Secondary Efficacy Outcomes from a Phase 2b, Randomized Dose-Finding Study of Tapinarof Cream for the Treatment of Plaque Psoriasis

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INTRODUCTION

- Psoriasis is a chronic, immune-mediated disease characterized by scaly, erythematous, and pruritic plaques that can be painful and disfiguring[1]
- The burden of psoriasis is comparable to other long-term conditions, such as congestive heart failure and chronic lung disease, and has a profound impact on the mental health and wellbeing of those affected[2]
- Although multiple options are available for the treatment of plaque psoriasis, there is a need for effective topical therapies that can be used without body surface area (BSA) restrictions or concerns for the duration of treatment
- Tapinarof cream is a novel therapeutic aryl hydrocarbon (AhR) receptor modulating agent (TAMA) under investigation for the treatment of psoriasis (ClinicalTrials.gov ID: NCT03956355) and atopic dermatitis
- This previously conducted Phase 2b, double-blind, six-arm, dose-finding, vehicle-controlled randomized study (ClinicalTrials.gov ID: NCT02564042) assessed the efficacy and safety of tapinarof cream in subjects with plaque psoriasis[3]
- Secondary efficacy outcomes support the primary endpoint analysis, which demonstrated that tapinarof cream was efficacious and well tolerated in adults with psoriasis and may represent an effective option in the topical treatment of the disease[3]

OBJECTIVES

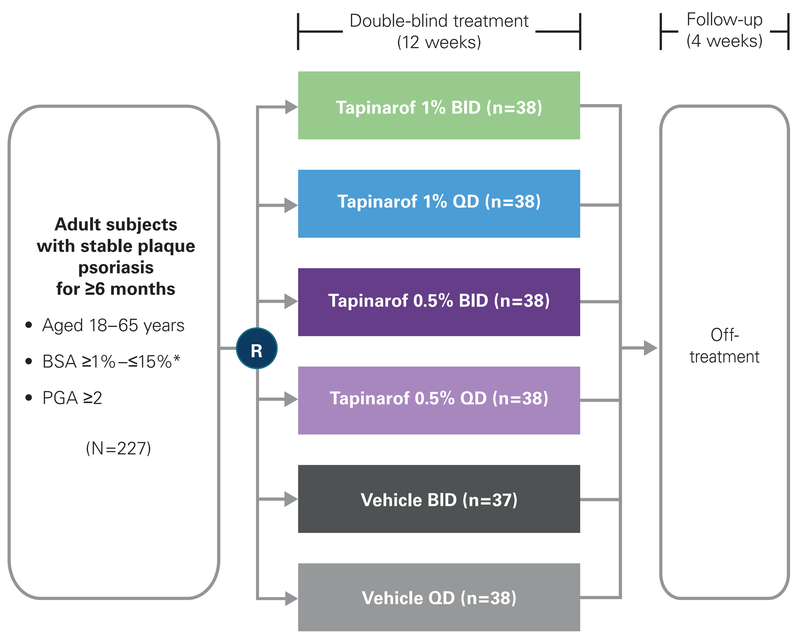
- To report the additional efficacy outcomes of mean Physician Global Assessment (PGA) scores and mean change from baseline in PGA, ≥50%, ≥75%, and ≥90% reduction in Psoriasis Area and Severity Index (PASI) from baseline (PASI50, PASI75, and PASI90), target lesion grading scores, and pruritus numeric rating scale (NRS) score

METHODS

Study Design

- In this multicenter (United States, Canada, and Japan), Phase 2b, double-blind, vehicle-controlled randomized study, adult subjects with psoriasis were randomized 1:1:1:1:1:1 to receive tapinarof cream 0.5% or 1% once (QD) or twice daily (BID) or vehicle QD or BID for 12 weeks and followed up for 4 more weeks (**Figure 1**)

Figure 1. Study Design



*Excluding scalp. BID, twice daily; BSA, body surface area; PGA, Physician Global Assessment; QD, once daily.

Study Outcomes and Statistical Analysis

- The primary endpoint was PGA response rates at Week 12, defined as the proportion of subjects with a PGA score of clear or almost clear (0 or 1) and ≥2-grade improvement in PGA score from baseline to Week 12[3]
- Additional efficacy outcomes reported here include mean PGA scores, mean change in PGA from baseline to Week 12, PASI50, PASI75 and PASI90 response rates at Week 12, total and mean target lesion grading scores change from baseline to Week 12, and ≥4 improvement in pruritus NRS score from baseline to Week 12 where baseline NRS score ≥4
- Incidence, frequency, and nature of adverse events (AEs) and serious AEs were collected from the start of study treatment until the end of study visit at Week 16
  - Investigators assessed the overall degree of application-site irritation using a scale from 0=no irritation to 4=very severe at each study visit
  - Subject-reported tolerability on a 5-point scale from 0=none to 4=strong/severe was used to assess the presence and degree of application-site burning/stinging and itching within 2 hours following application of tapinarof or vehicle
- *P* values for differences between tapinarof cream groups and the corresponding vehicle group for PASI response rates were calculated *post hoc* using Barnard's and Fisher's exact tests. *P* values for PGA scores and total target lesion grading scores were based on a *post-hoc* analysis of covariance with main effect of treatment and covariates of average baseline selected score and pooled country. Where *P* values were not available, differences between arms were considered statistically significant if 95% confidence intervals excluded 0

RESULTS

Subject Characteristics

- A total of 227 subjects (of 290 screened) were randomized (intent-to-treat population); of those randomized, 175 subjects (77%) completed the study, including the Week 16 follow-up visit
- Mean demographic and baseline characteristics were comparable across treatment groups (**Table 1**)
- Overall, 15% of subjects had a baseline PGA category of 2 (mild), 80% had a PGA category of 3 (moderate), and 5% had a PGA category of 4 (severe)
- Baseline mean PASI score was 8.8 (standard deviation [SD] 4.5)

Table 1. Baseline Subject Demographics and Characteristics

	Tapinarof 1% cream		Tapinarof 0.5% cream		Vehicle	
	BID (n=38)	QD (n=38)	BID (n=38)	QD (n=38)	BID (n=37)	QD (n=38)
Mean age, years (SD)	45.9 (11.9)	48.5 (10.6)	49.6 (10.9)	48.7 (9.7)	46.7 (12.6)	46.4 (10.2)
Male sex, n (%)	26 (68)	26 (68)	24 (63)	25 (66)	23 (62)	29 (76)
Mean weight, kg (SD)	85.6 (22.5)	86.7 (22.6)	88.6 (27.4)	89.3 (23.1)	87.8 (28.3)	91.6 (21.6)
PGA, mean (SD)	2.9 (0.4)	2.7 (0.5)	3.0 (0.5)	2.9 (0.4)	3.0 (0.3)	2.8 (0.4)
PASI, mean (SD)	10.6 (5.0)	8.5 (3.6)	8.2 (4.5)	7.9 (4.8)	9.0 (4.3)	8.7 (4.4)
% BSA affected, mean (SD)	8.2 (4.5)	6.5 (3.3)	7.2 (4.5)	6.1 (4.3)	6.6 (3.6)	7.0 (4.6)
Pruritus score, mean (SD)*	5.6 (2.6)	4.4 (2.9)	6.2 (2.2)	4.5 (2.6)	5.5 (2.8)	4.9 (2.4)
Total target lesion grading score, mean (SD)†	8.6 (1.3)	8.3 (1.5)	8.7 (1.9)	8.6 (1.2)	8.8 (1.1)	8.5 (1.4)

Baseline disease characteristics provided for the mITT population (n=196), which included subjects in the ITT population minus the subjects from one site due to protocol violation. Demographics (age, sex, and weight) provided for the safety population (n=227). *Mean scores based on an NRS of 0 'absent' to 10 'worst imaginable'; data provided for subjects with available results (n=32, 35, 30, 32, 29, and 32, respectively). †Erythema, scaling, and induration plaque thickness; maximum score of 12 with higher score indicating increased severity. BID, twice daily; BSA, body surface area; ITT, intent-to-treat; mITT, modified intent-to-treat; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QD, once daily; SD, standard deviation.

PGA Response Rates

- Primary endpoint: PGA response rates (defined as PGA score 0 or 1 and ≥2-grade improvement) at Week 12 were significantly higher (at 0.05 significance level) in the tapinarof cream groups than the vehicle groups (65% [1% BID], 56% [1% QD], 46% [0.5% BID], 36% [0.5% QD] vs 11% [vehicle BID] and 5% [vehicle QD]) and were maintained for 4 weeks after the end of study treatment in all active treatment groups except for the 0.5% BID group[3]

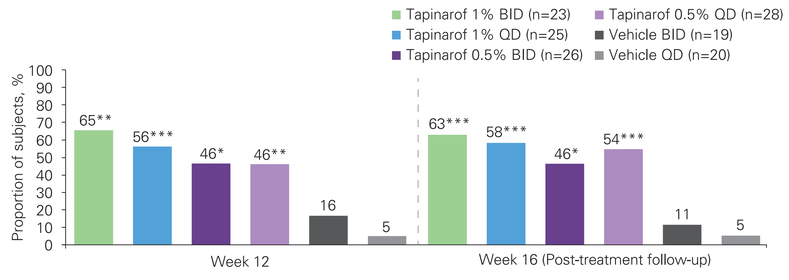
PGA Scores

- Mean improvements in PGA scores (SD) from baseline at Week 12 were significantly higher in all tapinarof cream treatment groups compared with the vehicle groups: –1.8 (0.9) [1% BID], –1.7 (1.0) [1% QD], –1.7 (1.1) [0.5% BID], –1.3 (0.8) [0.5% QD] vs –0.5 (0.8) [vehicle BID] and –0.4 (0.7) [vehicle QD]; all comparisons *P*<0.001

PASI50 Response Rates

- PASI50 response rates at Week 12 were significantly higher in all tapinarof cream treatment groups compared with the vehicle groups (83% [1% BID], 92% [1% QD], 85% [0.5% BID], 71% [0.5% QD] vs 32% [vehicle BID] and 10% [vehicle QD]; all comparisons *P*<0.001), and were maintained up to the Week 16 post-treatment follow-up

Figure 2. PASI75 Response Rates at Week 12 and Week 16 (Follow-up)



Difference vs vehicle is statistically significant at *P<0.05, **P<0.01, ***P<0.001. n is number of subjects with available results at Week 12. BID, twice daily; PASI75, ≥75% improvement in Psoriasis Area and Severity Index from baseline; QD, once daily.

PASI75 Response Rates

- PASI75 response rates at Week 12 (**Figure 2**) were significantly higher in all tapinarof cream treatment groups compared with the vehicle groups (65% [1% BID; *P*=0.001], 56% [1% QD; *P*<0.001], 46% [0.5% BID; *P*=0.035], 46% [0.5% QD; *P*=0.002] vs 16% [vehicle BID] and 5% [vehicle QD])
- Significant PASI75 response rates were maintained up to the Week 16 post-treatment follow-up (63% [1% BID; *P*<0.001], 58% [1% QD; *P*<0.001], 46% [0.5% BID; *P*=0.012], 54% [0.5% QD; *P*<0.001] vs 11% [vehicle BID] and 5% [vehicle QD])

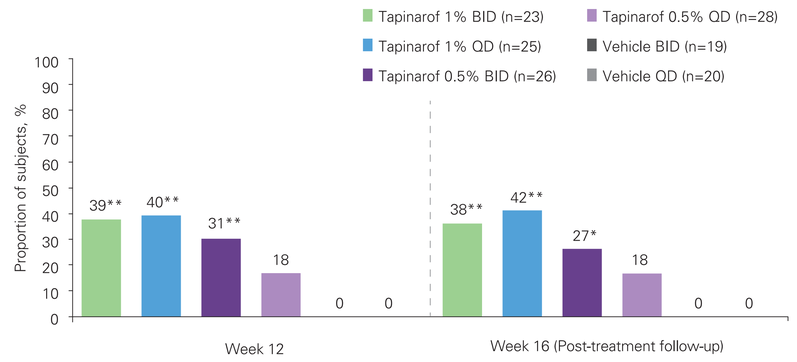
PASI90 Response Rates

- PASI90 response rates at Week 12 were significantly higher in all tapinarof cream treatment groups compared with the vehicle groups, except the 0.5% QD group (39% [1% BID; *P*=0.002], 40% [1% QD; *P*=0.001], 31% [0.5% BID; *P*=0.008], 18% [0.5% QD; *P*=0.057 vs 0% [vehicle BID] and 0% [vehicle QD]), and were maintained up to the Week 16 post-treatment follow-up (**Figure 3**)
- The time course of PASI50/75/90 responses with tapinarof generally showed a separation vs vehicle starting around Week 2 with significantly superior efficacy maintained from Week 12 through Week 16 post-treatment follow-up

Pruritis NRS

- In patients with a baseline pruritus NRS item score of ≥4, pruritus NRS response rates (defined as ≥4 improvement in pruritus NRS score from baseline) at Week 12 were 55–73% in the tapinarof 1% treatment groups and 56–57% in the tapinarof 0.5% treatment groups compared with 33–60% in the vehicle treatment groups

Figure 3. PASI90 Response Rates at Week 12 and Week 16 (Follow-up)

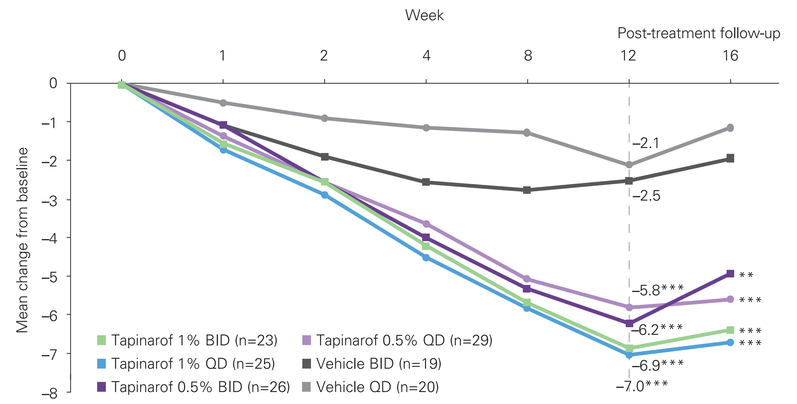


Difference vs vehicle is statistically significant at *P<0.05, **P<0.01. n is number of subjects with available results at Week 12. BID, twice daily; PASI90, ≥90% improvement in Psoriasis Area and Severity Index from baseline; QD, once daily.

Total Target Lesion Grading Scores

- Greater reductions in total target lesion grading scores from baseline were observed in all tapinarof cream treatment groups vs the vehicle groups from Week 2 onwards, with significantly greater reductions observed at Week 12 (all comparisons *P*<0.001); significant differences were maintained up to the Week 16 post-treatment follow-up (**Figure 4**)

Figure 4. Mean Change in Total Target Lesion Grading Scores† from Baseline to Week 12 and Week 16 (Follow-up)



Difference vs vehicle is statistically significant at **P<0.01, ***P<0.001. n is number of subjects with available results at Week 12. †Erythema, scaling, and induration of plaque thickness. BID, twice daily; QD, once daily.

Safety

- Overall, 46% (104/227) of subjects had treatment-emergent AEs (TEAEs): 56% in the tapinarof cream groups and 25% in the vehicle groups, and were mostly mild to moderate in severity
- The most common treatment-related TEAEs were folliculitis (10% tapinarof vs 1% vehicle), contact dermatitis (3%; all tapinarof), and headache (1%; all tapinarof)
- The majority of subjects had little to no investigator-assessed treatment-site irritation or self-reported application-site burning/stinging and itching throughout the study period with no apparent differences between tapinarof and vehicle groups

CONCLUSIONS

- These results support the previously reported primary outcomes that tapinarof cream is efficacious and well tolerated in adults with plaque psoriasis[3]
- Tapinarof cream resulted in clinically meaningful improvements in PASI50 and PASI75 from Week 2, which were statistically significant in all tapinarof groups at Week 12 through to Week 16 post-treatment follow-up
- *Post-hoc* PASI90 response assessments followed a similar trend, showing early, durable and statistically significant response with tapinarof cream compared with vehicle
- Total target lesion grading scores improved from Week 2 onwards with tapinarof cream compared with vehicle, and the difference was maintained up to Week 16
- Tapinarof cream was generally well tolerated with the majority of subjects having little to no irritation or burning/stinging and itching
- These results suggest that tapinarof cream may provide an important potential advance in topical treatment for plaque psoriasis
- A phase 3 study of tapinarof cream 1% QD in psoriasis is ongoing

REFERENCES

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