

The Effect on BSA of Proactive Management versus Reactive Management of Psoriasis With Fixed-Dose Cal/BD Foam in the PSO-LONG Study

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ABSTRACT

Reduction of psoriasis body surface area (BSA) is associated with improved patient quality of life. Post-hoc analyses of the PSO-LONG study compared impact on BSA of proactive management versus reactive management strategies using calcipotriol/betamethasone dipropionate (Cal/BD) foam. Mean BSA values, as well as normalized area under the curves (AUCs) for patient BSA were assessed.

Analyses found that after the PSO-LONG study's four-week open-label lead-in phase, when all patients received once-daily Cal/BD foam, mean BSA was significantly reduced. Thereafter, mean BSA remained at lower levels in patients on proactive management compared to reactive management. This was reflected in AUC BSA, which was consistently lower in the proactive management arm. Treatment-related differences were statistically significant when analyzing the full analysis set (FAS) population, as well as when restricting the analysis to study completers.

Additional analyses restricted the dataset to include only observations from psoriasis remission periods, or periods of disease relapse. Treatment-related differences in AUC were statistically significant in observations during remission, but not during relapse. This could be expected given the trial's design, wherein all patients who relapsed were offered the same rescue therapy with once daily Cal/BD foam. Similarly, for patients who dropped out, there was no treatment-related difference in mean BSA during the two weeks preceding dropout, likely due to the common occurrence of relapse in these patients. This paper found that proactive management, in addition to preventing more relapses as previously shown, also maintained BSA at a lower level during remission than reactive management.

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INTRODUCTION

A recent Phase III clinical study (PSO-LONG, NCT02899962) assessed the benefit of proactive management of psoriasis using twice-weekly calcipotriene/betamethasone dipropionate (Cal/BD) foam in patients successfully treated with once-daily Cal/BD foam. Patients who achieved treatment success, defined as Physician's Global Assessment (PGA) 'clear' or 'almost clear' scores, and a ≥2 grade improvement from baseline during an open-label phase of four weeks were randomized to 'proactive' management (Cal/BD foam twice weekly; n=256) or 'reactive' management (vehicle foam twice weekly; n=265) in the maintenance phase lasting 52 weeks. In both arms, a relapse (PGA ≥2) was treated with rescue treatment of Cal/BD foam given once daily for four weeks.[1]

The primary endpoint of PSO-LONG was time to first relapse and the secondary endpoints were time in remission and number of relapses, which are the focus of the main study publication.[1] Reduction of body surface area (BSA) affected by psoriasis is a clinically meaningful endpoint and is associated with improvement in quality of life for psoriasis patients.[2,3] This paper focuses on a post-hoc analysis of BSA from PSO-LONG.

AIMS AND OBJECTIVES

The impact of initiation of treatment with Cal/BD foam once daily for four weeks, and of proactive and reactive management in the maintenance phase on mean BSA was assessed. Additionally, the normalized area under the curve (AUC) was calculated for the two arms in the maintenance phase for the total population and for different disease status. Finally, the analysis assessed mean BSA at dropout and the difference across the two treatment arms.

STATISTICAL METHODS

Mean BSA in all patients randomized in the maintenance phase (full analysis set [FAS]) was estimated for each visit. The change in mean BSA between visits 1 and 2 (corresponding respectively to the beginning and end of the four-week open-label phase) was assessed using a paired t-test (Table 1).

TABLE 1.

Difference in Mean BSA Between Visit 1 and Visit 2

Population and treatment arm	N	Mean difference† (SD)	p-value‡
Full analysis set	521	-4.84 (5.38)	<0.0001

Notes: †BSA at visit one was 8.30 for all randomized patients; ‡Based on t-test.
Abbreviations: SD, standard deviation.

For each patient, the integrated AUC was calculated for BSA using the trapezoidal rule and subsequently normalized by number of days of exposure. The means and frequency distributions of AUC values were compared between the proactive and reactive arms, with statistical significance assessed using the Wilcoxson signed-rank test. To better understand the impact of patients' study participation and disease status on observed results, this FAS analysis was repeated, disaggregated by:

- completion status (completers, dropouts);
- disease status (remission, relapse).

Mean BSA at dropout was also estimated to assess whether the initial improvement observed in BSA was maintained in patients up to two weeks prior to their withdrawal from the study, with the difference tested statistically using a paired t-test.

RESULTS

A total of 521 patients comprised the FAS population in which the mean BSA was measured, the baseline characteristics for the randomized population are reported in the primary publication.[1] The AUC was calculated for 512 patients of the FAS population, in which one or more BSA estimate was measured. Roughly half of the patients included in the AUC analysis completed the study protocol (n=246), and the remainder dropped out before the end of the 52-week maintenance period (n=266).

Figure 1 shows mean BSA by visit number for both the proactive and reactive arm. The marked reduction in BSA from visit 1 to 2 of 4.8 points (Table 1), during the four-week open-label phase reflects the response to once daily Cal/BD foam treatment and was statistically significant (P<0.0001). Improvements in mean BSA were maintained throughout the study period of 52 weeks, with values remaining consistently lower for the proactive arm versus the reactive arm.

Figure 2 shows that AUC values were lower for the proactive arm versus the reactive arm regardless of completion status. This difference (Table 2) was statistically significant in the

FIGURE 1. Mean BSA by visit number for proactive and reactive management.

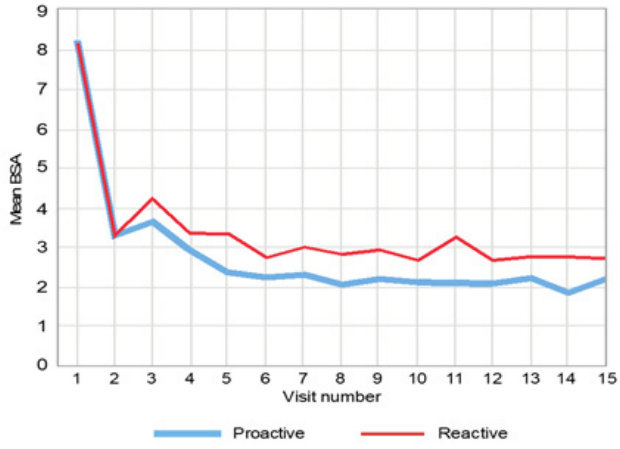

FIGURE 2. Distributions of AUC BSA scores by treatment arm and analysis population.

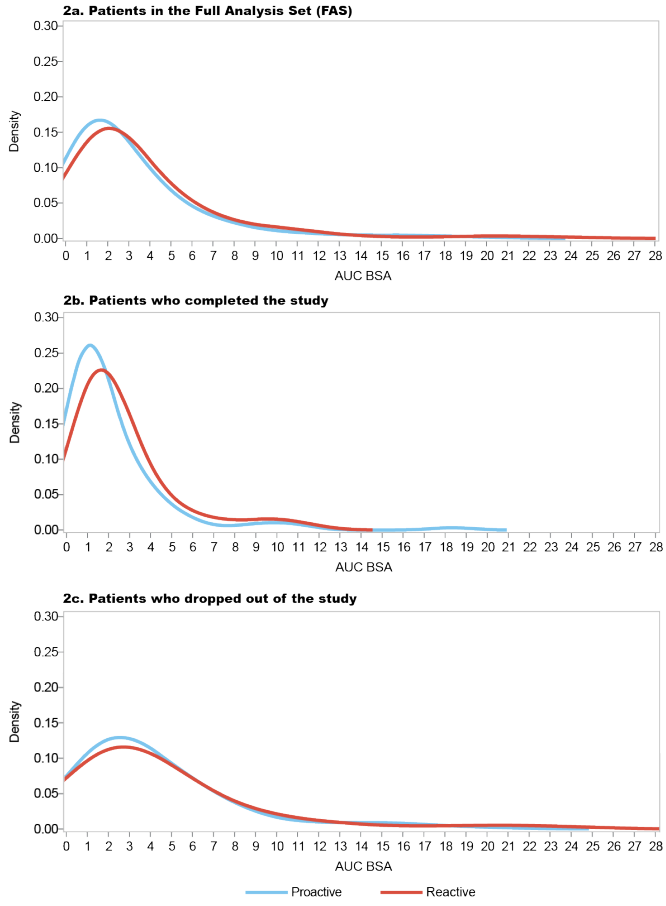

TABLE 2.

AUC BSA by Treatment Arm and Analysis Population

Population and treatment arm	N	AUC (SD)	Mean difference (SD)† AUC ratio‡	p-value*
Full analysis set				
Proactive	253	3.15 (3.35)	-0.55 (3.60)	0.013
Reactive	259	3.70 (3.82)	*0.85*	
Completers				
Proactive	128	2.12 (2.52)	-0.53 (2.44)	0.002
Reactive	118	2.64 (2.35)	*0.80*	
Dropouts				
Proactive	125	4.22 (3.76)	-0.37 (4.19)	0.709
Reactive	141	4.59 (4.54)	*0.92*	

Notes: †Calculated as mean AUC proactive Cal/BD – mean AUC reactive Cal/BD; ‡Ratio of AUCs proactive:reactive arms; *Based on Wilcoxson signed-rank test.
Abbreviations: AUC, area under the curve; SD, standard deviation.

FAS dataset (mean difference, -0.55, SD 3.6, $P<0.05$), and in completers (mean difference, -0.53, SD 2.44, $P<0.01$). AUC values were lower for completers (means, 2.12 and 2.64 for proactive arms and reactive arms, respectively) than dropouts (means, 4.22 and 4.59 for proactive arms and reactive arms, respectively). The difference between the two study arms was not statistically significant for dropouts (mean difference, -0.37, SD 4.19, $P=0.709$).

AUC values were estimated for BSA values observed during 'remission' versus periods of 'relapse' in the FAS (n=512) and in completers (n=246) as seen in Table 3. In the FAS, patients in the proactive arm had a statistically significant lower BSA during remission than those in the reactive arm (mean AUC difference, -0.50, SD 3.53, $P<0.05$). This result was also seen in the completers (mean AUC difference, -0.52, SD 2.36, $P<0.01$). The AUC BSA in patients experiencing relapse was lower in the proactive arm than in the reactive arm, but the difference was not statistically significant neither in the FAS (AUC difference, -0.21, SD 3.53, $P=0.72$) nor in completers (AUC difference, -0.07, SD 2.75, $P=0.46$).

TABLE 4.

Mean BSA at Dropout

Population and treatment arm	N	Mean BSA† (SD)	Mean difference (SD)	p-value‡
Full analysis set				
Proactive	124	4.61 (4.13)	-0.86 (5.03)	0.167
Reactive	143	5.47 (5.70)		

†Only BSA measurements occurring within 2 weeks prior to dropout were included; ‡Based on t-test.
Abbreviations: BSA, body surface area; SD, standard deviation.

TABLE 5.

Reasons for Dropout in PSO-LONG Study

	Full Analysis Set (n=521) N (%)	Proactive (n=256) N (%)	Reactive (n=265) N (%)
Total dropouts	275 (52.8)	128 (50.0)	147 (55.5)
Adverse event	3 (0.6)	2 (0.8)	1 (0.4)
Death	1 (0.2)	0 (0.0)	1 (0.4)
Lack of efficacy	33 (6.3)	17 (6.6)	16 (6.0)
Lost to follow-up	26 (5.0)	12 (4.7)	14 (5.3)
Other	15 (2.9)	5 (2.0)	10 (3.8)
Subject not 'clear' or 'almost clear' after post-relapse rescue therapy	132 (25.3)	62 (24.2)	70 (26.4)
Withdrawal by subject	65 (12.5)	30 (11.7)	35 (13.2)

Mean BSA values for patients who dropped out from the study were calculated at time of dropout (Table 4). Patients who dropped from the proactive arm had lower mean BSA than patients dropping out from the reactive arm, however the difference was not statistically significant ($P=0.167$). Main reasons for dropout did not differ markedly between treatment arms (Table 5).

TABLE 3.

AUC BSA by Treatment Arm, Disease State, and Analysis Population

Population and treatment arm	N		AUC		Mean difference (SD)	AUC ratio†	p-value*
Full analysis set	Proactive	Reactive	Proactive	Reactive			
Remission	253	259	3.08	3.58	-0.50 (3.53)	0.86	0.021
Relapse	207	236	3.78	3.98	-0.21 (3.94)	0.95	0.722
Study completers only							
Remission	128	118	2.09	2.61	-0.52 (2.36)	0.80	0.003
Relapse	98	112	2.77	2.84	-0.07 (2.75)	0.98	0.457

Notes: †Ratio of AUCs from proactive:reactive arms; ‡Based on Wilcoxson signed-rank test.
Abbreviations: AUC, area under the curve; SD, standard deviation.

DISCUSSION

These analyses provide useful insights on the impact of maintenance treatment on BSA. They demonstrated that Cal/BD foam once daily for four weeks significantly reduced BSA, an effect that was sustained over 52 weeks. Mean BSA was lower throughout the maintenance phase in the proactive arm compared to the reactive arm. Area under the curve BSA which compressed numerous observations to give a single estimate[4] was statistically significantly lower for patients in the proactive arm (FAS and completers). The difference in mean BSA and AUC values for dropouts was not statistically significant across treatment arms. This could be due to many dropouts (25%) occurring in combination with a relapse which could not be managed with rescue therapy

Differences in AUC BSA during remission and relapse were explored since AUC analysis over the whole period of 52 weeks may not reflect this variation in detail. This sub-analysis was more diagnostic than a proper assessment of treatment efficacy, since proactive management led to fewer relapses compared to reactive management,[1] it further illuminated the benefit provided by proactive management. Namely, patients in remission by proactive management had significantly lower BSA than patients in remission under a reactive management strategy.

Future research could assess the impact of proactive management with Cal/BD foam on BSA beyond 52 weeks, as there is a lack of evidence for longer term outcomes with topical treatments.[5]

CONCLUSIONS

Treatment with Cal/BD foam once daily for four weeks significantly reduced mean BSA. This effect was maintained with proactive or reactive management for 52 weeks. Proactive management resulted in consistently lower BSA compared to reactive management throughout the study period. The difference between treatment arms was statistically significant in the overall population and in study completers, but not in dropouts or in patients experiencing relapse. Therefore, in addition to longer time to first relapse, fewer relapses, and more time in remission,[1] proactive management results in lower BSA compared to reactive management.

DISCLOSURES

Henrik Thoning, Nanna Nyholm, and Bibi Petersen are employees at LEO Pharma.

Linda Stein Gold has been an investigator, speaker, consultant or an advisory board member for AbbVie Inc., Amgen, Arcutis Biotherapeutics, Inc., Bristol-Myers Squibb, Celgene, Eli Lilly and Company, LEO Pharma, Mayne Pharma, Novartis, Ortho Dermatologics Inc., Pfizer, and Sun Pharmaceutical Industries Ltd.

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