

Safety and Efficacy of a Fixed Combination Halobetasol and Tazarotene Lotion in the Treatment of Moderate-to-Severe Plaque Psoriasis: A Pooled Analysis of Two Phase 3 Studies

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ABSTRACT

Background: Topical corticosteroids (TCS) are the mainstay of psoriasis treatment. Safety concerns may limit use. Combination with tazarotene may optimize efficacy and minimize safety and tolerability concerns.

Objective: Investigate safety and efficacy of halobetasol propionate 0.01%/tazarotene 0.045% (HP/TAZ) lotion in moderate-to-severe plaque psoriasis.

Methods: Two multicenter, randomized, double-blind, vehicle-controlled phase 3 studies (N=418). Subjects randomized (2:1) to HP/TAZ lotion or vehicle once-daily for 8 weeks, 4-week follow-up. Primary efficacy assessment: treatment success (at least a 2-grade improvement from baseline in IGA score and 'clear' or 'almost clear'). Safety and treatment emergent AEs evaluated throughout.

Results: HP/TAZ lotion demonstrated statistically significant superiority over vehicle as early as week 2 (P=0.002). By week 8, 40.6% of subjects were treatment successes compared with 9.9% on vehicle (P<0.001). A third of subjects remained treatment successes post-treatment. HP/TAZ lotion was also superior in reducing psoriasis signs and symptoms, and Body Surface Area (BSA) involvement. Most frequently reported treatment related AEs were contact dermatitis (6.3%), application site pain (2.6%), and pruritus (2.2%).

Limitations: No data were collected beyond the 4-week follow-up.

Conclusions: HP/TAZ lotion provides synergistic efficacy that is both rapid and sustained, with good tolerability and safety over 8 weeks use.

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INTRODUCTION

Psoriasis is a chronic, immune-mediated disease affecting almost 2% of the population.[1-3] Topical therapy is a key component in the management of almost all psoriasis patients, considered first-line therapy for mild disease, and often used alone or in conjunction with systemic agents in more severe psoriasis.[4]

While the use of topical corticosteroids (TCS) are routine in psoriasis due to their efficacy, long-term safety concerns still limit their use to 2-4 weeks continuous use. Tazarotene too has also been shown to be an effective psoriasis treatment.[5,6] However, its use is limited by skin irritation.

The use of fixed combination topical treatments in dermatology is commonplace. Combining a TCS with tazarotene may prevent the irritancy effects of tazarotene, decrease the risk of steroid-induced atrophy,[7,16] and provide greater efficacy.[14,15]

Recently, phase 2 clinical data on 8 weeks' treatment of moderate-to-severe psoriasis with a novel fixed combination halobetasol propionate 0.01% and tazarotene 0.045% (HP/TAZ) lotion formulation were published.[8] The fixed combination was synergistic, providing clinical benefits beyond those expected from the efficacy of the individual active ingredients. In addition, it was well-tolerated following 8 weeks daily application, and efficacy was maintained 4 weeks post-treatment.

Here we further investigate the safety and tolerability of HP/TAZ lotion, reporting on the pooled data from two phase 3 clinical studies.

METHODS

Study Design

Two multicenter, double-blind, randomized, parallel-group phase 3 studies to assess the safety, tolerability and efficacy of a halobetasol propionate 0.01%/tazarotene 0.045% (HP/TAZ) fixed combination lotion in subjects with a clinical diagnosis of moderate-to-severe psoriasis (with an Investigator Global Assessment [IGA] score of 3 or 4, and an affected body surface area [BSA] of 3% to 12%).

Subjects were randomized (2:1) to receive HP/TAZ lotion or vehicle applied topically to the affected area once-daily for 8 weeks.

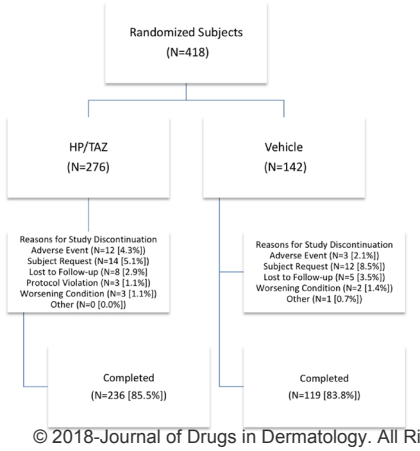
Inclusion and Exclusion Criteria

Key inclusion criteria included subjects of either gender, 18 years or older. A target lesion, defined primarily to assess signs of psoriasis, measuring 16-100 cm^2; with a score of ≥3 for two of the three different psoriasis signs (erythema, plaque elevation, and scaling), and summed score of ≥8, with no sign scoring <2. Subjects who had pustular psoriasis, or used phototherapy, photochemotherapy, or systemic psoriasis therapy within the last four weeks (or biologics within the last three months) or were diagnosed with skin conditions that would interfere with the interpretation of results, were excluded from the studies.

Study Oversight

Subjects provided written informed consent before study-related procedures were performed, and the protocol and consent were approved by institutional review boards (IRBs) or ethics committees at all investigational sites. The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki.

FIGURE 1. Summary of subject disposition in the two Phase 3 studies (all randomized patients, pooled data, N=418).



Efficacy Assessment

The key efficacy endpoint was the percent of subjects who were treatment successes at week 8; defined as those with at least a 2-grade improvement in their baseline IGA score, and a score equating to "clear" or "almost clear" (ie, 0 or 1). A 5-point scale ranging from 0 (clear) to 4 (severe) was used by the investigator at each study visit to assess the severity of overall psoriasis of the treatable areas. Treatment success was also evaluated at weeks 2, 4, 6, and week 12 (4-week post-treatment follow-up) to provide additional efficacy data.

Signs of psoriasis at the target lesion were assessed at each visit using individual 5-point scales ranging from ranging from 0 (clear) to 4 (severe). Here treatment success was defined as those subjects with at least a 2-grade improvement from baseline score for each of the key signs (erythema, plaque elevation, and scaling). Affected BSA was also assessed at each visit.

Safety Assessment

Information on reported and observed AEs was obtained at each visit. Routine safety laboratory tests were performed at screening, week 4, and week 8. An abbreviated physical examination was performed at baseline, week 8 (end of treatment), and week 12 (end of study).

Treatment areas were also examined by the investigator at each visit for presence/absence of significant known drug-related AEs; skin atrophy, striae, telangiectasia, and folliculitis.

Local Skin Reaction Assessment

Local skin reactions (LSRs) such as itching, dryness, and burning/stinging were evaluated at each study visit using 4-point scales ranging from 0 (clear) to 3 (severe). Given the nature of the disease, the presence of LSRs and symptoms at baseline is commonplace, and as such these evaluations identified both improvement and any emergent issues.

Statistical and Analytical Plan

The primary study goal was to assess treatment effect differences between HP/TAZ lotion and vehicle with respect to IGA. All statistical processing was performed using SAS® unless otherwise stated; statistical tests were two-sided and performed at the 0.05 level of significance. Markov Chain Monte Carlo (MCMC) multiple imputation was the primary method used to handle missing efficacy data. No imputations were made for missing safety data.

All subjects randomized, and dispensed study drug were included in the intent-to-treat (ITT) analysis set. This analysis was considered primary for the evaluation of efficacy. Data were analyzed using Cochran-Mantel-Haenszel (CMH) tests, stratified by analysis center. BSA data were analysed in a post-hoc analysis of covariance (ANCOVA) with factors of treatment and analysis

TABLE 1.

Summary of Baseline Patient Demographics (ITT Population)			
	Pooled Data		
	HP/TAZ Lotion (N=276)	Vehicle (N=142)	Total (N=418)
Age (years)			
Mean	50.0	51.0	50.3
SD	14.18	13.20	13.84
Gender (N/%)			
Male	175 (63.4%)	97 (68.3%)	272 (65.1%)
Female	101 (36.6%)	45 (31.7%)	146 (34.9%)
Ethnicity (N/%)			
Latino	78 (28.3%)	37 (26.1%)	115 (27.5%)
Non-Latino	198 (71.7%)	105 (73.9%)	303 (72.5%)
Race (N/%)			
White	232 (84.1%)	126 (88.7%)	358 (85.6%)
Black/African American	18 (6.5%)	9 (6.3%)	27 (6.5%)
Other	26 (9.4%)	7 (4.9%)	33 (7.9%)

center, and baseline BSA as a covariate. Subgroup analyses for IGA and BSA did not include analysis center as a factor.

The primary safety analysis was conducted at week 8 using the Safety analysis set which is all subjects who are randomized, received at least 1 confirmed dose of study drug, and have at least 1 post-baseline safety assessment. Adverse events were recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0). All reported treatment-emergent adverse events (TEAEs), defined as any AE with an onset on or after the date of first drug application, were summarized by treatment group and relationship to study drug. Each subject was counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively. A post-hoc Wilcoxon Rank-Sum test was conducted to compare itching, dryness, and burning/stinging scores at week 8 for HP/TAZ lotion vs vehicle.

RESULTS

Subject Disposition

Overall, 418 subjects from 32 study centers in the United States were randomized to HP/TAZ lotion or vehicle (Figure 1) and included in the ITT population. Across the two studies, 85.5% (N=236) and 83.8% (N=119) of subjects treated with HP/TAZ lotion or vehicle completed treatment. Main reasons for discontinuation with HP/TAZ lotion were subject request (6.2%, N=17), AEs (4.0%, N=11), or lost to follow-up (3.3%, N=9). Subject request (8.5%, N=12) was also the main reason for discontinuation in the vehicle arms.

TABLE 2.

Summary of Baseline Patient Disease Characteristics (ITT Population)			
	Pooled Data		
	HP/TAZ Lotion (N=276)	Vehicle (N=142)	Total (N=418)
IGA (N/%)			
Moderate	237 (85.9%)	119 (83.9%)	356 (85.2%)
Severe	39 (14.1%)	23 (16.2%)	62 (14.8%)
%BSA Affected			
Mean	6.0	5.7	5.9
SD	2.86	2.54	2.76
Size of Target Lesion (cm^2)			
Mean	36.4	39.7	37.5
SD	22.45	23.56	22.85
Erythema (N/%)			
Mild	25 (9.1%)	11 (7.7%)	36 (8.6%)
Moderate	211 (80.1%)	110 (77.5%)	331 (79.2%)
Severe	30 (10.9%)	21 (14.8%)	51 (12.2%)
Plaque Elevation (N/%)			
Mild	30 (10.9%)	14 (9.9%)	44 (10.5%)
Moderate	212 (76.8%)	108 (76.1%)	320 (76.6%)
Severe	34 (12.3%)	20 (14.1%)	54 (12.9%)
Scaling (N/%)			
Mild	36 (13.0%)	22 (15.5%)	58 (13.9%)
Moderate	203 (73.6%)	100 (70.4%)	303 (72.5%)
Severe	37 (13.4%)	20 (14.1%)	57 (13.6%)

A total of 410 subjects were included in the safety population, with no post-baseline safety evaluation in 8 subjects.

Subject Demographics and Baseline Characteristics

Demographic data were comparable across the two studies. Mean age was 50.3 years (SD 13.84). Overall, the majority of subjects were male (65.1%, N=272) and Caucasian (85.6%, N=358; Table 1).

Baseline disease characteristics were also comparable across the treatment groups. At baseline, subjects had moderate (85.2%, N=356) or severe (14.8%, N=62) disease, with a mean BSA of 5.9 (SD 2.76). Mean size of target lesion was 37.5cm^2 (SD 22.85). The majority of subjects had moderate (erythema [79.2%], plaque elevation [76.6%], and scaling [72.5%]) or severe (erythema [12.2%], plaque elevation [12.9%], and scaling [13.6%]) signs of psoriasis at the target lesion site (Table 2).

Efficacy Evaluation

Investigator's Global Assessment (IGA) of Disease Severity

HP/TAZ lotion was consistently more effective than its vehicle in achieving at least a 2-grade improvement from baseline

FIGURE 2. Treatment success: Proportion of subjects who achieved at least a 2-grade improvement in IGA from Baseline, and an IGA score equating to 'clear' or 'almost clear' at each study visit (Percent change from baseline to week 12, ITT population, Phase 3 studies, pooled data).

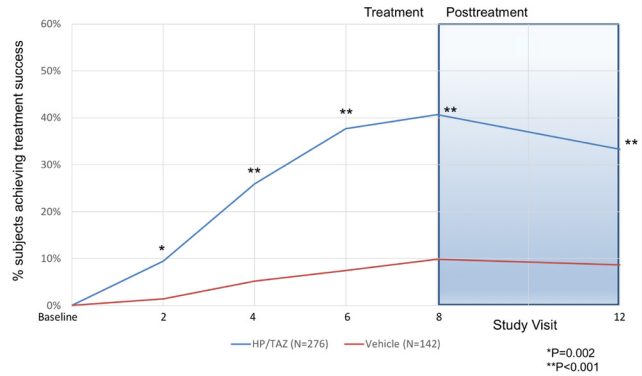


FIGURE 3. Treatment success: Proportion of subjects who achieved at least a 2-grade improvement in IGA from baseline, and an IGA score equating to 'clear' or 'almost clear' at week 8, by baseline IGA score (Percent change from baseline to week 8, ITT population, Phase 3 studies, pooled data).

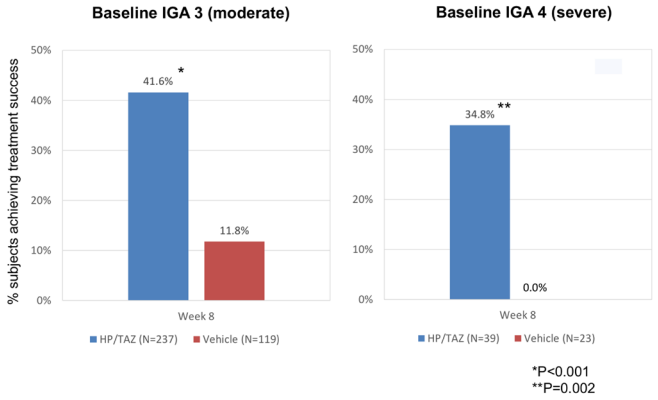
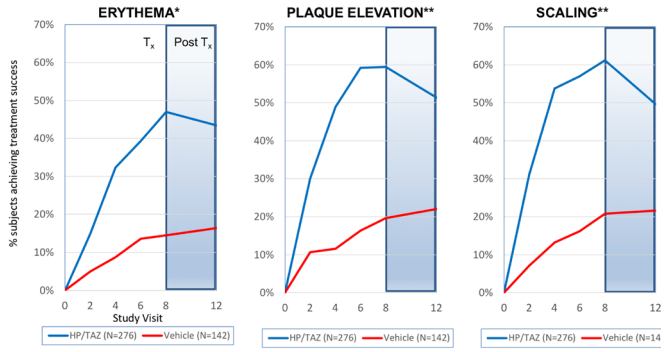


FIGURE 4. Treatment success: Proportion of subjects who achieved at least a 2-grade improvement in psoriasis signs of erythema, plaque elevation, and scaling at each study visit (Percent change from baseline to week 12, ITT population, Phase 3 studies, pooled data).



*P=0.001 at Week 2 and P<0.001 from Week 4
**P<0.001 from Week 2

in the IGA score, and a score of "Clear" or "Almost Clear" (treatment success). HP/TAZ lotion demonstrated statistically significant superiority over vehicle as early as week 2 (P=0.002). By week 8, 40.7% of subjects in the HP/TAZ group achieved the primary efficacy outcome compared with 9.9% in the vehicle group (P<0.001; Figure 2).

HP/TAZ lotion demonstrated a sustained therapeutic effect following the 4-week post-treatment period with 33.3% of subjects assessed as treatment successes at week 12, compared with 8.7% of subjects who had been treated with vehicle (P<0.001).

Overall, 41.6% of subjects who had moderate disease (IGA = 3) at baseline were treatment successes with HP/TAZ lotion at week 8, compared with 11.8% of subjects treated with vehicle. Over a third (34.8%) of subjects with severe disease (IGA = 4) were treatment successes, with at least a 3-grade improvement in IGA. No subjects with severe psoriasis treated with vehicle achieved treatment success at week 8 (see Figure 3).

Severity of Psoriasis Signs (Erythema, Plaque Elevation, and Scaling) at Target Lesion Site

HP/TAZ lotion was statistically superior to vehicle in reducing the psoriasis signs of erythema, plaque elevation, and scaling at the target lesion. At week 8, at least a 2-grade improvement from baseline (treatment success) in severity of psoriasis signs was achieved by 47.0% (erythema), 59.5% (plaque elevation), and 61.2% (scaling) of subjects; compared with 14.5%, 19.7% and 20.8%, respectively, with vehicle (all P<0.001; Figure 4).

HP/TAZ lotion demonstrated a sustained therapeutic effect in improving psoriasis signs four-weeks post-treatment. At week 12, treatment success was maintained in 43.4% (erythema), 51.4% (plaque elevation), and 49.6% (scaling) of subjects.

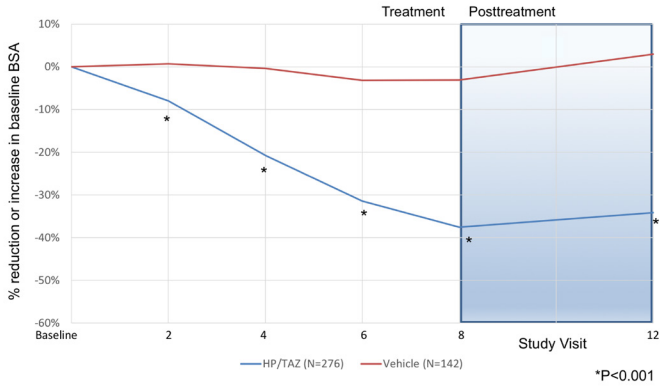
BSA Assessment

HP/TAZ lotion was statistically superior to vehicle in reducing BSA. At week 8 there was a 37.6% reduction in mean BSA (P<0.001 vs vehicle 3.1%; Figure 5). In those subjects who had baseline BSA ≤5 (mean, 3.7), there was a 36.0% reduction in BSA by week 8 that was maintained through week 12 (34.5%), compared with only a 1.6% reduction in baseline BSA with vehicle at week 8, and a 7.3% increase over the 4-week follow-up period (Figure 6). In those subjects who had baseline BSA >5 (mean, 8.5), there was a 39.7% reduction in BSA by week 8 that was maintained through week 12 (33.7%), compared with a 5.5% and 4.3% reduction in baseline BSA with vehicle at week 8 and 12.

Safety Evaluation

Overall, 97 subjects treated with HP/TAZ lotion reported AEs (35.9%) compared with 30 (21.4%) with vehicle (Table 3). The

FIGURE 5. Change in BSA: Percent reduction in BSA from baseline at each study visit (Percent change from baseline to week 12, ITT population, Phase 3 studies, pooled data).



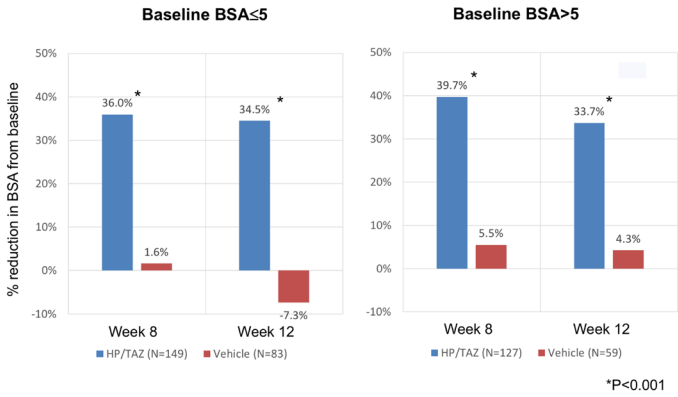
majority of HP/TAZ subjects (85.6%) had AEs which were mild or moderate. Just over half of the HP/TAZ subjects (56.7%) had AEs, which were felt to be treatment related. Most common treatment-related AEs were contact dermatitis (6.3%), pruritus (2.2%), and application site pain (2.6%). AEs such as skin atrophy, telangiectasia, or folliculitis were minimal and sporadic, and not consistent.

Only three subjects reported serious AEs (SAEs) following HP/TAZ treatment (1.1%). None of the SAEs were treatment-related (cellulitis staphylococcal, pneumonia/asthma, and anemia). There was no death reported in either study.

TABLE 3.

Summary of Treatment-Emergent and Related Adverse Events (pooled data – safety population)		
	HP/TAZ Lotion (N=270)	Vehicle Lotion (N=140)
Patients reporting any AE	97 (35.9%)	30 (21.4%)
Patients reporting any SAE	3 (1.1%)	0 (0.0%)
Patients who died	0 (0.0%)	0 (0.0%)
Patients who discontinued due to AE	17 (6.3%)	5 (3.6%)
Severity of AEs reported		
Mild	39 (14.4%)	11 (7.9%)
Moderate	44 (16.3%)	16 (11.4%)
Severe	14 (5.2%)	3 (2.1%)
Relationship to study drug		
Related	55 (20.4%)	11 (7.9%)
Unrelated	42 (15.6%)	19 (13.6%)
Treatment related AEs reported by ≥2% patients		
Application site pain	7 (2.6%)	1 (0.7%)
Pruritus	6 (2.2%)	4 (2.9%)
Contact dermatitis	17 (6.3%)	0 (0.0%)

FIGURE 6. Change in BSA: Percent reduction in BSA from baseline at week 8, and week 12, by baseline BSA severity (Percent change from baseline to week 8 and week 12, ITT population, Phase 3 studies, pooled data).



Local Skin Reactions (LSR)

Itching was the most common LSR at baseline, present in 68.0% of subjects. Subject-reported burning/stinging was less common, reported by a third of subjects (33.7%) at baseline. Investigator-reported dryness was noted in 57.3% of subjects at baseline. Most LSR at baseline were mild-to-moderate in severity.

There was a rapid improvement in subject-reported itching as early as week 2 that was sustained to the end of the studies, with more gradual improvements in skin dryness and burning/stinging. By week 8, mean scores for itching, dryness, and burning/stinging were significantly lower with HP/TAZ lotion compared to vehicle (P=0.002, 0.018, and 0.022, respectively). Improvements in itching were maintained 4-weeks post-treatment and there were continued improvements in dryness, burning/stinging (Figure 5).

DISCUSSION

Plaque psoriasis is a chronic condition. Despite the robust data demonstrating the utility of topical steroids and tazarotene for the treatment of psoriasis, the use of this combination has not been widely adopted and has largely been forgotten. Many of us who treat patients with psoriasis find combination products much easier to use for our patients with enhanced efficacy and better access as a single prescription. The rationale behind the development of a halobetasol propionate 0.01% and tazarotene 0.045% (HP/TAZ) fixed combination lotion was to provide optimal topical treatment for moderate-to-severe psoriasis: providing synergistic efficacy, reducing or minimizing the irritant effect of tazarotene and the local cutaneous AEs with halobetasol (such as skin atrophy, telangiectasia), allowing for the potential of prolonged use beyond 2-4 weeks; in a light, aesthetically pleasing lotion formulation that patients would prefer.

The recently published data on the phase 2 study of HP/TAZ lotion demonstrated synergistic benefits of the combination over the individual active ingredients, with a favorable irritation profile and much low incidence of application site reactions.[11]

Here we further report the safety and tolerability of HP/TAZ lotion, presenting data on two phase 3 clinical studies in moderate-to-severe psoriasis. Treatment success was rapid and achieved in over 40% of subjects by week 8; with substantial reductions in BSA, and a significant improvement in psoriasis signs and symptoms (erythema, plaque elevation and scaling). Reduction in mean BSA was similar in those subjects with moderate and more severe disease, while there was minimal improvement with vehicle. A similar picture was seen when subjects were categorized by baseline IGA. Indeed, no subjects with severe disease who were treated with vehicle achieved treatment success.

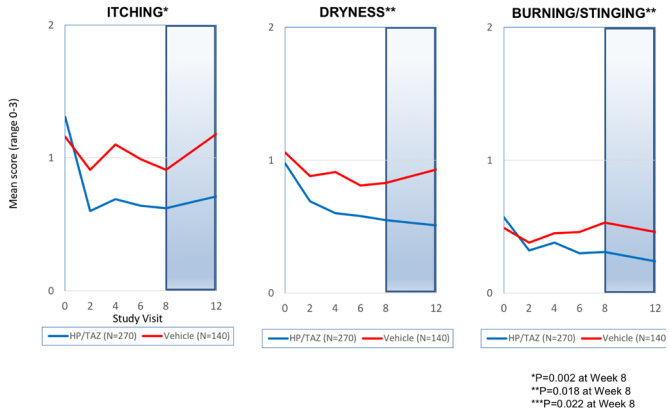
We also noted sustained improvement over the 4-week post-treatment period, likely influenced by the tazarotene component. Risk of rebound (a worsening of disease following treatment discontinuation) is an important, and often overlooked aspect of psoriasis management. Tazarotene appears to induce longer remission than TCS,[9] where disease rebound after treatment discontinuation has been reported. Although the follow-up period in our studies was relatively short, a high proportion of subjects were treatment success four weeks after cessation of therapy.

Treatment with HP/TAZ lotion also provided significant, rapid and sustained benefits in controlling itch, without any obvious deleterious effect of the tazarotene component which has reduced its use in psoriasis. Pruritus can be a very unpleasant and common psoriasis symptom,[10] affecting sleep and impairing QoL. Itching can also occur as a result of dry skin. Skin dryness was improved by 44% and burning/stinging reduced by 46% over the 8-week treatment period and continued to improve post-treatment.

Physicians continue to have long-term safety concerns with TCS,[4,11,12] patients remain concerned about the risk of skin thinning,[13] and product labelling restricts halobetasol consecutive use to two weeks. There were minimal safety concerns in our two studies using an 8-week treatment regimen with HP/TAZ lotion, and long-term studies are currently being evaluated to provide useful information to patients and clinicians on the potential benefits of this topical formulation.

HP/TAZ lotion was well tolerated with only three treatment related AEs reported by ≥2% subjects. While irritant contact dermatitis was the most common, it was not reported in the phase 2 study (with the exception of the tazarotene monotherapy arm) and here is likely the consequence of the tazarotene component in HP/TAZ lotion. In the majority of cases it was mild or moderate in severity. Pruritus was similar to the rates reported with vehicle (2.2% versus 2.9%). Application site pain was lower than that reported in the phase 2 study (2.9% versus 3.4%), and lower than that reported with tazarotene in the phase 2 study (6.9%).[8]

FIGURE 7. Change in local skin reactions: Mean scores for itching, dryness, and burning/stinging at each study visit (mean scores [range, 0-3] to week 12, safety population, Phase 3 studies, pooled data).



CONCLUSIONS

Halobetasol propionate 0.01%/ tazarotene 0.045% lotion provides synergistic efficacy, with rapid and sustained improvement in disease severity. HP/TAZ lotion was consistently more effective than vehicle in achieving treatment success, reducing the BSA affected by the disease, and reducing erythema, plaque elevation, and scaling at the target lesion. There were minimal safety concerns with using a longer treatment than is normal for TCS options and HP/TAZ lotion may provide a realistic long-term treatment option in patients with moderate-to-severe plaque psoriasis.

DISCLOSURES

Drs Sugarman, Weiss and Stein Gold are advisors to Ortho Dermatologics; JS, LGS, JB were principal investigators in the studies; and TL, GM, RK and RI are employees of Bausch Health.

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