus +6.5% (ESTEEM 1; $P < .0001$) and −29.0% versus −7.1% (ESTEEM 2; $P = .0052$). At week 16, apremilast produced greater NAPSI-50 response (50% reduction from baseline in target nail Nail Psoriasis Severity Index score) versus placebo (both studies $P < .0001$) and ScPGA response (Scalp Physician Global Assessment score 0 or 1) versus placebo (both studies $P < .0001$). Improvements were generally maintained over 52 weeks in patients with Psoriasis Area and Severity Index response at week 32.

From the Oregon Health and Science University[a]; SKiN Centre for Dermatology and Probity Medical Research, Peterborough[b]; Sorbonne Paris Cité Université Paris Diderot, Assistance Publique-Hôpitaux de Paris Hôpital Saint-Louis[c]; Celgene Corporation, Warren[d]; and Bakersfield Dermatology.[e]

These studies were sponsored by Celgene Corporation.

Disclosures: Dr Bachelez received honoraria/research funding as an advisory board member and/or consultant for AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Eli Lilly and Company, Janssen Pharmaceuticals, LEO Pharma, Novartis, Pfizer, Merck Sharp & Dohme, and Pierre Fabre. Dr Crowley received honoraria/research funding as a consultant for AbbVie, Amgen, Celgene Corporation, and Eli Lilly and Company; was an investigator for AbbVie, Amgen, Celgene Corporation, Eli Lilly and Company, Janssen Pharmaceuticals, Merck, and Pfizer; and was a speaker for AbbVie, Amgen, and Celgene Corporation. Drs Goncalves, Day, and Chen are employees of Celgene Corporation. Dr Gooderham received honoraria/research funding as a consultant for Janssen Pharmaceuticals; was a data safety monitoring board member for Kyowa Hakko Kirin Pharma; was an investigator for AbbVie, Amgen, Celgene Corporation, Dermira, Dr Reddy, Eli Lilly and Company, Forward Pharma, Galderma Laboratories, Kyowa Hakko Kirin Pharma, Kythera, LEO Pharma, MedImmune, Merck & Co Inc, Novartis, Pfizer, Regeneron, Roche Laboratories, and Takeda Pharmaceuticals USA Inc; and was a speaker for AbbVie, Actelion, Amgen, Astellas Pharma US Inc, Celgene Corporation, Eli Lilly and Company, Galderma Laboratories, LEO Pharma, and Novartis. Dr Rich received honoraria/research funding as an advisory board member for Eli Lilly and Company and Sandoz; was a consultant for Polichem; and was an investigator for AbbVie, Amgen, Celgene Corporation, Eli Lilly and Company, Janssen, Merck & Co Inc, Novartis, and Pfizer.

Accepted for publication September 1, 2015.
Reprints not available from the authors.

Correspondence to: Phoebe Rich, MD, Oregon Dermatology and Research Center, 2565 NW Lovejoy St, Portland, OR 97210. E-mail: phoeberich@aol.com.

Published online November 5, 2015.
0190-9622

http://dx.doi.org/10.1016/j.jaad.2015.09.001

Limitations: Baseline randomization was not stratified for nail/scalp psoriasis.

Conclusion: Apremilast reduces the severity of nail/scalp psoriasis. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.09.001.)

Key words: apremilast; nail psoriasis; phosphodiesterase 4 inhibitor; psoriasis; scalp psoriasis; systemic therapy.

CAPSULE SUMMARY

- Nail and scalp psoriasis negatively impact patient quality of life.
- Apremilast 30 mg twice daily significantly reduced the severity of nail and scalp psoriasis at week 16; these improvements were sustained over time.
- Apremilast is a viable oral treatment option for patients with difficult-to-treat nail or scalp psoriasis.

Psoriasis is a chronic, systemic inflammatory disease with a prevalence as high as 3.1% in the United States.[1] In patients with psoriasis, dysregulation of the immune response is thought to result in a chronic imbalance in the production of proinflammatory and anti-inflammatory cytokines.[2-4] Available therapies suppress inflammatory responses or target specific mediators implicated in the pathogenesis of psoriasis. However, long-term use of these therapies is often compromised by variable efficacy, safety, and tolerability issues, or need for administration via injection or infusion.[5,6]

Dermatologic signs and symptoms of psoriasis often occur in difficult-to-treat areas such as the nails and scalp. Nail involvement occurs in approximately 50% of patients with plaque psoriasis, with a lifetime incidence of 80% to 90%[7-9]; scalp involvement affects up to 80% of patients with psoriasis.[10,11] Involvement of these difficult-to-treat areas may have particularly detrimental effects on patient quality of life.[7,10-12] Treatment of nail and scalp psoriasis with topical therapy is often challenging because of the poor diffusion into the nail tissue and the inaccessibility of scalp lesions.[8,11] Patient satisfaction and compliance with current treatment modalities for nail and scalp psoriasis are often low because of difficulties in administration to the scalp, poor compliance, and inadequate long-term efficacy.[13-15]

Cyclic adenosine monophosphate is a key modulator of immune cell responses, and its levels are regulated by phosphodiesterase 4.[16] Apremilast, an oral phosphodiesterase 4 inhibitor, increases intracellular cyclic adenosine monophosphate levels, thus regulating production of proinflammatory and anti-inflammatory mediators.[17] Apremilast was approved by the US Food and Drug Administration in 2014 and by the European Commission in 2015 for the treatment of adult patients with active psoriatic arthritis and for patients with moderate to severe plaque psoriasis.[18,19]

The approval of apremilast for psoriasis was based on the findings of the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase III clinical trial program, comprising 2 multicenter, randomized, placebo-controlled studies that evaluated the efficacy, safety, and tolerability of apremilast in adults with moderate to severe plaque psoriasis. The efficacy of apremilast in patients with nail and scalp psoriasis over 16 weeks of treatment has been reported.[20,21] This report describes the efficacy of apremilast in the subsets of patients from the phase III ESTEEM trials with nail psoriasis and moderate to very severe scalp psoriasis with up to 52 weeks of treatment.

METHODS

Study design and participants

ESTEEM 1 and 2 were similarly designed phase III, multicenter, randomized, double-blind, placebo-controlled studies of apremilast 30 mg twice daily (BID) in patients with moderate to severe plaque psoriasis (Fig 1). Full details of the study design, inclusion and exclusion criteria, patient population, and primary safety and efficacy results for ESTEEM 1 and 2 have been described previously.[20,21]

Nail and scalp assessments

Nail and scalp assessments were made in all patients at baseline using the Nail Psoriasis Severity Index (NAPSI) and Scalp Physician Global Assessment (ScPGA). NAPSI is a composite score of physician assessment of nail psoriasis[22]; a target nail was used to assess nail involvement, if nail involvement (NAPSI score ≥1) was present at baseline. Target nail NAPSI scores range from 0 to 8; higher scores indicate greater severity, and a decrease in NAPSI score indicates improvement. The target thumbnail or fingernail that represented the worst nail psoriasis at baseline was assessed. Nail assessments included the percent change from baseline in