Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients With Moderate to Severe Plaque Psoriasis: Pruritus and DLQI Correlations at Week 16 (ESTEEM 1 and 2)

Steven R. Feldman, MD, PhD1; Diamant Thaci, MD2; Mark Ling, MD3; Melinda Gooderham, MD, MSc4; ChiaChi Hu, EdM, MS5; Robert M. Day, PhD5; Mark Goodfield, MD, FRCP6

1Wake Forest University School of Medicine, Winston-Salem, NC, USA; 2University Hospital Schleswig-Holstein, Lübeck, Germany; 3MedaPhase Inc., Newnan, GA, USA; 4SKiN Centre for Dermatology, Peterborough, ON, Canada; 5Celgene Corporation, Warren, NJ, USA; 6Leeds General Infirmary, Leeds, UK

Presented at: the 73rd Annual Meeting of the American Academy of Dermatology; March 20-24, 2015; San Francisco, CA.

This study was sponsored by Celgene Corporation.
Disclosures

- Dr. Steven R. Feldman has received honoraria and research grants as an investigator, speaker, and/or consultant for Abbott Labs, Amgen, Anacor Pharmaceuticals, Baxter, Caremark, Celgene, Galderma, Gerson Lehrman Group, Guidepoint Global, Hanall Pharmaceutical, Janssen, Kikaku, LEO Pharma, Lilly, Merck, Merz, Mylan, Novartis, Pfizer, Qurient, Stiefel/GSK, Suncare Research, Taro, and Xenoport; and has received royalties or owns stock in Causa Technologies, Informa Healthcare, Medical Quality Enhancement Corporation, UpToDate, and Xlibris.

- Prof. Dr. Diamant Thaci has received honoraria as a speaker, advisory board member, and/or a consultant for Celgene, AbbVie, Amgen, Biogen-Idec, Dignity, Janssen-Cilag, LEO Pharma, Lilly, Maruho, Mitsubishi, Merck, Novartis, Pfizer, UCB, and XenoPort.

- Dr. Mark Ling has served as an investigator for AbbVie, Amgen, Celgene, Johnson & Johnson/Janssen, Pfizer, and Valeant and as an advisory board member for PhotoMedex.

- Dr. Melinda Gooderham has been an investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Coherus, Eli Lilly, Galderma, Kyowa Hakko Kirin Pharma, LEO Pharma, Merck, Novartis, and Pfizer, and has served as a speaker for AbbVie, Amgen, Astellas, Galderma, Janssen, Leo Pharma, Novartis, and Pfizer.

- Ms. ChiaChi Hu and Dr. Robert M. Day are employees of Celgene Corporation.

- Dr. Mark Goodfield has received honoraria and research grants as an investigator and/or advisory board member for AbbVie, Celgene, Galderma, Janssen-Cilag, LEO Pharma, Novartis, and Pfizer.
Abstract

**Background:** Itching is one of the most bothersome psoriasis symptoms.\(^1\) ESTEEM 1 and 2 evaluated the effect of apremilast (APR) on itch in pts with moderate to severe plaque psoriasis.

**Methods:** Pts (PASI ≥12, BSA ≥10%, sPGA ≥3) were randomized (2:1) to APR 30 mg BID (APR30) or placebo (PBO). At Wk16, PBO pts switched to APR30 through Wk32. This was followed by a randomized treatment withdrawal phase up to Wk52. The correlation of pruritus with health-related quality of life was explored using Spearman correlations between pruritus (VAS 0-100 mm; 0=no itch, 100=worst itch) and Dermatology Life Quality Index (DLQI) score (0-30; 30=worst QOL) at baseline (BL) and Wk16. The results of pts who achieved minimal clinically important differences (MCID) in pruritus VAS score (improvement: ≥20%)\(^2\) and DLQI score (improvement: ≥5 points [MCID] or score 0-1)\(^3\) are summarized.

**Results:** The full analysis set included 844 pts from ESTEEM 1 (PBO: n=282; APR30: n=562) and 411 from ESTEEM 2 (PBO: n=137; APR30: n=274). At Wk16, mean changes from BL in pruritus VAS (mm) scores were significantly greater with APR30 (ESTEEM 1: -31.5; ESTEEM 2: -33.5) vs PBO (ESTEEM 1: -7.3; ESTEEM 2: -12.2; \(P<0.0001\)). Mean changes from BL with APR30 represented a nearly 50% decrease in pruritus severity, and improvement in pruritus was observed as early as Wk2 (\(P<0.001\) vs PBO; post hoc analysis). At Wk16, MCID in pruritus VAS was achieved by significantly more pts receiving APR30 (ESTEEM 1: 70.6%; ESTEEM 2: 67.5%; \(P<0.0001\)) vs PBO (ESTEEM 1: 33.7%; ESTEEM 2: 40.9%). Pruritus severity and DLQI scores were moderately correlated at BL (correlation coefficient, 0.55 [ESTEEM 1]; 0.48 [ESTEEM 2]; \(P<0.0001\)). Improvement in pruritus correlated with an improvement in DLQI (correlation coefficient, ≥0.43 in either group; \(P<0.0001\)) in ESTEEM 1 and 2. At Wk16, MCID in pruritus VAS score and DLQI (decrease ≥5 points) were achieved by more pts receiving APR30 (ESTEEM 1: 46.4%; ESTEEM 2: 47.1%) than PBO (ESTEEM 1: 12.8%; ESTEEM 2: 24.8%). MCID in pruritus VAS score and a DLQI score of 0-1 were achieved by more pts with APR30 (ESTEEM 1: 25.1%; ESTEEM 2: 28.5%) vs PBO (ESTEEM 1: 5.3%; ESTEEM 2: 8.0%).

**Conclusion:** Improvements in pruritus were seen with APR30 as early as Wk2, and approximately 70% of patients achieved an MCID in pruritus VAS at Wk16. Improvement in pruritus severity was correlated with an improvement in QOL.

Introduction and Objective

- Psoriasis is a chronic, systemic inflammatory disease that affects 1% to 3% of the world’s population.\(^1-3\)
- Itching is one of the most bothersome psoriasis symptoms for patients and an important factor contributing to disease severity.\(^4\)
- Apremilast, an oral PDE4 inhibitor, works intracellularly to regulate inflammatory mediators.\(^5\)
- Apremilast was approved by the FDA in 2014 and by the EC in 2015 for the treatment of psoriasis and psoriatic arthritis.\(^6,7\)
- ESTEEM is a phase 3 clinical trial program comprising 2 randomized, placebo-controlled studies evaluating the efficacy, safety, and tolerability of apremilast for the treatment of moderate to severe plaque psoriasis.
- The objective of the current analysis is to evaluate the effect of apremilast on pruritus and the correlation of pruritus with health-related quality of life* at Week 16 in ESTEEM 1 and ESTEEM 2.

*As measured by the Dermatology Life Quality Index.

EC=European Commission; ESTEEM=Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; FDA=US Food and Drug Administration; PDE4=phosphodiesterase 4.

Study Population

• Diagnosis of chronic plaque psoriasis, with moderate to severe plaque psoriasis at screening and baseline

Pruritus and health-related quality of life (QOL) endpoints:

– Pruritus visual analog scale (VAS)
  ▪ 100 mm scale: 0=no itch at all, 100=worst itch imaginable
  ▪ Minimal clinically important difference (MCID): ≥20% improvement from baseline

– Dermatology Life Quality Index (DLQI)²
  ▪ DLQI score to QOL impact “bands” (effect on QOL):
    o 0 to 1=no effect, 2 to 5=small effect, 6 to 10=moderate effect, 11 to 20=very large effect, 21 to 30=extremely large effect
  ▪ MCID: ≥5 points³

Improvement in pruritus was observed as early as Week 2 with apremilast vs. placebo. At Week 16, decrease in pruritus was significantly greater with apremilast vs. placebo (ESTEEM 1: -31.5 mm vs. -7.3 mm; ESTEEM 2: -33.5 mm vs. -12.2 mm, both \( P<0.0001 \)) – These changes represent a decrease of ~50% from baseline in the severity of pruritus.

Pruritus was measured on a 100-mm VAS. Baseline values: ESTEEM 1 – 65.0 mm (placebo) and 66.1 mm (apremilast 30 mg BID); ESTEEM 2 – 65.3 mm (placebo) and 67.7 mm (apremilast 30 mg BID). Data are as observed (figure) or last observation carried forward (bullet). In ESTEEM 1 at Week 16, n=248 (placebo) and n=500 (apremilast 30 mg BID); in ESTEEM 2 at Week 16, n=110 (placebo) and n=238 (apremilast 30 mg BID).

\*\( P<0.001 \) vs. placebo (post hoc analysis).
MCID achievement in pruritus VAS is defined as an improvement of ≥20% over baseline.¹

Patients in the full analysis set with a non-zero baseline value and at least one post-baseline value using last observation carried forward are included. MCID=minimal clinically important difference; VAS=visual analog scale. ESTEEM 1 N=844; ESTEEM 2 N=411.

MCID achievement is defined as an improvement of ≥5 points in DLQI score over baseline.1

Patients in the full analysis set with a baseline DLQI >5 are included, using last observation carried forward.

ESTEEM 1=695; ESTEEM 2=345

At Week 16, decrease in DLQI score was significantly greater with apremilast vs. placebo (ESTEEM 1: -6.6 vs. -2.1; ESTEEM 2: -6.7 vs. -2.8, both \( P<0.0001 \)).

At Week 16, 46.4% of patients receiving apremilast achieved MCID for both pruritus and DLQI.

*Data for line graphs are based on patients with pruritus VAS \( \geq 10 \) mm and DLQI \( \geq 5 \). Baseline pruritus VAS values: ESTEEM 1 – 66.1 mm (apremilast); ESTEEM 2 – 67.7 mm (apremilast). Baseline DLQI scores: ESTEEM 1 – 12.7 (apremilast); ESTEEM 2 – 12.6 (apremilast).

Reference line represents MCID, defined as an improvement of \( \geq 5 \) points in DLQI score or an improvement of \( \geq 20\% \) in pruritus VAS from baseline.\(^{1,2}\)

- Pruritus severity and DLQI scores were moderately correlated at baseline (correlation coefficient, 0.55 [ESTEEM 1] and 0.48 [ESTEEM 2]; \( P < 0.0001 \)).
- Improvement in pruritus correlated with an improvement in DLQI at Week 16 in ESTEEM 1 and 2 (correlation coefficient, \( \geq 0.43 \) in either group, \( P < 0.001 \)).

*Clustering in the left lower quadrant (denoted within the red square) demonstrates MCID improvement in both DLQI and pruritus.*
Overview of Safety Results (ESTEEM 1 & 2, Pooled)

- The most frequently reported AEs (>5%) during Period A (placebo-controlled period) were nausea, diarrhea, nasopharyngitis, URTI, tension headache, and headache.
- Most AEs were mild or moderate in severity and did not lead to discontinuation.
  - Discontinuation rates due to AEs were low across treatment groups (placebo: 3.8%; apremilast: 5.4%).
- The incidence of serious AEs was low and comparable across treatment groups (placebo: 2.6%; apremilast: 2.0%).
- Deaths (occurring in ESTEEM 1) were due to completed suicide (placebo) and cardiac failure (apremilast).
- Changes in laboratory parameters were transient and not clinically meaningful over time; no trend was observed.

*Full analysis set includes all randomized patients who received ≥1 dose of study medication. AE=adverse event; URTI=upper respiratory tract infection.
Conclusions

- Improvements in pruritus and DLQI were consistent between both ESTEEM studies.
- Improvements in pruritus were seen with apremilast 30 mg BID as early as Week 2.
- Approximately 70% of patients receiving apremilast 30 mg BID achieved an MCID in pruritus VAS at Week 16.
- Improvement in pruritus severity was correlated with an improvement in patient quality of life.
  - At Week 16, approximately 46% of patients receiving apremilast 30 mg BID achieved MCID for both pruritus and DLQI.
- Apremilast 30 mg BID demonstrated an acceptable safety profile and was generally well tolerated.