Tapinarof Cream 1% QD for the Treatment of Plaque Psoriasis: Efficacy and Safety in Two Pivotal Phase 3 Trials

Mark Lebwohl,[1] Linda Stein Gold,[2] Bruce Strober,[3] Kim Papp,[4] April Armstrong,[5] Jerry Bagel,[6] Leon Kircik,[1,7] Benjamin Ehst,[8] H Chih-ho Hong,[9] Jennifer Soung,[10] Jeff Fromowitz,[11] Scott Guenthner,[12] Stephen C Piscitelli,[13] David S Rubenstein,[13] Philip M Brown,[13] Anna M Tallman,[13] Robert Bissonnette[14]

[1]Icahn School of Medicine, Mount Sinai, New York, NY, USA; [2]Henry Ford Health System, Detroit, MI, USA; [3]Yale University, New Haven and Central Connecticut Dermatology Research, Cromwell, CT, USA; [4]Probity Medical Research, Waterloo, ON, Canada; [5]Keck School of Medicine University of Southern California, Los Angeles, CA, USA; [6]Psoriasis Treatment Center of New Jersey, NJ, USA; [7]Skin Sciences, PLLC, Louisville, KY, USA; [8]Oregon Medical Research Center, Portland, OR, USA; [9]University of British Columbia and Probity Medical Research, Surrey, BC, Canada; [10]Southern California Dermatology, Santa Ana, CA, USA; [11]Dermatology of Boca, Boca Raton, FL, USA; [12]The Indiana Clinical Trials Center, PC, Plainfield, IN, USA; [13]Dermavant Sciences, Inc., Durham, NC, USA; [14]Innovaderm Research Inc., Montreal, QC, Canada

BACKGROUND

- Psoriasis is a chronic, immune-mediated disease characterized by scaly, erythematous, and pruritic plaques that can be painful and disfiguring[1]
- There is a need for efficacious topical therapies for plaque psoriasis without concerns for duration of treatment due to potential for long-term adverse effects or local intolerance. However, no topicals with novel mechanisms have been FDA approved in recent years
- Tapinarof is a first-in-class, non-steroidal, topical therapeutic aryl hydrocarbon receptor modulating agent (TAMA) in development for the treatment of psoriasis and atopic dermatitis
- PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980) were two pivotal Phase 3 studies designed to assess the efficacy and safety of tapinarof cream 1% once daily (QD) in patients with plaque psoriasis

OBJECTIVE

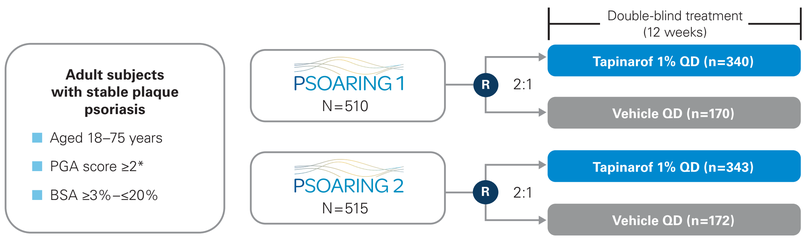
- To present the pivotal Phase 3 primary efficacy endpoint (proportion of patients who achieved a Physician Global Assessment [PGA] response at Week 12), key secondary efficacy endpoint (proportion of patients who achieved ≥75% improvement in Psoriasis Area and Severity Index [PASI75] from baseline at Week 12), and safety results of PSOARING 1 and 2

METHODS

Study Design

- In two identical, Phase 3, multicenter (US and Canada), double-blind, vehicle-controlled, randomized studies, patients with mild to severe plaque psoriasis were randomized 2:1 to receive tapinarof cream 1% QD or vehicle QD for 12 weeks (**Figure 1**)
- Following the double-blind period, patients could enroll in a separate open-label, long-term extension study for an additional 40 weeks of treatment, or complete a follow-up visit 4 weeks after the end of treatment (Week 16)

Figure 1. Study Design



*PGA of 2 (mild) or 4 (severe) was limited to ~10% each of the total randomized population; ~80% of the randomized population had a PGA of 3 (moderate). BSA, body surface area; PGA, Physician Global Assessment; QD, once daily; R, randomized

Endpoints and Statistical Analysis

- The primary endpoint was PGA response at Week 12, defined as the proportion of patients with a PGA score of clear (0) or almost clear (1) and ≥2-grade improvement in PGA score from baseline to Week 12
- The key secondary efficacy endpoint was the proportion of patients who achieved PASI75 from baseline to Week 12
- The incidence, frequency, and nature of adverse events (AEs) and serious AEs were monitored from the start of study treatment until the end-of-study visit
- Efficacy endpoints were derived from the intent-to-treat (ITT) population using multiple imputation analysis
- *P* values for differences between tapinarof cream 1% QD and vehicle in both studies were calculated using Cochran-Mantel-Haenszel analysis and stratified by baseline PGA score

RESULTS

Patient Disposition and Baseline Characteristics

- In PSOARING 1 and 2, a total of 510 and 515 patients were randomized (ITT), respectively, across 97 sites in the US and Canada
- Overall, mean demographic and baseline characteristics were comparable across treatment groups and studies (**Table 1**)
- At baseline, 79.2% and 83.9% of patients had a PGA score of 3, mean (standard deviation [SD]) PASI score was 8.9 (4.1) and 9.1 (3.8), and mean (SD) body surface area was 7.9% (4.8) and 7.6% (4.3) in PSOARING 1 and 2, respectively

Table 1. Baseline Patient Demographics and Characteristics

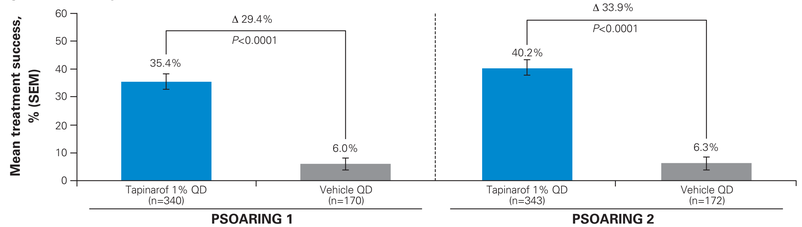
	PSOARING 1		PSOARING 2	
	Tapinarof 1% QD (n=340)	Vehicle QD (n=170)	Tapinarof 1% QD (n=343)	Vehicle QD (n=172)
Mean age, years (SD)	49.8 (13.7)	49.1 (13.3)	50.0 (13.1)	50.0 (13.7)
Male, n (%)	213 (62.6)	86 (50.6)	188 (54.8)	102 (59.3)
Weight, kg, mean (SD)	91.7 (24.6)	92.8 (22.7)	92.9 (24.3)	89.6 (19.9)
BMI, kg/m^2, mean (SD)	31.4 (7.8)	32.5 (7.6)	31.8 (7.7)	30.7 (6.3)
PGA, n (%)				
2 – Mild	39 (11.5)	21 (12.4)	28 (8.2)	15 (8.7)
3 – Moderate	271 (79.7)	133 (78.2)	288 (84.0)	144 (83.7)
4 – Severe	30 (8.8)	16 (9.4)	27 (7.9)	13 (7.6)
PASI, mean (SD)	8.7 (4.0)	9.2 (4.4)	9.1 (3.7)	9.3 (4.0)
BSA affected, %, mean (SD)	7.8 (4.6)	8.2 (5.1)	7.8 (4.4)	7.3 (4.1)

ITT population. BMI, body mass index; BSA, body surface area; ITT, intent-to-treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment, QD, once daily; SD, standard deviation.

Primary Endpoint: PGA Response

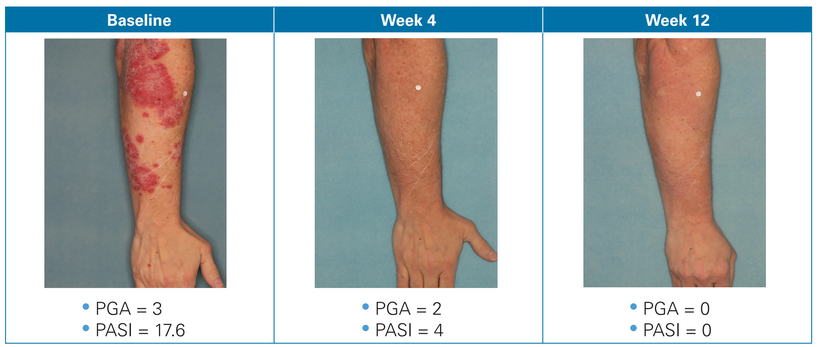
- The primary endpoint (PGA of 0 or 1 and ≥2-grade improvement at Week 12) was met; PGA response rates were highly statistically significant in the tapinarof cream 1% QD group versus the vehicle group in both PSOARING 1 and 2: 35.4% vs 6.0% (*P*<0.0001) and 40.2% vs 6.3% (*P*<0.0001), respectively (**Figure 2**)
- **Figure 3** displays photographs of the clinical response of a patient treated with tapinarof 1% QD who achieved the primary and secondary efficacy endpoints at Week 12

Figure 2. PGA Response at Week 12



ITT population. *P* value based upon Cochran-Mantel-Haenszel analysis stratified by baseline PGA score. ITT, intent-to-treat; PGA, Physician Global Assessment; QD, once daily; SEM, standard error of mean.

Figure 3. Clinical Response of Patient with Plaque Psoriasis Treated with Tapinarof 1% QD

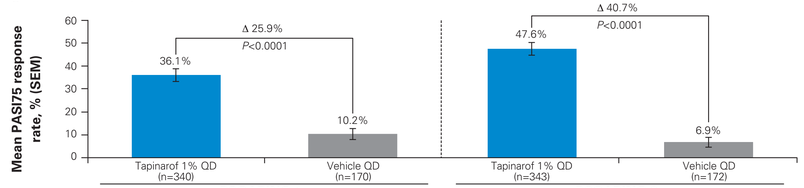


PGA and PASI are global efficacy assessments. Example of one representative target lesion of one tapinarof 1% QD treated patient; individual results may vary. Photographs demonstrate improvement in PGA and PASI at Week 4 and 12. PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QD, once daily.

Secondary Endpoint: PASI75

- PASI75 response rates at Week 12 were highly statistically significant in the tapinarof cream 1% QD group versus the vehicle group in both PSOARING 1 and 2: 36.1% vs 10.2% (*P*<0.0001) and 47.6% vs 6.9% (*P*<0.0001), respectively (**Figure 4**)

Figure 4. PASI75 Response at Week 12



ITT population. *P* value based upon Cochran-Mantel-Haenszel analysis stratified by baseline PGA score. ITT, intent-to-treat; PASI75, ≥75% improvement in Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QD, once daily; SEM, standard error of mean

Safety

- Overall, treatment-emergent AEs (TEAEs) in PSOARING 1 and 2 were comparable, in which the majority were mild or moderate in severity and most did not lead to study discontinuation (**Table 2**)
- The most common (≥1% in any group) treatment-related TEAEs were folliculitis, contact dermatitis, headache, pruritus, and dermatitis
  - Folliculitis was mostly mild or moderate in severity in both studies, and study discontinuation due to folliculitis was low in PSOARING 1 and 2: 1.8% (6/340) vs 0.0% (0/170) and 0.9% (3/343) vs 0.0% (0/172), respectively

Table 2. Safety Overview

	PSOARING 1		PSOARING 2	
Patients, n (%)	Tapinarof 1% QD (n=340)	Vehicle QD (n=170)	Tapinarof 1% QD (n=343)	Vehicle QD (n=172)
TEAE	171 (50.3)	38 (22.4)	187 (54.5)	45 (26.2)
Mild	76 (22.4)	16 (9.4)	80 (23.3)	17 (9.9)
Moderate	82 (24.1)	22 (12.9)	98 (28.6)	28 (16.3)
Severe	11 (3.2)	0 (0.0)	8 (2.3)	0 (0.0)
Serious TEAE	9 (2.6)	0 (0.0)	7 (2.0)	0 (0.0)
Study discontinuation due to AEs	19 (5.6)	0 (0.0)	20 (5.8)	1 (0.6)
Most common treatment-related TEAEs (≥1% in any group)				
Folliculitis	70 (20.6)	2 (1.2)	54 (15.7)	1 (0.6)
Contact dermatitis	13 (3.8)	1 (0.6)	16 (4.7)	0 (0.0)
Headache	5 (1.5)	1 (0.6)	1 (0.3)	0 (0.0)
Pruritus	4 (1.2)	0 (0.0)	2 (0.6)	0 (0.0)
Dermatitis	1 (0.3)	0 (0.0)	4 (1.2)	0 (0.0)
Study discontinuation due to AESI				
Folliculitis	6 (1.8)	0 (0.0)	3 (0.9)	0 (0.0)
Contact dermatitis	5 (1.5)	0 (0.0)	7 (2.0)	0 (0.0)
Headache	1 (0.3)	0 (0.0)	2 (0.6)	0 (0.0)
Severity of folliculitis, **n (%) among subset of patients with AESI of folliculitis**				
Mild	51 (63.8)	1 (50.0)	44 (72.1)	0 (0.0)
Moderate	28 (35.0)	1 (50.0)	17 (27.9)	1 (100.0)
Severe	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)

A patient is counted once only for each MedDRA preferred term.
Safety population. TEAE defined as an AE that starts on or after the date of first dose of study drug. AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Both the primary and secondary endpoints were met, demonstrating highly statistically significant and clinically meaningful efficacy with tapinarof cream 1% QD compared with vehicle
- Tapinarof cream 1% QD was well tolerated, consistent with previous studies[2,3]
- Tapinarof cream 1% QD has the potential to provide physicians and patients with a novel non-steroidal topical treatment option that is highly effective and well-tolerated

REFERENCES

1. Menter A, et al. *J Am Acad Dermatol.* 2008;58:826–850; 2. Robbins K, et al. *J Am Acad Dermatol.* 2019;80:714–721;
3. Stein Gold L, et al. *J Am Acad Dermatol.* 2020; doi: 10.1016/j.jaad.2020.04.181.

ACKNOWLEDGMENTS

This study was funded by Dermavant Sciences, Inc. The authors thank the participating investigators, patients and their families, and colleagues involved in the conduct of the study. Editorial and medical writing support under the guidance of the authors was provided by Apothecom, UK, and was funded by Dermavant Sciences, Inc. in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med.* 2015;163:461–464). Contact Dr Mark Lebwohl at lebwohl@aol.com with questions or comments.