ORIGINAL RESEARCH

Long-Term Proactive Treatment of Plaque Psoriasis with Calcipotriene/Betamethasone Dipropionate Foam Prolongs Remission and Reduces Relapses Irrespective of Patient Baseline Characteristics

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ABSTRACT

Introduction: The phase 3 PSO LONG study (NCT02899962) demonstrated superior efficacy of proactive (PM) versus reactive management (RM) using calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) foam in adults with psoriasis. Here, we evaluated whether certain baseline parameters had an effect on time to first relapse (TTFR), number of relapses, and assessed interactions between treatment effect.

Methods: PSO LONG included an initial 4-week open-label phase (once-daily Cal/BD foam) and a 52-week maintenance phase where patients were randomized to twice-weekly Cal/BD (PM) or vehicle foam (RM), with a 4-week once-daily Cal/BD foam rescue treatment for relapse. Baseline parameters analyzed using a stepwise variable selection procedure included body surface area, modified Psoriasis Area Severity Index (mPASI), Physician Global Assessment (PGA), body mass index, age, sex, Dermatology Life Quality Index, and duration of psoriasis. Continuous variables were divided into groups based on standard criteria.

Results: Overall, the effect of treatment on TTFR did not vary across any baseline parameters. Variables with a statistically significant effect on TTFR were: treatment group (PM vs. RM hazard ratio [HR]: 0.56; $p < 0.001$); PGA (moderate vs. mild HR: 1.42; severe vs. mild HR: 2.32; overall $p = 0.009$); mPASI (moderate vs. mild HR: 1.19; severe vs. mild HR: 1.77; overall $p = 0.009$); and sex (women vs. men HR: 1.26; $p = 0.030$). Variables with a significant effect on the number of relapses were: treatment group (PM vs. RM, rate ratio [RR] 0.52; $p < 0.001$); PGA at baseline (moderate vs. mild, RR 1.38; severe vs. mild, RR 2.22; overall $p < 0.001$); and mPASI (moderate vs. mild, RR 1.25; severe vs. mild, HR 1.70; overall $p = 0.002$).

Conclusion: All patients benefitted from long-term PM versus RM with Cal/BD foam regardless of baseline characteristics, and the benefit of treatment increased with greater disease severity.

Trial Registration: ClinicalTrials.gov identifier, NCT02899962.

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Key Summary Points
Why carry out this study?
The phase 3 clinical trial PSO LONG assessed the long-term efficacy and safety of proactive psoriasis management with twice-weekly calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) foam
In this post hoc analysis, we examined whether patient baseline parameters, such as modified Psoriasis Area Severity Index, Physician Global Assessment, body mass index, age, sex, Dermatology Life Quality Index, and duration of psoriasis, have a significant predictive effect on the time to first relapse and number of relapses
What was learned from this study?
We show that all patients benefitted from long-term proactive management versus reactive management with Cal/BD foam regardless of baseline characteristics
Patients with more severe disease at baseline showed greater benefit with the proactive management approach than those with milder disease

INTRODUCTION

Psoriasis vulgaris (plaque psoriasis) is a chronic inflammatory skin disease with a relapsing course that requires a long-term management strategy [1]. Topical therapies are a mainstay in the treatment of psoriasis either as monotherapy or to complement systemic treatments. The influence of patient characteristics on treatment outcome was studied in the moderate-to-severe patient population treated with systemic therapies (either orals or biologics). Thus far, long-term results from the use of topical therapies are lacking [2, 3].

Conventional long-term management with topical treatments uses a reactive approach where the treatment is used after relapse has occurred versus a proactive approach to maintain remission. Fixed-dose combination calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) aerosol foam (Enstilar®; LEO Pharma, Ballerup, Denmark) is indicated for the topical treatment of plaque psoriasis [4, 5].

The phase 3 PSO-LONG clinical trial assessed the long-term efficacy and safety of proactive psoriasis management with twice-weekly Cal/BD foam [6]. The trial comprised a 4-week open-label treatment phase, followed by a randomized 52-week maintenance phase and an 8-week follow-up phase. During the maintenance phase of the trial, median time to first relapse (TTFR), the primary endpoint, estimated using the Cox proportional hazards model was 56 days for patients in the proactive treatment group versus 30 days for the reactive treatment group with a prolongation by 26 days for the proactive group. Patients in the proactive group had an additional 41 days in remission versus the reactive group ($p < 0.001$) over the 1-year period. Number of relapses per year of exposure was 3.1 for the proactive group versus 4.8 for the reactive group. Assessment of the 4-week open-label lead-in phase of PSO-LONG showed that Cal/BD foam achieved 80% treatment success in 4 weeks [7]. Here, we examined whether patient baseline parameters have a significant predictive effect on the primary and secondary endpoints.

METHODS

Study Design

This was a post hoc analysis of the PSO LONG phase 3 trial (NCT02899962). A statement of ethics was provided for the primary study upon which this post hoc analysis is based [6]. Approval for the clinical trial protocol was obtained from the relevant institutional review boards or independent ethics committees and

regulatory authorities for each participating site before patient enrollment. All patients provided written informed consent. The trial was conducted in accordance with Good Clinical Practice and Ethical Principles for Medical Research Involving Human Subjects [6]. The trial design has been described previously and is shown in Fig. 1 [6]. Patients who achieved treatment success, defined as a Physician Global Assessment (PGA) score of clear/almost clear (PGA < 2) with a ≥ 2-grade improvement from baseline, entered the maintenance phase. During the long-term maintenance phase, patients were randomly assigned to apply either Cal/BD foam or vehicle twice weekly to the disease site that was previously cleared (or almost cleared) during the preceding open-label phase. Interventions and patient eligibility for PSO LONG have been described previously [6]. For eligibility, patients had to be ≥ 18 years with truncal or limb psoriasis, or both, involving 2% to 30%

of the body surface area (BSA), PGA disease severity score of mild or higher (PGA ≥ 2), and modified Psoriasis Area and Severity Index (mPASI) score ≥ 2 at baseline of the open-label lead-in phase (referred to as baseline) [6].

Subgroup Statistical Analysis

The subgroup analysis was used to investigate whether certain baseline parameters have a significant predictive effect on the primary and secondary endpoints. The goal was to examine potential interaction effects between the treatment effect and the baseline parameters (i.e., examine whether the treatment effects vary across patient subgroups). TTFR was measured in days since randomization and was analyzed by means of a Cox proportional hazard model with treatment group, pooled sites, and baseline parameters tested for significance of the variables. Number of relapses was analyzed by
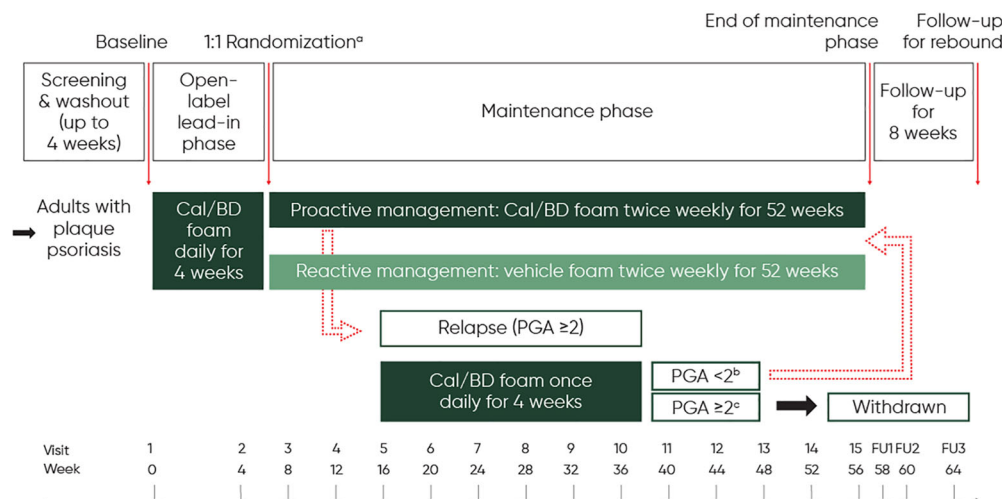

Fig. 1 PSO LONG trial design. [a]Patients with treatment success at end of open-label lead-in phase (PGA score 'clear'/'almost clear' [PGA < 2] with ≥ 2-grade improvement from baseline) were randomized 1:1 in the maintenance phase. [b]Following 4 weeks of once-daily rescue treatment, patients who regained PGA < 2 ('clear'/'almost clear') re-started the twice-weekly maintenance treatment according to the original randomization scheme. [c]Patients who did not regain a PGA score < 2 ('clear'/'almost clear') following 4 weeks of once-daily rescue treatment were withdrawn from the trial. *Cal/BD* calcipotriene

0.005%/betamethasone dipropionate 0.064%, *FU* follow-up, *PGA* Physician Global Assessment. Reprinted from *J Am Acad Dermatol*. 2021;84(5). Lebwohl M, Kircik L, Lacour JP, Liljedahl M, Lynde C, Mørch MH, Papp KA, Perrot JL, Gold LS, Takhar A, Thaçi D, Warren RB, Wollenberg A. Twice-weekly topical calcipotriene/betamethasone dipropionate foam as proactive management of plaque psoriasis increases time in remission and is well tolerated over 52 weeks (PSO-LONG trial). Pages 1269–1277, Copyright (2020), with permission from Elsevier

means of a Poisson regression model with treatment group, pooled sites, and baseline parameters as factors and time at risk as an off-set variable. Random subject effect was also included.

The stepwise variable selection included the following baseline parameters:

- BSA: mild ≤ 3, moderate 4–10, severe > 10.
- mPASI: mild ≤ 5, moderate 6–12, severe > 12.
- PGA: clear (0), almost clear (1), mild (2), moderate (3), severe (4).
- Body mass index: normal ≤ 25 kg/m^2, over-weight 26–30 kg/m^2, obese > 30 kg/m^2.
- Age: 18–64 years, ≥ 65 years.
- Sex: men, women.
- Dermatology Life Quality Index: 0–1, 2–5, 6–10, 11–20, > 20.
- Duration of psoriasis: ≤ 5 years, 6–10 years, 11–20 years, 21–30 years, 31–40 years, > 40 years.

There was no adjustment for multiplicity. The trial was not powered for subgroup analyses, and the results may be affected by the grouping of parameters.

RESULTS

The distribution of baseline parameters in the analysis is shown in Table 1. The analysis included 521 patients; most patients were men (67.37%), were aged 18–64 years (78.12%), and had moderate psoriasis as assessed by PGA (85.22%) and BSA (54.51%) measures. Overall, the effect of treatment on TTFR did not vary across any baseline parameters. The TTFR was associated with severity of disease at baseline and sex of the patients (Table 2). Variables with a significant effect on TTFR were: treatment group (proactive management vs. reactive management, hazard ratio [HR] 0.56, $p < 0.001$); PGA at baseline (overall $p = 0.009$; moderate vs. mild, HR 1.42, $p = 0.072$; severe vs. mild, HR 2.32, $p = 0.003$); mPASI (overall $p = 0.009$; moderate vs. mild, HR 1.19, $p = 0.160$; severe vs. mild, HR 1.77, $p = 0.002$); and sex (women vs. men, HR 1.26, $p = 0.027$).

Table 1 Distribution of baseline parameters included in the analysis

Category	$N = 521$
Age, n (%)	
18–64 years	407 (78.12)
≥ 65 years	114 (21.88)
Sex, n (%)	
Women	170 (32.63)
Men	351 (67.37)
BMI, n (%)	
Normal (≤ 25 kg/m^2)	130 (24.95)
Overweight (26–30 kg/m^2)	197 (37.81)
Obese (> 30 kg/m^2)	194 (37.24)
BSA, n (%)	
Mild (≤ 3)	110 (21.11)
Moderate (4–10)	284 (54.51)
Severe (> 10)	127 (24.38)
mPASI[a] n (%)	
Mild (≤ 5)	138 (26.49)
Moderate (6–12)	318 (61.04)
Severe (> 12)	65 (12.48)
PGA, n (%)	
Mild (2)	43 (8.25)
Moderate (3)	444 (85.22)
Severe (4)	34 (6.53)
DLQI[b] n (%)	
0–1	40 (7.68)
2–5	153 (29.37)
6–10	187 (35.89)
11–20	113 (21.69)
> 20	28 (5.37)
Duration of psoriasis, n (%)	
≤ 5 years	94 (18.04)
6–10 years	93 (17.85)
11–20 years	149 (28.60)

Table 1 continued

Category	N = 521
21–30 years	86 (16.51)
31–40 years	56 (10.75)
> 40 years	43 (8.25)

BMI body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *mPASI* modified Psoriasis Area and Severity Index, *PGA* Physician Global Assessment

[a] The PASI is a composite tool that combines the assessment of disease severity and BSA involvement into a single score ranging from 0 (no disease) to 72 (maximum disease) [11]

[b] The patient-reported outcome measure DLQI evaluates patient perception of psoriasis on health-related quality of life [12]

Number of relapses was dependent on baseline disease severity, and the effect of treatment on number of relapses did not vary across baseline parameters. Variables with a significant effect on the number of relapses were: treatment group (proactive management vs. reactive management, rate ratio [RR] 0.52, $p < 0.001$); PGA at baseline (overall $p < 0.001$; moderate vs. mild, RR 1.38, $p = 0.043$; severe vs. mild, RR 2.22, $p < 0.001$); and mPASI (overall $p = 0.002$; moderate vs. mild, RR 1.25, $p = 0.035$; severe vs. mild, RR 1.70, $p < 0.001$). Overall, patients with more severe disease at baseline had a greater benefit from proactive management with Cal/BD foam than those with milder disease.

DISCUSSION

Data on the proactive management of psoriasis are lacking. The findings herein add to the report by Lebwohl et al. that long-term proactive management with Cal/BD foam demonstrated superior efficacy compared with reactive management [6]. Patients with psoriasis often present with comorbid conditions and have a variety of detrimental characteristics (e.g., obesity, severity of disease, long duration of disease) that can negatively affect treatment outcomes [8]. Analysis of baseline characteristics related to treatment outcome was reported for psoriasis systemic treatments (oral and biologic) [2, 3]. However, such data have not yet been produced for topical treatments as Cal/BD foam is the first drug receiving a label for long-term treatment. Our findings show that the benefits of long-term proactive management of psoriasis with Cal/BD foam are not dependent on patients' baseline parameters; in fact, patients with more severe disease at baseline showed greater benefit with the proactive management approach than those with milder disease.

A recent study investigated the possible correlations between baseline clinical/dermoscopic features of psoriatic plaques, specifically on lesions targeted for treatment, and therapeutic response to Cal/BD foam after 4 weeks of therapy in patients presenting with moderate-to-severe plaque psoriasis [9]. The purpose was to better optimize the use of Cal/BD foam. The investigators confirmed that Cal/BD foam is effective for the treatment of plaque psoriasis. The study found that degree of infiltration of lesions at baseline and localization on the legs adversely affected treatment response, but no association was observed between treatment response and lesion duration, sex of the patient, baseline Local Psoriasis Severity Index, or baseline erythema/scaling.

Although this post hoc analysis did not address the safety of Cal/BD foam for proactive management of psoriasis, the incidence of adverse events in PSO LONG was similar between treatment groups, and Cal/BD foam was well tolerated [6]. The risk of hypothalamic-pituitary–adrenal (HPA) axis suppression with topical corticosteroid use in patients with psoriasis is well documented with no evidence of clinically significant HPA axis suppression due to absorption of topical steroids [10]. A subgroup of patients in the PSO LONG trial were monitored for HPA axis suppression during the course of the primary study. No clinically relevant effects on the HPA axis were observed in this subgroup of patients [6]. Additional investigations are underway on the long-term effects

Table 2 Effect of baseline characteristics on the TTFR and the number of relapses

TTFR[a]

Variables	HR (95% CI; p value)
Treatment group	Overall $p < 0.001$
Proactive Cal/BD management vs. reactive management	0.56 (95% CI, 0.46–0.68; $p < 0.001$)
PGA	Overall $p = 0.009$
Moderate vs. mild	1.42 (95% CI, 0.97–2.08; $p = 0.072$)
Severe vs. mild	2.32 (95% CI, 1.35–3.99; $p = 0.003$)
mPASI[b]	Overall $p = 0.009$
Moderate vs. mild	1.19 (95% CI, 0.93–1.52; $p = 0.160$)
Severe vs. mild	1.77 (95% CI, 1.22–2.55; $p = 0.002$)
Sex	Overall $p = 0.027$
Women vs. men	1.26 (95% CI, 1.03–1.54; $p = 0.027$)
Number of relapses[c]	
Variables	RR (95% CI; p value)
Treatment group	Overall $p < 0.001$
Proactive Cal/BD management vs. reactive management	0.52 (95% CI, 0.45–0.61; $p < 0.001$)
PGA	Overall $p < 0.001$
Moderate vs. mild	1.38 (95% CI, 1.01–1.88; $p = 0.043$)
Severe vs. mild	2.22 (95% CI, 1.54–3.19; $p < 0.001$)
mPASI[b]	Overall $p = 0.002$
Moderate vs. mild	1.25 (95% CI, 1.02–1.54; $p = 0.035$)
Severe vs. mild	1.70 (95% CI, 1.28–2.25; $p < 0.001$)

BSA body surface area, *Cal/BD* calcipotriene 0.005%/betamethasone dipropionate 0.064%, *HR* hazard ratio, *mPASI* modified Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *RR* rate ratio, *TTFR* time to first relapse
[a] TTFR was analyzed by means of a Cox proportional hazard model
[b] The PASI is a composite tool that combines the assessment of disease severity and BSA involvement into a single score ranging from 0 (no disease) to 72 (maximum disease) [11]
[c] Number of relapses was analyzed by means of a Poisson regression model

of proactive management of psoriasis with Cal/BD foam on the HPA axis.

Limitations

This post hoc analysis was not powered for comparison with the original study by Lebwohl et al. [4]; thus, any inference of statistical comparisons between this baseline analysis and primary findings in Lebwohl et al. should be done with caution.

CONCLUSION

Our findings show that all patients benefited from long-term proactive management versus

reactive management with Cal/BD foam regardless of baseline characteristics, and the benefit of treatment increased with greater disease severity.

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Compliance with Ethics Guidelines. This was a post hoc analysis of the PSO LONG study (NCT02899962). A statement of ethics was provided for the primary study upon which this post hoc analysis is based. Approval for the clinical trial protocol was obtained from the relevant institutional review boards or independent ethics committees and regulatory authorities for each participating site before patient enrollment. All patients provided written informed consent. The trial was conducted in accordance with Good Clinical Practice and Ethical Principles for Medical Research Involving Human Subjects.

Data Availability. Because this was a post hoc analysis, data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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