Tapinarof Cream 1% Once Daily for Plaque Psoriasis: Secondary Efficacy Outcomes from Two Pivotal Phase 3 Trials

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SYNOPSIS

- Psoriasis is a chronic, immune-mediated disease characterized by scaly, erythematous, and pruritic plaques that can be painful, disfiguring, and severely impact quality of life[1]
- There is a need for efficacious and well-tolerated topical therapies for plaque psoriasis without restrictions on duration, site, and extent of use, or concerns due to long-term adverse effects or local intolerance. However, no topicals with novel mechanisms have been US Food and Drug Administration (FDA)-approved in over 20 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 trials designed to assess the efficacy and safety of tapinarof cream 1% once daily (QD) in patients with mild-to-severe plaque psoriasis
- Primary efficacy endpoints and safety results from the two pivotal trials have been previously reported, demonstrating highly statistically significant efficacy and good tolerability of tapinarof cream 1% QD versus vehicle QD at 12 weeks[2]

OBJECTIVE

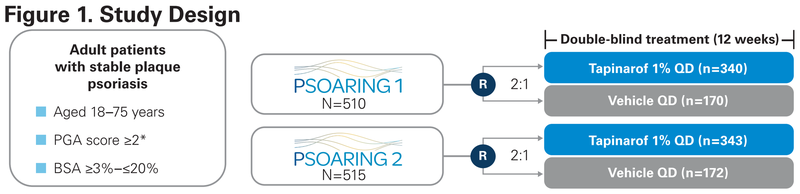
- To present the secondary efficacy endpoints in two pivotal phase 3 trials of tapinarof cream 1% QD for the treatment of plaque psoriasis

METHODS

Study Design

- In two identically designed, phase 3, multicenter (US and Canada), double-blind, vehicle-controlled randomized trials, patients with mild-to-severe plaque psoriasis were randomized 2:1 to tapinarof cream 1% QD or vehicle QD for 12 weeks (**Figure 1**)
- Following the double-blind period, patients could enroll in an open-label, long-term extension trial 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 efficacy endpoint was Physician Global Assessment (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[2]
- Secondary and exploratory endpoints included the following:
  - Proportion of patients with ≥75% improvement in Psoriasis Area and Severity Index (PASI75) score from baseline at Week 12
  - Proportion of patients with a PGA score of clear (0) or almost clear (1) at Week 12
  - Mean change in percentage body surface area (%BSA) affected from baseline to Week 12
  - Proportion of patients with ≥90% improvement in Psoriasis Area and Severity Index (PASI90) score from baseline at Week 12
  - Proportion of patients with a PASI75, PGA score of clear (0) or almost clear (1), or PASI90; and the mean change in %BSA affected from baseline at each visit
- 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 intention-to-treat (ITT) population using multiple imputation analysis for missing data
- For categorical endpoints, *P* values for differences between tapinarof cream and vehicle in both trials were calculated using Cochran-Mantel-Haenszel analysis and stratified by baseline PGA score. *P* values for continuous variables were analyzed using analysis of covariance, with randomized treatment as a factor, baseline PGA score as a covariate, and baseline value as a continuous covariate; treatment effect is presented as least squares mean

RESULTS

Patient Disposition and Baseline Characteristics

- In PSOARING 1 and 2, a total of 510 and 515 patients were randomized (ITT population), respectively, across 97 sites in the US and Canada
- Mean demographic and baseline characteristics were comparable across treatment groups and trials (**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) %BSA affected was 7.9 (4.8) and 7.6 (4.3) in PSOARING 1 and 2, respectively

Table 1. Baseline Patient Demographics and Disease 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/m², 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, intention-to-treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QD, once daily; SD, standard deviation.

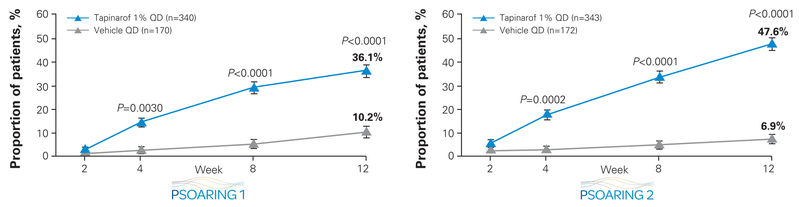
Primary Endpoint: PGA Response[2]

- As previously reported, 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% and 40.2% vs 6.3% (both *P*<0.0001), respectively

PASI75 Response Rate from Baseline to Weeks 2, 4, 8, and 12

- Significance in PASI75 response was demonstrated as early as Week 4 in both PSOARING 1 (*P*=0.0030) and 2 (*P*=0.0002), with a significantly higher mean proportion of patients in the tapinarof group than the vehicle group achieving PASI75 response at Week 12: 36.1% vs 10.2% and 47.6% vs 6.9% (both *P*<0.0001), respectively (**Figure 2**)

Figure 2. PASI75 Response Rates from Baseline to Weeks 2, 4, 8, and 12

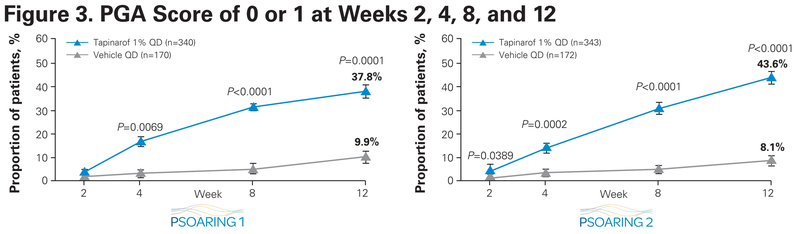


ITT, MI. Mean proportion (SE). ITT, intention-to-treat; MI, multiple imputation; PASI75, ≥75% improvement in Psoriasis Area and Severity Index; QD, once daily; SE, standard error.

PGA Score of Clear (0) or Almost Clear (1) at Weeks 2, 4, 8, and 12

- Significance in achievement of PGA score of 0 (clear) or 1 (almost clear) was demonstrated as early as Week 4 in PSOARING 1 (*P*=0.0069) and Week 2 in PSOARING 2 (*P*=0.0389), with a significantly higher mean proportion of patients in the tapinarof group than the vehicle group achieving a PGA score of 0 or 1 at Week 12: 37.8% vs 9.9% (*P*=0.0001) and 43.6% vs 8.1% (*P*<0.0001), respectively (**Figure 3**)

Figure 3. PGA Score of 0 or 1 at Weeks 2, 4, 8, and 12

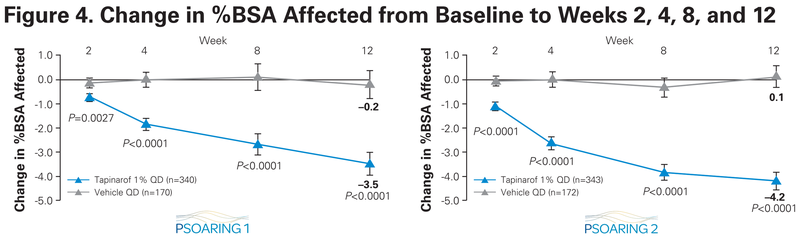


ITT, MI. Mean proportion (SE). ITT, intention-to-treat; MI, multiple imputation; PGA, Physician Global Assessment; QD, once daily; SE, standard error.

Mean Change in %BSA Affected from Baseline to Weeks 2, 4, 8, and 12

- Mean %BSA affected was rapidly reduced with tapinarof versus vehicle, with significant improvements from Week 2 (*P*≤0.0027) reaching –3.5 vs –0.2 and –4.2 vs 0.1 at Week 12 in PSOARING 1 and 2, respectively (*P*<0.0001 in both trials) (**Figure 4**)

Figure 4. Change in %BSA Affected from Baseline to Weeks 2, 4, 8, and 12

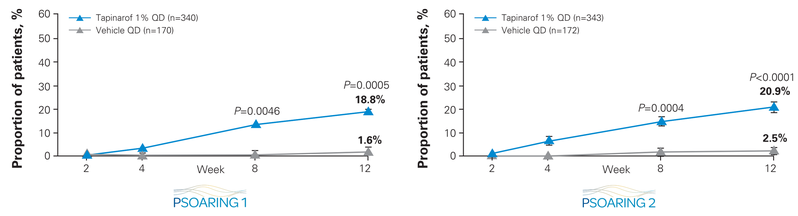


ITT, MI. Least squares mean (SE). %BSA, percentage body surface area; ITT, intention-to-treat; MI, multiple imputation; QD, once daily; SE, standard error.

PASI90 Response Rate from Baseline to Weeks 2, 4, 8, and 12

- Significance in PASI90 response was demonstrated as early as Week 8 in both PSOARING 1 (*P*=0.0046) and 2 (*P*=0.0004), with a significantly higher mean proportion of patients in the tapinarof group than the vehicle group achieving PASI90 response at Week 12: 18.8% vs 1.6% (*P*=0.0005) and 20.9% vs 2.5% (*P*<0.0001), respectively (**Figure 5**)

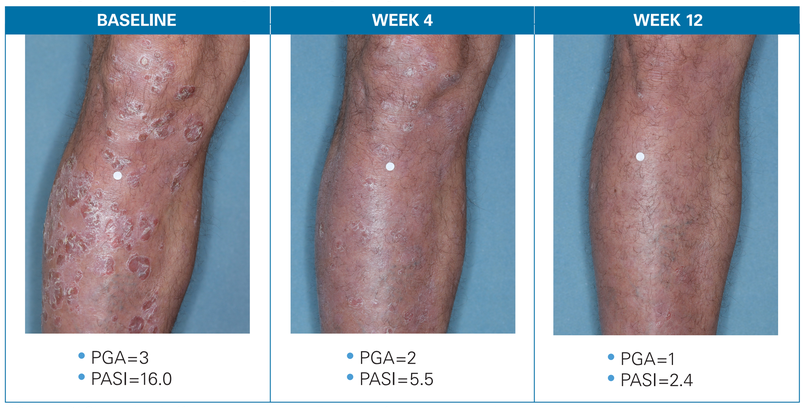
Figure 5. PASI90 Response Rate from Baseline to Weeks 2, 4, 8, and 12



ITT, MI. Mean proportion (SE). ITT, intention-to-treat; MI, multiple imputation; PASI90, ≥90% improvement in Psoriasis Area and Severity Index; QD, once daily; SE, standard error.

- **Figure 6** displays photographs of the clinical response of a patient treated with tapinarof cream who achieved the primary and secondary efficacy endpoints

Figure 6. Clinical Response of a Patient with Plaque Psoriasis who Achieved Primary and Secondary Efficacy Endpoints



PGA and PASI are global efficacy assessments. Example of one representative target lesion of one tapinarof-treated patient from PSOARING 1 clinical trial. Individual results may vary.

PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

Safety

- As previously reported,[2] most treatment-emergent AEs (TEAEs) in PSOARING 1 and 2 were mild or moderate in severity, consistent with previous studies,[3,4] and most did not lead to study discontinuation
- 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

CONCLUSIONS

- Tapinarof cream 1% QD significantly improved all measures of disease activity and showed rapid, clear, and consistent separation versus vehicle as early as the first clinical assessment at Week 2
- These findings are consistent with the superior clinical efficacy and good tolerability profile of tapinarof cream reported previously[2–4]
- Early improvements continued throughout the trials and did not reach maximal effect by Week 12, as confirmed by results from a long-term extension trial[5]
- Tapinarof cream 1% QD has the potential to be the first topical, non-steroidal psoriasis treatment with a novel mechanism of action in over 20 years

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