Research Review™
STUDY REVIEW

Efficacy and safety of apremilast in patients with moderate-to-severe plaque psoriasis of the scalp: the STYLE study

Making Education Easy 2021

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Abbreviations used in this review:

AE = adverse events; **BSA =** body surface area; **DLQI =** Dermatology Life Quality Index; **ITT =** intent-to-treat; **MI =** multiple imputation; **NRS =** Numeric Rating Scale; **PDE4 =** phosphodiesterase 4; **PSAI =** Psoriasis Area and Severity Index; **sPGA =** Static Physician Global Assessment; **ScPGA =** Scalp Physician Global Assessment.

This publication presents data from the STYLE study, the first prospective, randomised, placebo-controlled trial that investigated the efficacy and safety of apremilast for the treatment of scalp psoriasis.[1,2] Data from both the initial 16-week, placebo-controlled phase,[1] and the 32-week extension phase[2] will be reviewed.

Study background

The scalp is commonly involved in patients with psoriasis, with 80% of patients with psoriasis having psoriasis in this region of the body.[3] Psoriasis of the scalp is associated with significant burden and can affect patients' quality of life and daily functioning.[3,4]

The treatment of scalp psoriasis may be difficult and challenging.[3] Topical therapies are generally used in the first-line treatment of mild-to-moderate scalp psoriasis.[5] Adherence to topical therapies for scalp psoriasis can be low, because of the challenge of applying them to the scalp area and the difficulty of removing them from the hair.[5] Moreover, patients with more severe scalp psoriasis may need treatment with systemic or biologic agents, which may require close monitoring for adverse events.[3,6]

Effective, well-tolerated systemic therapies for patients with moderate-to-severe scalp psoriasis or patients whose scalp psoriasis is inadequately controlled with topical therapies are needed.

Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), is approved in Australia for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[7]

The STYLE study (ClinicalTrials.gov: NCT03123471) evaluated the efficacy and safety of apremilast 30 mg twice daily compared with placebo in patients with moderate-to-severe plaque psoriasis of the scalp both during an initial 16-week, placebo-controlled phase,[1] and a 32-week extension phase.[2]

Study design and methods

Design

This phase 3, multicentre, randomised, double-blind, placebo-controlled trial assigned patients, in a 2:1 ratio, to treatment with apremilast 30 mg twice daily or placebo for 16 weeks.[1] Doses were titrated (in 10-mg increments) over the first week of treatment to mitigate potential gastrointestinal adverse effects.[1] At week 16, all patients continued or switched to apremilast 30 mg twice daily until week 32, with dummy titration or titration during week 16 for patients initially randomised to apremilast or placebo, respectively.[1,2] All patients completed a 4-week post-treatment observational follow-up phase and were restricted from using any concomitant medication.

Patients

Key inclusion and exclusion criteria for the STYLE trial are shown in **Table 1**.[1]

Table 1. Key inclusion and exclusion criteria[1]

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Moderate-to-severe plaque psoriasis of the scalp (defined as Scalp Physician Global Assessment [ScPGA] score of ≥3) • Psoriasis involved scalp surface area of ≥20% • Inadequate response or intolerance to at least one topical therapy for plaque psoriasis of the scalp, at screening and baseline • Moderate-to-severe plaque psoriasis (defined as Psoriasis Area and Severity Index [PASI] score ≥12) • Psoriasis-involved body surface area (BSA) of ≥10% • Static Physician Global Assessment (sPGA) score of ≥3	• Current or planned concurrent use of topical therapies (including medicated shampoos, coal tar, and salicylic acid preparations) within 2 weeks • Conventional systemic therapy for psoriasis within 4 weeks • Intralesional corticosteroids on the scalp within 2 weeks • Phototherapy treatment of body or scalp lesions within 4 weeks • Use of biologics within 12 to 24 weeks • Prolonged sun or ultraviolet light exposure

Study endpoints

The primary endpoint was the proportion of patients achieving an ScPGA response (score of 0 or 1 with a ≥2-point reduction from baseline) at week 16.[1] The ScPGA measure is a 5-point scale (0 [clear], 1 [almost clear], 2 [mild], 3 [moderate], 4 [severe]).

Secondary efficacy endpoints included:[1]

- the proportion of patients with ≥4-point improvement from baseline in Whole Body Itch Numeric Rating Scale (NRS; rated on a scale of 0 [no itch] to 10 [worst imaginable itch]) at week 16 and at earlier visits;
- the proportion of patients with ≥4-point improvement from baseline in the Scalp Itch NRS score (rated on a scale of 0 [no itch] to 10 [worst imaginable itch]) at week 16 and at earlier visits;
- change from baseline in Dermatology Life Quality Index (DLQI) total score (ranging from 0 to 30, with higher scores corresponding to poorer health-related quality of life) at week 16.

Safety was evaluated based on treatment-emergent adverse events (AEs), laboratory test results, and vital signs.[1]

Primary and secondary endpoints were analysed in the intent-to-treat (ITT) population and involved all randomised patients.[1] Missing values were imputed using the multiple imputation (MI) method as the primary analysis.[1]

Study results

A total of 303 patients underwent randomisation and were included in the ITT population; 102 patients received placebo and 201 patients received apremilast 30 mg twice daily.[1]

Patient characteristics

Key baseline characteristics are shown in **Table 2**.[1]

Table 2. Key demographic and clinical characteristics at baseline[1]

	Placebo (n=102)	Apremilast (n=201)
Mean age, years	46.7	47.0
Male, n (%)	62 (60.8)	125 (62.2)
Mean psoriasis duration, years	14.8	15.7
Mean psoriasis-involved scalp surface area, %	58.2	61.9
ScPGA, n (%)		
Moderate (3)	78 (76.5)	155 (77.1)
Severe (4)	24 (23.5)	46 (22.9)
sPGA, n (%)		
Moderate (3)	76 (74.5)	153 (76.1)
Severe (4)	26 (25.5)	48 (23.9)
Mean scalp itch NRS score	6.7	6.6
Mean whole body itch NRS score	7.2	7.2
Mean psoriasis-involved BSA, %	21.2	19.0
Mean PASI score	18.2	17.2
Mean DLQI score	12.6	12.6
Prior use of psoriasis medications, n (%)		
Phototherapy	21 (20.6)	45 (22.4)
Conventional systemic therapy	27 (26.5)	62 (30.8)
Biologic	31 (30.4)	55 (27.4)

BSA = Body surface area; **DLQI** = Dermatology Life Quality Index; **NRS** = Numeric Rating Scale; **PASI** = Psoriasis Area and Severity Index; **ScPGA** = Scalp Physician Global Assessment; **sPGA** = static Physician Global Assessment.

A total of 252 patients completed the 16-week, placebo-controlled phase (82.4% in the placebo group; 83.6% in the apremilast group). Reasons for discontinuation during the placebo-controlled phase included patient withdrawal (7.3%), adverse events (3.6%), lack of efficacy (2.3%), noncompliance with study drug (1.0%), and lost to follow-up (1.3%).[1]

A total of 249 patients entered the STYLE extension phase (weeks 16–32), with 216 patients completing the extension, including 76/84 (90.5%) who had been randomised to placebo during the first 16 weeks and 140/165 (84.8%) who continued with apremilast.[2]

Efficacy

Primary endpoint: Significantly more patients treated with apremilast 30 mg twice daily, compared with placebo, achieved an ScPGA response at week 16 (43.3% vs 13.7%; p<0.0001) (**Figure 1**).[1] The proportion of patients achieving ScPGA response was significantly higher with apremilast than placebo as early as week 2 (**Figure 1**).[1]

Patients initially assigned to apremilast during the 16-week, placebo-controlled phase sustained their ScPGA response (45.5%) through to week 32 weeks, and more patients initially assigned to placebo who were switched to apremilast in the extension phase experienced a ScPGA response (63.1%) at week 32 (**Figure 1**).[2]

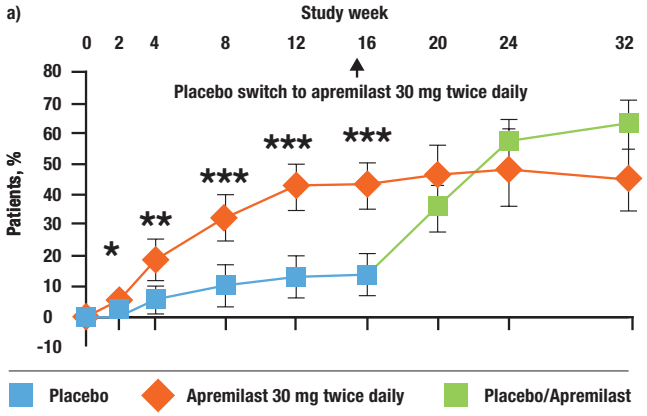

Figure 1. The proportion of patients achieving ScPGA response during the initial 16-week, placebo-controlled phase and through to week 32 during the extension phase[2]

ScPGA is evaluated on a 5-point scale ranging from 0 (clear) to 4 (severe), assessing the severity of erythema, scaling, and plaque elevation. ScPGA response was defined as the proportion of patients achieving ScPGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-point reduction from baseline. *p<0.05, **p<0.001, ***p<0.0001 vs placebo. **ScPGA** = Scalp Physician Global Assessment.

Adapted from Van Voorhees AS, et al. Br J Dermatol. 2021.

Secondary endpoints: At week 16 of the placebo-controlled phase, significantly more patients treated with apremilast, compared with patients treated with placebo, achieved a ≥4-point improvement from baseline on the Scalp Itch NRS at week 16 (47.1% vs 21.1%, p<0.0001) and on the Whole Body Itch NRS (45.5% vs 22.5%, p<0.0001).[1] Improvements were observed in significantly more apremilast-treated patients than placebo-treated patients for both these measures as early as week 2 (**Figure 2**).[1]

At week 32 of the extension phase, 49.3% of patients in both treatment groups achieved a Scalp Itch NRS response.[2] In addition, 45.7% of those who continued with apremilast and 59.7% of those who switched from placebo to apremilast achieved the Whole Body Itch NRS response (**Figure 2**).[2]

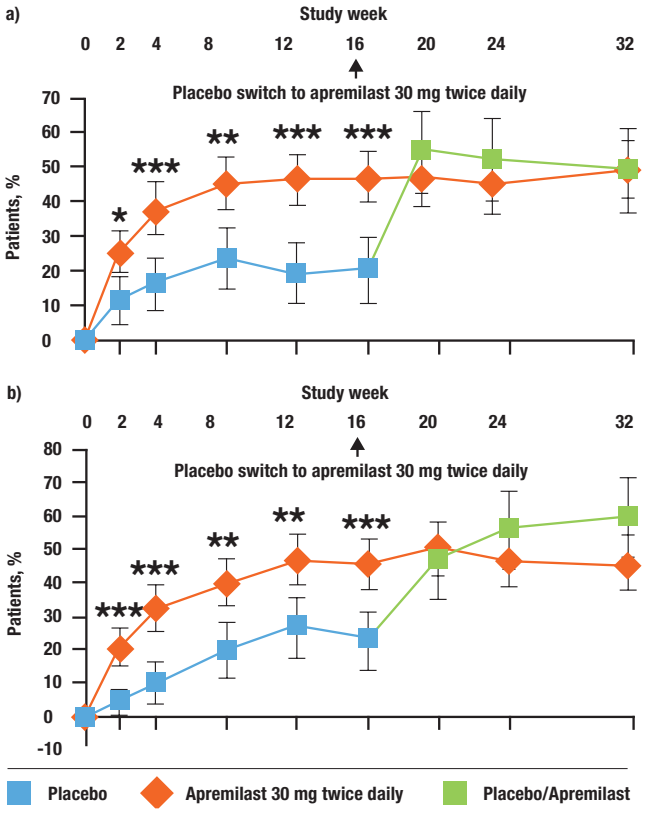

Figure 2. The proportion of patients achieving ≥4-point improvement from baseline in (a) Scalp Itch NRS response and (b) Whole Body Itch NRS response during the initial 16-week, placebo-controlled phase and through to week 32 during the extension phase[2]

*p<0.01, **p<0.001, ***p<0.0001 vs placebo. **NRS** = numeric rating scale.

Adapted from Van Voorhees AS, et al. Br J Dermatol. 2021.

At week 16, the mean improvement from baseline in DLQI total score was significantly greater with apremilast than with placebo (least-squares mean, -6.7 vs -3.8, p<0.0001).[1] In the extension phase of the study, the mean improvement in the DLQI total score was -6.8 in the apremilast/apremilast group and -8.0 in the placebo/apremilast group by week 32.[2]

Subgroup analysis: ScPGA response, Scalp Itch NRS response, and Whole Body Itch NRS response at week 16 was generally higher with apremilast compared with placebo, according to subgroup analyses based on sex, baseline body mass index category, number of prior conventional systemic treatments, and number of failed prior topical scalp psoriasis or shampoo treatments.[2]

Safety

From weeks 0 to 16, the most common AEs (≥5% in any treatment group) in apremilast-treated patients were diarrhoea, nausea, headache, and vomiting, with most being mild to moderate in severity (**Table 3**).[1] The proportion of patients with ≥1 serious AEs during the 16-week, placebo-controlled period was 1% in both treatment groups and was not considered to be related to treatment (**Table 3**).[1]

Discontinuations due to AEs were reported in 5.5% of patients treated with apremilast and 2.9% of patients in the placebo group.[1]

The mean change from baseline in body mass index at the end of the 16-week, placebo-controlled phase was -0.1 kg/m^2 in the placebo group and -0.3 kg/m^2 in the apremilast group. The mean change from baseline in weight at the end of the placebo-controlled phase was -0.2 kg with placebo versus -0.9 kg with apremilast.[1]

The AEs reported in the STYLE during the 16-week, placebo-controlled phase are summarised in **Table 3**.[1]

Table 3. Summary of adverse events (AEs) in the STYLE during the 16-week, placebo-controlled phase[1]

Patients, n (%)	Placebo (n=102)	Apremilast 30 mg twice daily (n=200)
≥1 AE	52 (51.0)	135 (67.5)
≥1 Serious AE	1 (1.0)	2 (1.0)
≥1 Severe AE	2 (2.0)	5 (2.5)
AEs leading to drug withdrawal	3 (2.9)	11 (5.5)
Deaths	0	0
AEs occurring in ≥5% of patients		
Diarrhoea	11 (10.8)	61 (30.5)
Nausea	6 (5.9)	43 (21.5)
Headache	5 (4.9)	24 (12.0)
Vomiting	2 (2.0)	11 (5.5)

*The n values for the placebo and apremilast 30 mg twice daily groups reflect the number of patients initially randomised at week 0 who received a ≥1 dose of study medication.

Across the total apremilast-exposure period (0–32 weeks), most adverse events were mild or moderate in severity and consistent with safety profile of apremilast reported during the placebo-controlled period.[2] The most common AEs (≥5%) were diarrhoea (26.8%), nausea (19.4%), headache (9.9%), and vomiting (5.3%).[2]

Expert's comment

Scalp psoriasis is notoriously difficult for dermatologists to manage and even more difficult for patients to live with. Topical agents tend to be ineffective and messy, and the regimes tricky to comply with over the long term. There is also considerable social stigma associated with itchy and flaky scalp conditions, with many sufferers expressing concern that others are worried they might "catch" an infection from scalp psoriasis sufferers. Apremilast is available in Australia for patients with severe chronic plaque psoriasis,[7] and highlighted in this review is STYLE, a prospective study assessing the efficacy of apremilast in treating scalp psoriasis symptoms and signs.[1,2] Patients enrolled in this placebo-controlled study had chronic plaque psoriasis with a mean PASI of around 18, and either moderate (grade 3) or severe (grade 4) ScPGA, and at least 20% scalp surface involvement.

The results from the STYLE study showed that apremilast led to significant improvement in ScPGA as early as week 2, and importantly a reduction of scalp as well as body pruritis.[1,2] Apremilast was generally well tolerated and there was no difference in frequency of withdrawal from the study or serious adverse events between the apremilast-treated and placebo groups[1,2] Patients receiving apremilast did initially experience more nausea, headache, vomiting, and diarrhoea, as has been shown in previous studies and in real-world experience with apremilast.[8-11]

Study interpretation

The STYLE study is the first prospective, randomised, placebo-controlled phase 3 trial to evaluate the efficacy of apremilast in patients with moderate-to-severe plaque psoriasis of the scalp.[1,2] This study demonstrated that apremilast was effective for the treatment of scalp psoriasis in different types of patients, including those with scalp psoriasis inadequately controlled by other therapies.[1,2]

These efficacy and safety outcomes are consistent with the subgroup analyses of the phase 3 ESTEEM 1 and 2 studies[12] and the phase 3b LIBERATE trial,[13] in which significantly more patients with moderate-to-severe plaque psoriasis with scalp involvement at baseline (ScPGA score ≥3) treated with apremilast 30 mg twice daily, compared with placebo, achieved a ScPGA response at week 16. Systemic, injectable treatments, such as etanercept and secukinumab, have demonstrated efficacy in scalp psoriasis, although comparisons of these treatments with apremilast are difficult as different definitions of scalp psoriasis and improvement measures were used in the relevant clinical studies.[14,15]

The AE profile of apremilast in the STYLE study was consistent with that previously reported in patients with psoriasis.[8,9] Adverse events tend to be transient and often resolve during the first 4 weeks of treatment.[7]

Although the study was well designed and executed, it does have some limitations. The lack of an active comparator arm did not allow for direct comparisons with other treatments for plaque psoriasis of the scalp.[1] In addition, the study did not include patients with mild scalp psoriasis, so that conclusions regarding the safety and efficacy of apremilast in this subgroup of patients cannot be made.[1]

Take-home messages

- The STYLE study was the first prospective, randomised, placebo-controlled phase 3 trial to evaluate the efficacy of apremilast in patients with moderate-to-severe plaque psoriasis of the scalp.
- In the STYLE study, treatment with apremilast 30 mg twice daily resulted in clinically and statistically significant improvements in scalp psoriasis, scalp and whole body itch, and quality of life as early as week 2 after treatment initiation, with the improvements in these measures being sustained with longer term treatment (up to 32 weeks).
- The efficacy of apremilast was demonstrated across multiple clinically relevant patient subgroups.
- The AE profile of apremilast in the STYLE study was consistent with that previously reported.

Expert's concluding remarks

Although we now have several biologics available to manage moderate-to-severe chronic plaque psoriasis in Australia, not all patients will either qualify for PBS-subsidised therapies nor wish to have regular subcutaneous injections, and the prospect of oral therapies is more appealing and the half-life is managed more flexibly. It is reassuring to see that apremilast resulted in significant improvement of ScPGA, scalp pruritis, and DLQI, when administered up to 32 weeks in this highlighted study.[1,2] We are becoming more familiar with this medication now that it is available through PBS in Australia in some circumstances where methotrexate is contraindicated, not tolerated, or not effective, and its overall safety profile is favourable. The initial gastrointestinal effects are mitigated somewhat by upward titrating of the dosage, and it is worth asking patients to persist with apremilast if they do experience these, as they settle well, and patients go on to show a good response to continued therapy.

References

1. Van Voorhees AS, Stein Gold L, Lebwohl M, et al. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: Results of a phase 3b, multicenter, randomized, placebo-controlled, double-blind study. J Am Acad Dermatol. 2020;83(1):96-103.
2. Van Voorhees AS, Stein Gold L, Lebwohl M, et al. Efficacy and safety of apremilast in patients with moderate-to-severe plaque psoriasis of the scalp: results up to 32 weeks from a randomized, phase III study. Br J Dermatol. 2021;185(4):840-2.
3. Wang TS, Tsai TF. Managing scalp psoriasis: An evidence-based review. Am J Clin Dermatol. 2017;18(1):17-43.
4. Heydendael VM, de Borgie CA, Spuls PI, et al. The burden of psoriasis is not determined by disease severity only. J Investig Dermatol Symp Proc. 2004;9(2):131-5.
5. Blakely K, Gooderham M. Management of scalp psoriasis: current perspectives. Psoriasis (Auckl). 2016;6:33-40.
6. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019;80(4):1029-72.
7. Amgen Australia Pty Ltd. OTEZLA® (apremilast) tablets - Australian product information. 2020. Available from: 'www.amgen.com.au/Otezla.PI'.
8. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37-49.
9. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol. 2015;173(6):1387-99.
10. Vujic I, Herman R, Sanlorenzo M, et al. Apremilast in psoriasis - a prospective real-world study. J Eur Acad Dermatol Venereol. 2018;32(2):254-9.
11. Phan C, Beneton N, Delaunay J, et al. Real-world effectiveness and safety of apremilast in older patients with psoriasis. Drugs Aging. 2020;37(9):657-63.
12. Rich P, Gooderham M, Bachelez H, et al. 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). J Am Acad Dermatol. 2016;74(1):134-42.
13. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol. 2017;31(3):507-17.
14. Bagel J, Duffin KC, Moore A, et al. The effect of secukinumab on moderate-to-severe scalp psoriasis: Results of a 24-week, randomized, double-blind, placebo-controlled phase 3b study. J Am Acad Dermatol. 2017;77(4):667-74.
15. Bagel J, Lynde C, Tyring S, et al. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. J Am Acad Dermatol. 2012;67(1):86-92.

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