Maximal Use Study of Tapinarof Cream 1% in Subjects with Extensive Plaque Psoriasis

John E Jett,[1] Michael McLaughlin,[1] Mark S Lee,[2] Lawrence Charles Parish,[3] Glenn Tabolt,[1] Timothy Wilson,[1] Matthew C Somerville,[1] Wayne DellaMaestra,[1] Stephen C Piscitelli[1]

[1]Dermavant Sciences, Inc., Durham, NC, USA; [2]Progressive Clinical Research, San Antonio, TX, USA; [3]Paddington Testing Company, Inc., Philadelphia, PA, USA

SYNOPSIS

- 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 introduced in recent years
- Tapinarof is a novel, first-in-class, non-steroidal, topical therapeutic aryl hydrocarbon receptor modulating agent (TAMA) in clinical development for the treatment of psoriasis and atopic dermatitis
- This Phase 2a, multicenter, open-label study was designed to assess the safety and tolerability, pharmacokinetics (PK), and efficacy of tapinarof cream 1% once daily (QD) under maximal use conditions for 29 days in adults with plaque psoriasis and a body surface area (BSA) involvement of ≥20%

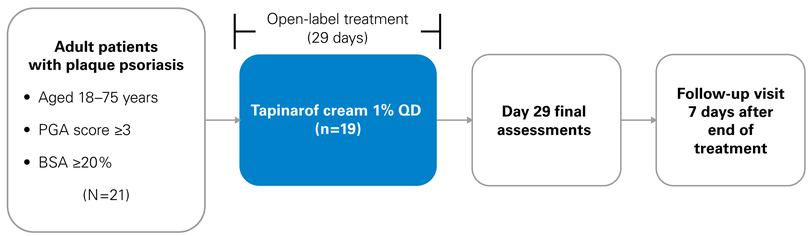
OBJECTIVES

- The primary objectives were to evaluate the safety and tolerability, and PK of topical tapinarof cream 1% in adult patients with extensive plaque psoriasis
- The secondary objectives were to exclude clinically relevant effects on QT interval corrected for heart rate using Fridericia's formula (QTcF) and evaluate the efficacy of tapinarof cream 1% in adult patients with extensive plaque psoriasis

METHODS

- In this Phase 2a, multicenter, open-label study, patients with extensive plaque psoriasis received tapinarof cream 1% QD for 29 days (**Figure 1**)
- Key inclusion and exclusion criteria are presented in **Table 1**

Figure 1. Study Design



BSA, body surface area; PGA, Physician Global Assessment; QD, once daily.

Endpoints and Statistical Analysis

- Safety and tolerability were evaluated by assessment of clinical laboratory tests, physical examinations, vital signs, electrocardiogram (ECG), and local tolerability scales
- Plasma PK parameter estimates for tapinarof and its metabolite, tapinarof sulfate, on Days 1 and 29 were calculated using non-compartmental analysis of the plasma concentration versus time data, as data permitted. Assay lower limits of quantitation were 50 pg/mL for tapinarof and 10 pg/mL for tapinarof sulfate
- To exclude effects of tapinarof cream 1% on QTcF, change in QTcF at each time point after application and by tapinarof plasma concentration were analyzed based on linear mixed-effects models as previously described.[2] QT prolongation was assessed per the Food and Drug Administration (FDA) requirements for all investigational drugs
- Mean and percent change in Physician Global Assessment (PGA), Psoriasis Area and Severity Index (PASI), and BSA from baseline to Day 29 were summarized descriptively and analyzed with a one-sample t-test. Treatment success, 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, was assessed

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria
Males and females aged 18–75 years
Confirmed chronic psoriasis and stable disease for ≥6 months
BSA involvement ≥20%
PGA score ≥3 at screening
Key Exclusion Criteria
Psoriasis other than plaque variant
Infection of any of the psoriatic plaques
Evidence of significant concurrent diseases that would affect participation or interpretation of results
Laboratory values significantly outside normal ranges or QTcF interval >470 milliseconds
Concomitant use of medications or ultraviolet light therapy that could affect efficacy assessments

BSA, body surface area; PGA, Physician Global Assessment; QTcF, QT interval corrected for heart rate using Fridericia's formula.

RESULTS

Study Population

- In total, 21 patients (of 36 screened) were enrolled into the study and received tapinarof cream 1% QD; 19 patients (90.5%) completed the study, one patient (4.8%) withdrew consent, and one patient (4.8%) was lost to follow-up
- Patient demographics and baseline disease characteristics are presented in **Table 2**

Table 2. Baseline Patient Demographics and Characteristics

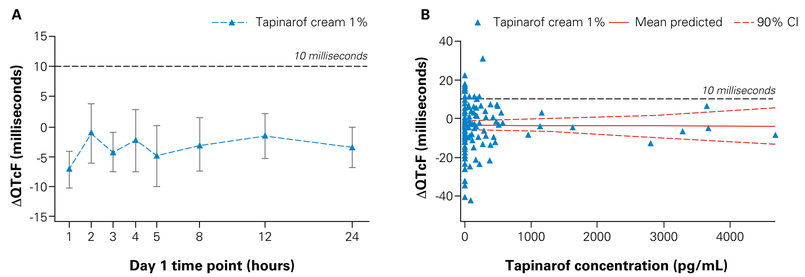
Baseline Demographics and Characteristics	Tapinarof 1% QD (N=21)
Age, years, mean (SD)	51.8 (13.9)
Male, n (%)	13 (61.9)
Female, n (%)	8 (38.1)
Childbearing potential = yes	2 (25.0)
Ethnicity, n (%)	
Hispanic or Latino	9 (42.9)
Not Hispanic or Latino	12 (57.1)
Race, n (%)	
American Indian or Alaska Native	1 (4.8)
Black or African American	3 (14.3)
White	16 (76.2)
Not reported	1 (4.8)
PGA of 3 – moderate, n (%)	13 (61.9)
PGA of 4 – severe, n (%)	8 (38.1)
%BSA affected, mean (SD)	27.2 (7.5)
%BSA affected, median (min, max)	25.5 (20.5, 46.0)
PASI, mean (SD)	24.7 (7.1)
PASI, median (min, max)	22.2 (14.4, 36.9)

BSA, body surface area; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; SD, standard deviation.

Safety and Cardiodynamic Results

- Tapinarof was well tolerated at application sites, including in seven patients (33.3%) who applied tapinarof to sensitive areas, such as genitals, face, neck, and skin folds
- There were no treatment interruptions and no patient discontinued study drug due to treatment-emergent adverse events (TEAEs)
- Twelve patients (57.1%) reported TEAEs; the most frequently reported TEAEs related to the study drug were folliculitis (n=4) and headache (n=2)
- There were no clinically meaningful changes in clinical laboratory values, vital signs, QTc interval, or other ECG parameter values
- Cardiodynamic analysis by time point (**Figure 2A**) and by concentration–QT modeling (**Figure 2B**) demonstrated tapinarof had no clinically relevant effects on QTcF following application and at plasma concentrations up to ~4600 pg/mL. A QTcF effect exceeding 10 milliseconds can be excluded within the range of tapinarof plasma concentrations up to ~4600 pg/mL

Figure 2. Change from Baseline QTcF by Time Point (A) and QTcF by Concentration–QT Modeling (B)

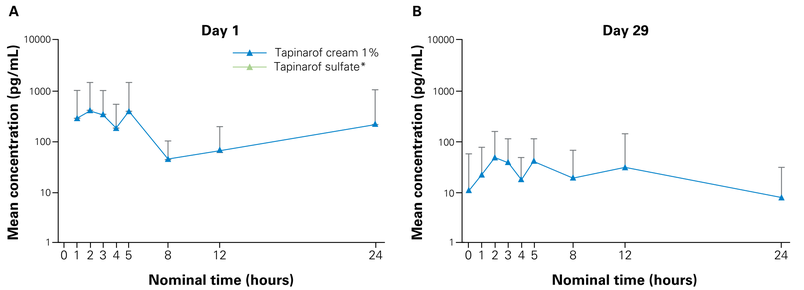


Error bars represent 90% CI. Dotted horizontal line represents QTcF effect exceeding 10 milliseconds. CI, confidence interval; QTcF, QT interval corrected for heart rate using Fridericia's formula.

PK Results

- Tapinarof plasma exposure was low, with 68% of samples below the lower limit of quantitation (50 pg/mL)
- The highest tapinarof plasma concentrations were observed on Day 1 (Figure 3A), which were approximately 10-fold lower by Day 29 (**Figure 3B**)
- No patient had measurable concentrations of tapinarof sulfate at any time point

Figure 3. Mean (SD) Tapinarof Plasma Concentration Versus Time Curves on Days 1 (A) and 29 (B)



*All tapinarof sulfate concentrations were below the LLOQ of 10 pg/mL. Tapinarof LLOQ was 50 pg/mL. LLOQ, lower limit of quantitation. SD, standard deviation.

Efficacy Results

- Nineteen patients who completed the study were included in the efficacy analysis (**Table 3**)
- Mean (standard deviation) change in PGA score from baseline at Day 29 was –1.2 (1.03) (P<0.0001)
- At Day 29, 14 patients (73.7%) had ≥1-grade improvement in PGA score, six patients (31.6%) had ≥2-grade improvement, and four patients (21.1%) achieved PGA score of 0 or 1 and ≥2-point improvement in PGA score
- At Day 29, 18 patients (95%) demonstrated improvement in PASI and 17 patients (89%) demonstrated improvement in BSA during the study
- Mean percent change in PASI score from baseline at Day 29 was –59.6% (P<0.0001)
- Mean percent change in BSA from baseline at Day 29 was –49.8% (P<0.0001)

Table 3. Efficacy Following 29 Days of Treatment

Efficacy parameter	Tapinarof 1% QD (N=19)
Patients with ≥1-point improvement in PGA score, n (%)	14 (73.7)
Patients with ≥2-point improvement in PGA score, n (%)	6 (31.6)
Patients with PGA score of 0 or 1 and ≥2-point improvement in PGA score, n (%)	4 (21.1)
Mean change in PGA from baseline to Day 29 (SD)	–1.2 (1.0)
Mean % change in PASI score from baseline to Day 29 (SD)	–59.6 (29.0)
Mean % change in BSA from baseline to Day 29 (SD)	–49.8 (32.5)
Patients who achieved PASI75, n (%)	7 (36.8)

BSA, body surface area; PASI, Psoriasis Area and Severity Index; PASI75, ≥75% improvement in PASI from baseline; PGA, Physician Global Assessment; QD, once daily; SD, standard deviation.

CONCLUSIONS

- Tapinarof cream 1% has a favorable safety profile and is well tolerated, including in sensitive areas, with no clinically meaningful effect on QTc interval or other ECG parameters per FDA requirements for all investigational drugs
- Application of tapinarof cream 1% QD resulted in limited systemic exposure, even in subjects with extensive plaque psoriasis up to 46% BSA
- Tapinarof cream 1% QD demonstrated significant efficacy after only 4 weeks of treatment in subjects with moderate to severe plaque psoriasis
- These findings support the safety and efficacy of tapinarof demonstrated in other clinical studies,[3,4] including the pivotal Phase 3 trials PSOARING 1 and PSOARING 2
- Tapinarof cream may address many of the limitations of each of the current therapeutic classes for psoriasis, with the potential to be used across the disease spectrum, providing physicians and patients with a highly effective treatment option

REFERENCES

1. Menter A, et al. *J Am Acad Dermatol.* 2008;58:826–850;
2. Garnett C, et al. *J Pharmacokinet Pharmacodyn.* 2018;45:383–397;
3. Robbins K, et al. *J Am Acad Dermatol.* 2019;80:714–721;
4. 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 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 Stephen C Piscitelli at Steve.Piscitelli@Dermavant.com with questions or comments.