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Halobetasol Propionate 0.01%/Tazarotene 0.045% Lotion for Moderate-to-Severe Psoriasis: Pooled Phase 3 Analysis of Lower Extremities

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ABSTRACT

Background: Plaque psoriasis can occur in all body regions, with the trunk and extremities among the most commonly affected areas. A fixed combination halobetasol propionate 0.01%/tazarotene 0.045% (HP/TAZ) lotion demonstrated efficacy and safety in patients with moderate-to-severe localized plaque psoriasis. This analysis evaluated patients where a psoriatic target lesion was identified on the leg.

Methods: In two phase 3, multicenter, double-blind studies, participants were randomized (2:1) to receive HP/TAZ or vehicle lotion once-daily for 8 weeks. This pooled, post hoc analysis included a subset of participants who had a leg target lesion (HP/TAZ, n=148; vehicle, n=71). Efficacy assessments included treatment success (≥2-grade improvement) in psoriasis signs (erythema, plaque elevation, scaling) on the leg target lesion, and overall treatment outcomes, including overall treatment success (≥2-grade improvement in Investigator's Global Assessment [IGA] score and score of clear/almost clear), affected Body Surface Area (BSA), and IGAxBSA composite score.

Results: Psoriasis signs were reduced by week 8, with more HP/TAZ treated participants achieving treatment success for erythema (41.6%), plaque elevation (58.5%), and scaling (59.5%) on the leg compared with vehicle (12.5%, 19.2%, and 21.0%, respectively; $P<0.001$ all). Significantly more participants achieved overall treatment success at week 8 with HP/TAZ versus vehicle (36.4% vs 10.4%; $P<0.001$). The HP/TAZ group also had a greater mean reduction in affected BSA and IGAxBSA score versus vehicle ($P<0.001$, both). The most frequently reported treatment-related adverse event (incidence, ≥3%) with HP/TAZ was contact dermatitis.

Conclusions: HP 0.01%/TAZ 0.045% lotion was associated with significant reductions in disease severity and good tolerability following 8 weeks of treatment in patients where a psoriatic target lesion was identified on the leg.

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INTRODUCTION

Psoriasis is a chronic, immune-mediated disease that varies widely in its clinical expression.[1] Although there are different types of psoriasis, plaque psoriasis is by far the most common type and makes up approximately 90% of cases.[2] Plaque psoriasis can occur across all regions of the body, though the trunk and extremities are among the most commonly affected areas.[3]

The impact of psoriasis on overall disease burden and patient quality of life may vary depending on the location of psoriatic lesions.[4] In addition, the treatment of certain body regions can be more problematic than others,[5,6] with certain areas being more resistant to treatment or requiring longer treatment periods to achieve clearance of symptoms.[5-8] However, more data is needed to better understand the relationship between psoriasis location and treatment response.

The use of topical therapy is a key component in the management of almost all psoriasis patients.[9] However, long-term safety of corticosteroids remains a concern, as use is limited to 2-3 consecutive weeks for most topical steroids. Recent phase 3 clinical data have demonstrated that a once-daily, fixed-combination halobetasol propionate 0.01% and tazarotene 0.045% (HP/TAZ) lotion was significantly more effective than vehicle

after 8 weeks of treatment in patients with moderate-to-severe localized plaque psoriasis.[10,11] Additionally, these studies demonstrated the ability of HP/TAZ lotion to minimize the irritant effects of tazarotene and halobetasol-related adverse events (AEs) without the limitation of short-term use common in topical corticosteroids.[10,11] However, the efficacy and tolerability of HP/TAZ in specific body regions have not been evaluated. This post hoc analysis evaluated the efficacy and safety of HP/TAZ lotion in participants where a psoriatic target lesion was identified on the leg.

METHODS

Study Design

Data from two phase 3, multicenter, randomized, double-blind studies (Study 1 [NCT02462070]; Study 2 [NCT02462122]) of HP/TAZ fixed combination lotion in patients with moderate-to-severe psoriasis were pooled for this post hoc analysis.[10,11] The methodology for the 2 individual studies has been previously published[10,11] and is described briefly here. Participants were randomized (2:1) to receive HP/TAZ lotion or vehicle lotion once-daily for 8 weeks, with a 4-week posttreatment follow-up. Participants were instructed to apply a thin layer of HP/TAZ or vehicle lotion over the affected areas as designated by the investigator; the maximum allowable weekly usage was 50 gm. CeraVe® hydrating cleanser and CeraVe® moisturizing lotion (L'Oreal, NY) were provided as needed for optimal moisturization/cleaning of the skin.

All participants were required to be ≥18 years of age and have a clinical diagnosis of psoriasis, an Investigator's Global Assessment (IGA) score of 3 or 4 (5-point scale; 0=clear and 4=severe), and affected Body Surface Area (BSA) of 3% to 12%; face, scalp, palms, soles, axillae, and intertriginous areas were excluded from these calculations. For all participants, the target lesion must have covered an area between 16-100 cm^2 in size and could not be located on any area covering bony prominences (eg, knees). In addition, the lesion must be associated with a score of ≥3 for at least 2 of 3 signs of psoriasis (erythema, plaque elevation, and scaling [5 point scale; 0=clear and 4=severe]), a score sum of at least 8, and could not have had a score of 0 or 1 for any one of the signs.

Written informed consent was required from participants prior to the conduct of any study-related procedures. The protocol was approved by institutional review boards (IRBs) or ethics committees at all investigational sites. Studies were conducted in accordance with the protocol, the ethical principles of Good Clinical Practice (GCP), International Council for Harmonisation (ICH), and the Declaration of Helsinki.

Post Hoc Analyses

Post hoc analyses were conducted using data from the subset of patients from the pooled overall intent-to-treat population (ITT) whose target lesion was on the lower extremities (leg). Treatment success at the leg target lesion, was defined as a ≥2-grade improvement from baseline and was evaluated for each individual sign of psoriasis (erythema, plaque elevation, and scaling). Overall treatment success, which considered all treatment areas in addition to the target lesion was defined as a ≥2-grade improvement from baseline in IGA score and a score of 'clear' or 'almost clear' [0 or 1]. Reductions from baseline in overall mean BSA and the IGAxBSA composite tool were also evaluated. Change from baseline in IGAxBSA was calculated by multiplying the IGA score by the total BSA. Reductions from baseline of ≥50% and ≥75% in IGAxBSA score (IGAxBSA-50 and IGAxBSA-75) were also tabulated. The IGA, BSA, and IGAxBSA composite assessments did not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas; palms and soles with psoriasis could be treated with the study drug but were not included in these assessments.

Efficacy analyses were conducted in the ITT analysis population, defined as participants who were randomized, received study drug, and presented with a target lesion on the leg. Safety parameters were assessed using the safety population, defined as participants from the ITT analysis population who had post-baseline safety data. Treatment success data (signs of psoriasis and overall) were analyzed by using Cochran-Mantel-Haenszel (CMH) tests stratified by analysis center with all values adjusted for multiple imputations. Markov chain Monte Carlo (MCMC) multiple imputation was used to impute missing values. Affected BSA was evaluated using an analysis of covariance with factors of treatment and study center and baseline affected BSA as a covariate; there was no imputation of missing data. Mean change in IGAxBSA composite tool was examined using a Wilcoxon Rank Sum Test with last observation carried forward (LOCF) used to impute missing IGA and BSA data through week 8 prior to analysis. IGAxBSA-50 and -75 parameters were assessed using CMH test with LOCF used to impute missing values through week 8. Safety was evaluated via assessment of AEs through week 8. All treatment areas were examined at each visit for the presence or absence of skin atrophy, striae, telangiectasia, and folliculitis, AEs known to be related to HP/TAZ.

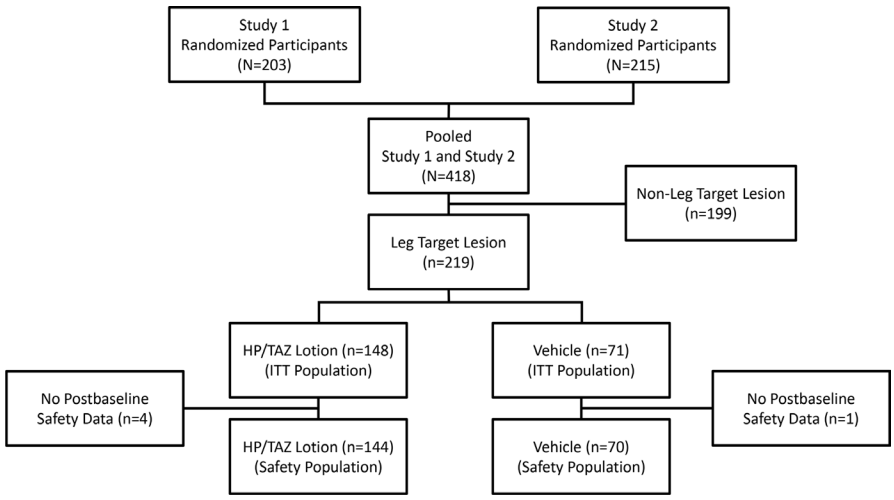
RESULTS

Participant Disposition and Baseline Characteristics

A total of 418 participants were randomized to once-daily HP/TAZ or vehicle lotion (Study 1, n=203 [HP/TAZ, n=135; vehicle, n=68]; Study 2, n=215 [HP/TAZ, n=141; vehicle, n=74]) (Figure 1). A total of 219 participants (52.4%) were identified as having a leg target lesion and were included in the analysis. Of those, 148 participants received once-daily HP/TAZ lotion and 71 received vehicle. A total of 82.4% of participants completed HP/TAZ treatment compared with 78.9% that completed vehicle treatment.

Demographics and baseline characteristics were generally

FIGURE 1. Participants.



HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045%; ITT, intent-to-treat.

TABLE 1.

Participant Demographics and Baseline Characteristics (ITT Population, Pooled)			
	HP/TAZ Lotion (n=148)	Vehicle Lotion (n=71)	Total (n=219)
Age, mean (SD), y	49.6 (14.2)	50.3 (12.1)	49.8 (13.5)
Sex, n (%)			
Male	87 (58.8)	51 (71.8)	138 (63.0)
Female	61 (41.2)	20 (28.2)	81 (37.0)
Ethnicity, n (%)			
Hispanic/Latino	41 (27.7)	15 (21.1)	56 (25.6)
Not Hispanic/Latino	107 (72.3)	56 (78.9)	163 (74.4)
Race, n (%)			
White	122 (82.4)	64 (90.1)	186 (84.9)
Asian	10 (6.8)	2 (2.8)	12 (5.5)
Black/African American	9 (6.1)	4 (5.6)	13 (5.9)
Other[a]	7 (4.7)	1 (1.4)	8 (3.7)
IGA, n (%)			
3 – Moderate	128 (86.5)	58 (81.7)	186 (84.9)
4 – Severe	20 (13.5)	13 (18.3)	33 (15.1)
Overall BSA, mean (SD), %[b]	5.6 (2.6)	5.6 (2.6)	5.6 (2.6)
Size of Leg Lesion, mean (SD), cm^2	39.8 (24.2)	45.0 (24.9)	41.5 (24.5)
Erythema, n (%)[c]			
2 – Mild	15 (10.1)	6 (8.5)	21 (9.6)
3 – Moderate	115 (77.7)	53 (74.6)	168 (76.7)
4 – Severe	18 (12.2)	12 (16.9)	30 (13.7)
Plaque Elevation, n (%)[c]			
2 – Mild	23 (15.5)	4 (5.6)	27 (12.3)
3 – Moderate	107 (72.3)	59 (83.1)	166 (75.8)
4 – Severe	18 (12.2)	8 (11.3)	26 (11.9)
Scaling, n (%)[c]			
2 – Mild	20 (13.5)	16 (22.5)	36 (16.4)
3 – Moderate	106 (71.6)	46 (64.8)	152 (69.4)
4 – Severe	22 (14.9)	9 (12.7)	31 (14.2)

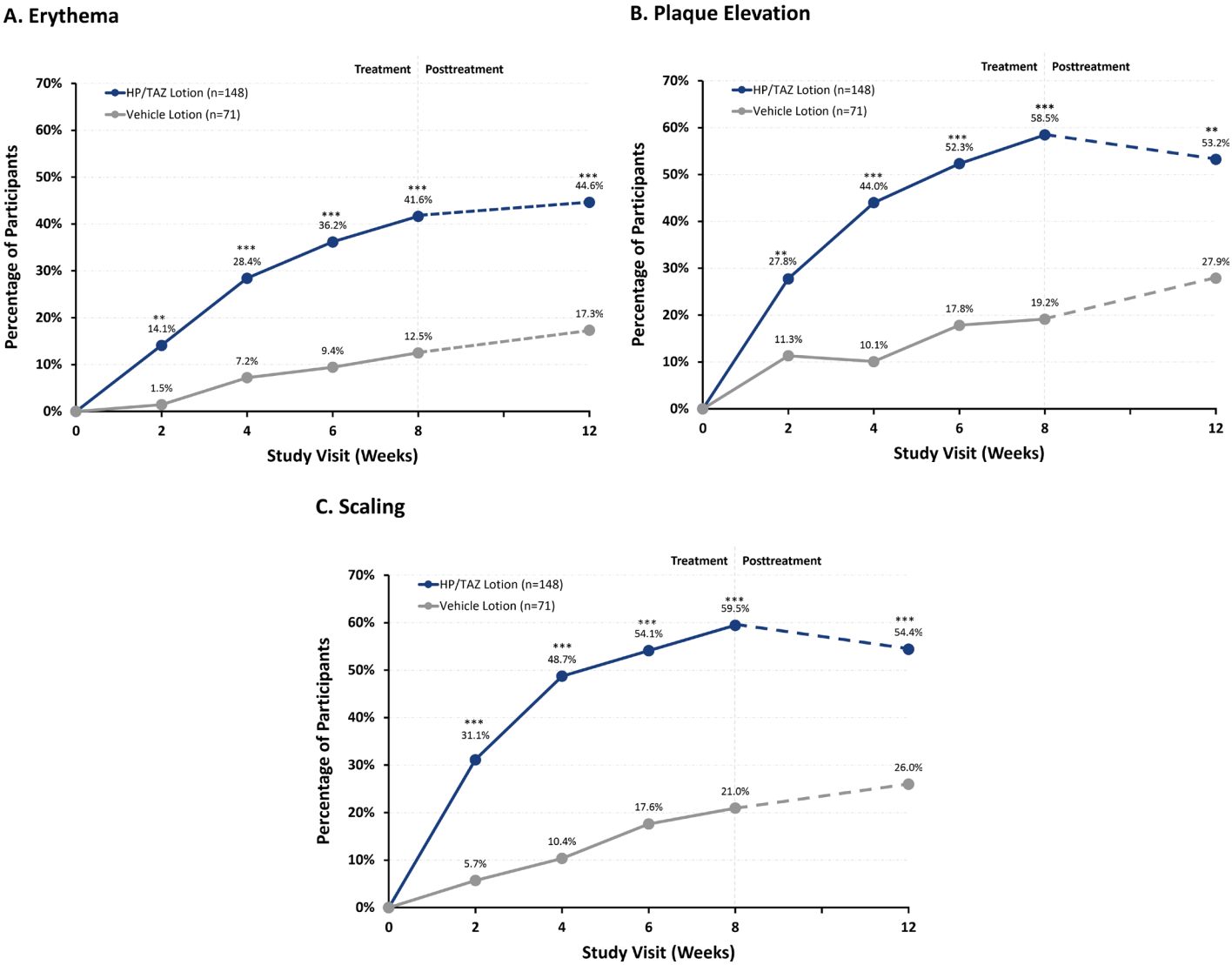
[a]Includes American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander. [b]Excludes face, scalp, palms, soles, axillae, and other intertriginous areas. [c]Sign of psoriasis in the leg target lesion. BSA, Body Surface Area; HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045%; IGA, Investigator's Global Assessment; ITT, intent-to-treat; SD, standard deviation.

similar among HP/TAZ and vehicle lotion groups (Table 1). Participants in both treatment groups at baseline had a mean (SD) overall BSA of 5.6% (2.6%). Mean (SD) leg lesion (target) area in HP/TAZ and vehicle lotion groups was 39.8 (24.2) cm^2 and 45.0 (24.9) cm^2, respectively. At baseline, >80% of participants in both treatment groups had signs of psoriasis (erythema, plaque elevation, scaling) that were categorized as mild or moderate in severity; >80% also had a moderate IGA score.

Efficacy Evaluations

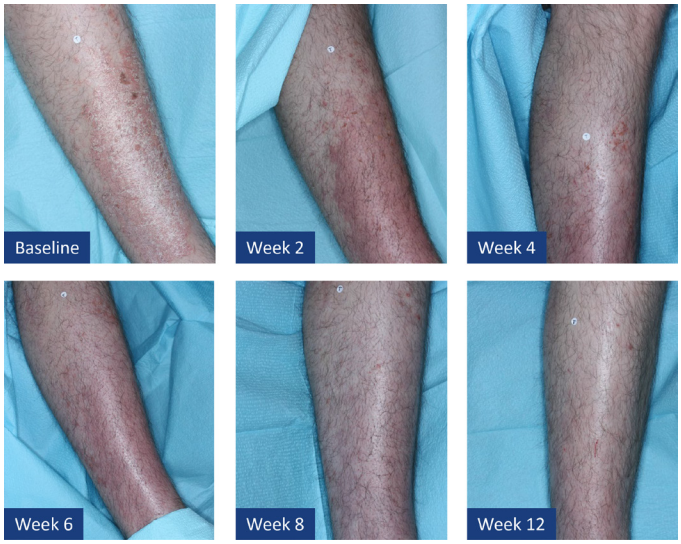
At the end of the 8-week treatment period, a significantly greater proportion of participants receiving HP/TAZ lotion achieved treatment success at the target lesion (leg), with 41.6%, 58.5%, and 59.5% achieving a ≥2-grade reduction in erythema, plaque elevation, and scaling severity on the leg, compared with 12.5%, 19.2%, and 21.0% of those treated with vehicle, respectively (P<0.001 all; Figure 2). Therapeutic effects of HP/TAZ lotion were sustained through week 12, with treatment success in 44.6% (erythema), 53.2% (plaque elevation), and 54.4% (scaling) of HP/TAZ-treated participants versus 17.3%, 27.9%, and 26.0%, respectively, of those in the vehicle-treated group (P<0.01 all). Significant differences versus vehicle were observed by week 2

FIGURE 2. Treatment success[a] in psoriasis signs of (A) erythema, (B) plaque elevation, and (C) scaling on the leg target lesion (ITT population, pooled).



**P<0.01 vs vehicle, ***P<0.001 vs vehicle.
[a]Treatment success is defined as a ≥2-grade improvement from baseline in each individual sign of psoriasis at the target lesion.
HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045%; IGA, Investigator's Global Assessment; ITT, intent-to-treat.

FIGURE 3. Psoriasis improvement over time on a leg target lesion.



Photograph from a representative patient. Individual results may vary.

for all signs of psoriasis. Figure 3 illustrates improvement over time with HP/TAZ lotion on the leg target lesion.

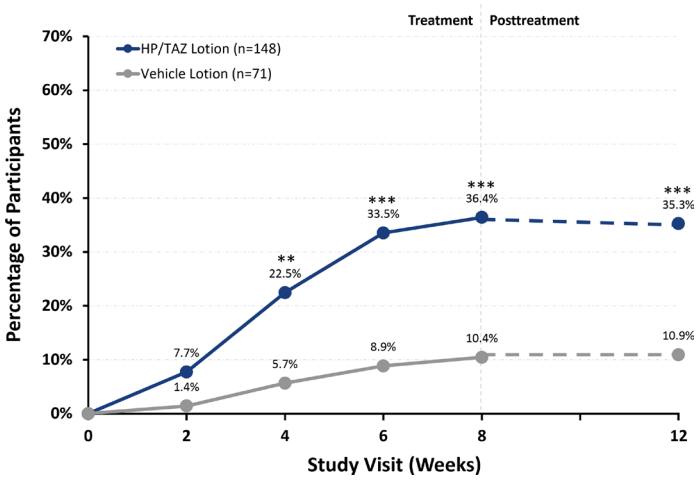
At week 8, overall treatment success across all treatment areas (IGA score of 0 or 1 and ≥2-grade improvement) was achieved in 36.4% of participants treated with HP/TAZ lotion compared with 10.4% treated with vehicle (*P*<0.001; Figure 4). Treatment success was maintained through the 4-week posttreatment follow-up, with overall treatment success at week 12 achieved in 35.3% vs 10.9% of participants treated with HP/TAZ or vehicle, respectively (*P*<0.001). A significant difference in favor of HP/TAZ versus vehicle for overall treatment success was observed by week 4.

Mean overall affected BSA was reduced by 32.7% at week 8 in HP/TAZ-treated participants compared with a 1.0% reduction in vehicle-treated participants (*P*<0.001; Figure 5). At week 12, mean reductions in BSA were 34.8% in HP/TAZ-treated participants compared with a 7.3% increase in vehicle-treated participants (*P*<0.001). Mean BSA reductions were significantly greater in HP/TAZ-treated participants than vehicle-treated participants as early as week 2.

Mean percent reduction from baseline to week 8 in IGAxBSA composite score was also significantly greater with HP/TAZ treatment (-47.3%) than with vehicle (-4.5%; *P*<0.001) and was sustained at week 12 (-47.2% vs -8.5%; *P*<0.001; Figure 6). Significant reductions versus vehicle in IGAxBSA were observed as early as week 2.

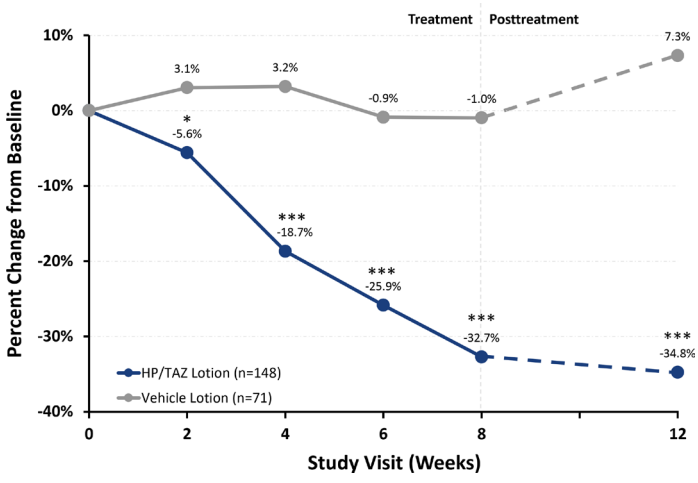
A significantly greater percentage of participants in the HP/TAZ group (37.8%) compared with the vehicle group (12.7%) achieved a ≥75% reduction from baseline in IGAxBSA (IGAxBSA-75) score at week 8 (*P*<0.001); this difference was sustained at week 12 (45.2% vs 12.3%, respectively; *P*<0.001). Similarly, a significant difference in the percentage of participants with IGAxBSA-50 achievement at week 8 was also found between HP/TAZ-treated participants and those treated with vehicle (53.4% vs 14.1%, respectively; *P*<0.001); at week 12, the percentage of participants

FIGURE 4. Overall treatment success[a] on IGA assessment of disease severity (ITT population, pooled).



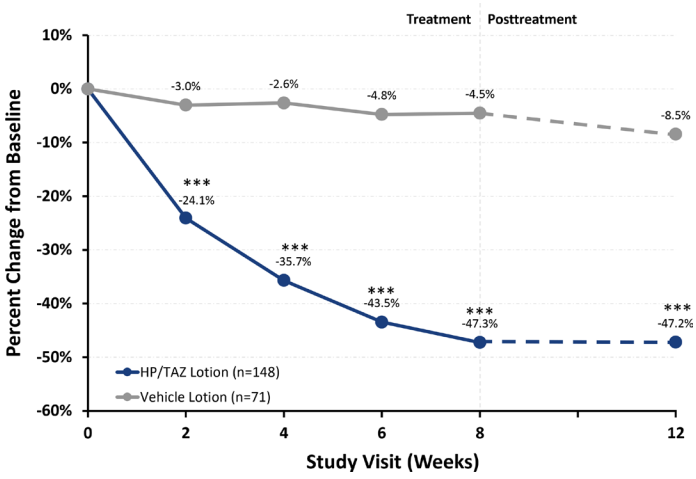
**P<0.01 vs vehicle, ***P<0.001 vs vehicle.
[a]Treatment success is defined as a ≥2-grade improvement from baseline in IGA score and a score of 'clear' or 'almost clear' (0 or 1).
HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045%; IGA, Investigator's Global Assessment; ITT, intent-to-treat.

FIGURE 5. Mean percent change from baseline in overall affected BSA (ITT population, pooled).



**P<0.05 vs vehicle; ***P<0.001 vs vehicle.
BSA, Body Surface Area; HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045%; ITT, intent-to-treat.

FIGURE 6. Mean percent change from baseline in IGAxBSA composite score (ITT population, pooled).



***P<0.001 vs vehicle.
BSA, Body Surface Area; HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045%; IGA, Investigator's Global Assessment; ITT, intent-to-treat.

with an IGAxBSA-50 achievement was also significantly greater among HP/TAZ-treated participants than those treated with vehicle (58.1% vs 26.3%, respectively; P<0.001).

Safety Evaluations

Of the participants treated with HP/TAZ lotion, 36.1% reported treatment-emergent AEs (TEAEs) compared with 22.9% of those treated with vehicle; TEAEs were categorized as mild or moderate in severity in most patients (Table 2). Only 3 participants (2.1%) reported serious AEs following treatment with HP/TAZ lotion. The most common treatment-related TEAEs (incidence ≥2%) in HP/TAZ-treated participants were contact dermatitis (7.6%), skin atrophy (2.8%), folliculitis (2.8%), and excoriation (2.1%); no AEs of striae were identified. In the 4 patients with a TEAE of skin atrophy, all cases were mild or moderate in severity and were resolved/resolving with either a dose reduction or no change in treatment. In the vehicle-group, frequently reported treatment-related TEAEs were pruritus, skin burning sensation, and burning sensation (nervous system disorder; 2.9% for all).

DISCUSSION

This pooled post hoc analysis of 2 phase 3 studies evaluated the efficacy and safety of HP/TAZ lotion in patients with moderate to severe plaque psoriasis of the lower extremities (target lesion of the leg). At the end of the 8-week treatment period, HP/TAZ lotion demonstrated significant efficacy in improving signs of psoriasis (erythema, plaque elevation, and scaling) at the leg target le-

TABLE 2.

Treatment-Emergent Adverse Events Through Week 8 (Safety Population)		
Parameter, n (%)	**HP/TAZ Lotion (n=144)**	**Vehicle Lotion (n=70)**
Any TEAE	52 (36.1)	16 (22.9)
SAE	3 (2.1)	0
Discontinuation due to TEAE	11 (7.6)	4 (5.7)
Severity of TEAEs reported		
Mild	13 (9.0)	4 (5.7)
Moderate	29 (20.1)	9 (12.9)
Severe	10 (6.9)	3 (4.3)
Relationship of TEAEs to study drug		
Related	34 (23.6)	7 (10.0)
Unrelated	18 (12.5)	9 (12.9)
Treatment-related TEAEs reported in ≥2% of participants in any treatment group		
Contact dermatitis	11 (7.6)	0
Skin atrophy	4 (2.8)	0
Folliculitis	4 (2.8)	0
Excoriation	3 (2.1)	0
Pruritis	2 (1.4)	2 (2.9)
Skin burning sensation	2 (1.4)	2 (2.9)
Burning sensation (nervous system disorders)	2 (1.4)	2 (2.9)

HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045%; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

sion. Treatment success on these signs were achieved in almost half of participants treated with HP/TAZ compared with <25% of those treated with vehicle; these significant therapeutic effects were observed as early as week 2 and sustained posttreatment. In addition to demonstrating efficacy at psoriasis lesions on the lower extremities, treatment with HP/TAZ also was effective for reducing overall psoriasis severity in this population.

Following 8 weeks of HP/TAZ treatment, a significantly greater percentage of participants achieved overall treatment success, defined as a 2-grade improvement and a score of clear or almost clear on the IGA across all treatment areas. Overall affected BSA levels were also significantly reduced compared with vehicle at week 8. Similar results were also observed using the IGAxBSA composite tool, with significantly greater mean reductions in IGAxBSA score at week 8 for HP/TAZ- versus vehicle-treated patients. A reduction of ≥75% from baseline IGAxBSA score (IGAxBSA-75) was achieved by approximately 38% of HP/TAZ-treated participants versus 13% of vehicle-treated participants at week 8. Effects of HP/TAZ at week 8 were sustained at week 12 for all efficacy measures. The safety and tolerability of HP/TAZ in this subpopulation of participants was consistent with that reported in the overall population from previous studies.[10,11] In this subpopulation, the most common treatment-related TEAEs in HP/TAZ-treated participants were contact dermatitis, skin atrophy, folliculitis, and excoriation. Although AEs such as skin thinning are a concern with higher potency topical corticosteroids,[12] skin atrophy was reported in only 4 participants in this study. All cases were mild or moderate in severity and resolved or were resolving at the end of the study with either no change in treatment or a dose reduction.

The lower extremities represent one of the most commonly affected areas associated with chronic plaque psoriasis.[3,7] This was found to be the case for the current analysis as well, with over half of participants from the original phase 3 studies having an investigator-identified target lesion on the leg. Of note, the percentage of participants from these studies with psoriasis affecting the lower extremities is likely higher than 52%, as the subpopulation evaluated in this study was limited to only those with a target lesion on the leg and did not necessarily include all patients with psoriasis affecting the lower extremities. Demographic and disease characteristics in this post hoc subpopulation were generally similar to that observed in the overall population, with the exception of a slightly higher target lesion size in patients with a target lesion of the leg (41.5 cm^2) versus those in the overall pooled population (37.5 cm^2).[11]

Very few studies have specifically evaluated treatment efficacy by specific body region. However, evidence from a recent observational study of biologic agents in real-world clinical practice suggested that the most common sites of recalcitrant psoriasis include the lower leg and elbows.[7] Other studies have similarly found that psoriasis lesions located on lower extremities are often among the slowest areas to respond to biologic treatment.[5,6,8]

Evidence for the efficacy of topical treatments for psoriasis of the lower extremities is lacking. Results from the current study demonstrate that HP/TAZ was effective in reducing the signs of psoriasis at lower extremity lesions, and that these effects were rapid, occurring within 2 weeks of initiation of treatment. In addition, effects of HP/TAZ were sustained during the 4-week posttreatment period, which may reflect the benefit of adding tazarotene to the potent effects of halobetasol. Application of this combination lotion formulation is not limited to the 2 consecutive weeks of use common with superpotent topical corticosteroids[10] since HP/TAZ has been shown to cause only minimal irritant effects commonly caused by tazarotene, and also minimizes local halobetasol-related AEs.[13]

There are several limitations to this post hoc analysis that should be considered. While this analysis was able to identify and select patients with a target lesion on the lower extremities, the target lesion was restricted to the leg, had to be between 16-100 cm^2 in size, and could not include areas covering bony prominences (eg, knees). As a result, the likelihood exists that some participants with psoriasis affecting the lower extremities may not have been included. Additionally, study criteria limited the population to participants with BSA of 3-12%, and patients with greater severity were not included in the studies. Finally, efficacy data for HP/TAZ in areas other than the leg were not evaluated in this study, so comparisons between body regions are not possible. However, the results of this subanalysis were generally consistent with results reported for the overall population.[11]

CONCLUSIONS

Fixed combination halobetasol propionate 0.01% and tazarotene 0.045% lotion provided rapid and sustained efficacy versus vehicle following 8 weeks of therapy in patients where the leg was identified as the target lesion. HP/TAZ was effective at reducing erythema, plaque elevation, and scaling as well as overall IGA scores and affected BSA levels. HP/TAZ was safe and well-tolerated and may provide a reasonable treatment option for patients with psoriasis affecting the lower extremities.

DISCLOSURES

Stephen Tyring has acted as an investigator for Ortho Dermatologics. Leon H. Kircik has acted as an investigator, advisor, speaker, and consultant for Ortho Dermatologics. Paul Yamauchi has served as speaker, consultant, and investigator for AbbVie, Amgen, Janssen, Novartis, Lilly, LEO, Ortho Dermatologics, and Sun Pharma. Abby Jacobson and Tina Lin are employees of Ortho Dermatologics and may hold stock and/or stock options in its parent company.

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