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

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

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 (TAMRA) under investigation for the treatment of psoriasis (ClinicalTrials.gov ID: NCT03396365) and atopic dermatitis

This previously conducted Phase 2b, double-blind, six-arm, dose-finding, vehicle-controlled randomized study (ClinicalTrials.gov ID: NCT03656404) assessed the efficacy and safety of tapinarof cream in subjects with plaque psoriasis

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

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

- Double-blind treatment (12 weeks)
- Follow-up (4 weeks)
- Adult subjects with stable plaque psoriasis for 28 months
  - Age 18–65 years
  - BSA ≥1%–<51%
  - PGA ≤2
  - N=227
- Tapinarof 1% BID (n=38)
- Tapinarof 1% QD (n=38)
- Tapinarof 0.5% BID (n=38)
- Tapinarof 0.5% QD (n=38)
- Vehicle BID (n=37)
- Vehicle QD (n=38)

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

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, PASI50 and PASI75 target lesion grading scores from baseline to Week 12, and ≥4 improvement in pruritus NRS score from baseline to Week 12 where 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 18

– 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 PGA 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)

Table 1. Baseline Subject Demographics and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tapinarof 1% cream</th>
<th>Tapinarof 0.5% cream</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>45.9 (11.9)</td>
<td>48.5 (10.6)</td>
<td>46.7 (12.6)</td>
</tr>
<tr>
<td>Mean sex, % (M/F)</td>
<td>48 (62)</td>
<td>51 (49)</td>
<td>51 (49)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>85.6 (22.5)</td>
<td>86.7 (23.6)</td>
<td>87.8 (28.2)</td>
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<tr>
<td>PGA, mean (SD)</td>
<td>3.2 (1.4)</td>
<td>3.3 (1.0)</td>
<td>3.3 (1.2)</td>
</tr>
<tr>
<td>PASI50, mean (SD)</td>
<td>14.4 (5.8)</td>
<td>14.5 (5.8)</td>
<td>14.5 (5.8)</td>
</tr>
<tr>
<td>PASI75, mean (SD)</td>
<td>19.5 (6.9)</td>
<td>19.6 (6.9)</td>
<td>19.6 (6.9)</td>
</tr>
<tr>
<td>PASI90, mean (SD)</td>
<td>24.5 (7.8)</td>
<td>25.0 (7.8)</td>
<td>25.0 (7.8)</td>
</tr>
</tbody>
</table>

Table 1. Baseline Subject Demographics and Characteristics

Subjects had a BMI of 25.9 (5.5) for tapinarof 1% BID, 25.7 (5.6) for tapinarof 0.5% BID, 26.1 (5.7) for vehicle BID, 25.6 (5.7) for tapinarof 1% QD, 25.7 (5.6) for tapinarof 0.5% QD, and 26.0 (5.6) for vehicle QD

The majority of subjects had little to no investigator-assessed treatment-site irritation or pruritus

The most common treatment-related TEAEs were folliculitis (10% tapinarof vs 1% vehicle), pruritus (5% tapinarof vs 0% vehicle), and headache (4% tapinarof vs 0% vehicle)

Tapinarof cream resulted in clinically meaningful improvements in PASI50 and PASI75 responses over the 12-week treatment period and maintained for 4 weeks after the end of study treatment in all active treatment groups except for the 0.5% BID group

Mean PASI90 response rates were 38% (tapinarof 0.5% BID), 42% (tapinarof 1% BID), 16% (vehicle BID), and 18% (vehicle QD)

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

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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