Exposure–Response Analysis Demonstrates Tapinarof is Driven by Local Effects at Sites of Application

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INTRODUCTION

Tapinarof (VTAMA®; Dermavant Sciences, Inc.; USA) is a first-in-class, non-steroidal, topical, aryl hydrocarbon receptor agonist approved by the Food and Drug Administration for the treatment of plaque psoriasis in adults, and under investigation for the treatment of plaque psoriasis in children 2 years of age and older for atopic dermatitis (AD) in children down to 2 years of age.

Tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two identical, 12-week, phase 3 trials, PSORIANG 1 (NCT02593565) and PSORIANG 2 (NCT02593633).

In the long-term extension trial, PSORIANG 3 (NCT04558359), tapinarof was well tolerated and demonstrated a high rate of complete disease clearances—smooth and remote-free effect on therapy and on therapy up to 52 weeks.

Topical agents that are locally effective with minimal systemic exposure are desirable for dermatologic conditions.

There is a need for efficacious, non-steroidal topical therapies for patients with psoriasis, without restrictions relating to duration, extent of use, and application sites.

In a phase 2a, topical application of tapinarof cream 1% QD under maximal use conditions in patients with extensive disease (≥20% BSA involvement), tapinarof cream (0.5%, 1%), or frequency (QD, BID) of application was well tolerated and resulted in minimal systemic exposure.

OBJECTIVE

To evaluate the hypothesis that there is no relationship between topical plasma exposure and either safety or efficacy.

METHODS

Trial Design

Analyses included data from 4 clinical trials of tapinarof in patients with AD or plaque psoriasis across a range of doses, patient populations, and BSA involvement (Table 1).

Pharmacokinetic Sampling and Exposure Parameters

AD, atopic dermatitis; BID, twice daily; BSA, body surface area; IGA, Investigator Global Assessment; PGA, Physician Global Assessment; PK, pharmacokinetic; QD, once daily.

Endpoints and Statistical Analysis

To investigate any relationship between tapinarof exposure and safety endpoints, tapinarof exposure (Cmax and C0-24h) was categorized as follows:

- QD (patients randomized to vehicle)
- ≤≤BLQ (patients with undetectable tapinarof exposure)
- >BLQ and ≤2×BLQ (patients with measurable tapinarof concentrations)

The primary endpoint was then grouped into tertiles of exposure.

Safety assessments included adverse events of special interest (AESIs): folliculitis, contact dermatitis, and headache.

Efficacy assessments in patients with psoriasis included Physician Global Assessment (PGA) scores on Day 29 and change from baseline in Psoriasis Area and Severity Index (PASI) scores on Day 29.

Exposure–Response analyses were not measured in patients with AD.

Exposure–Response analyses were assessed in all patients who received ≥1 dose of trial drug and had ≥1 PK sample per patient population.

RESULTS

Patient Baseline Characteristics

The majority of patients (58.9% [340/587]) had plaque psoriasis; 53.8% overall were male, and the mean age was 41.8 years (Table 2).

Overall, 67.6% (398/591) of patients received tapinarof 3.2% and 32.2% (180/563) received vehicle.

Among patients in the tapinarof group, most (86.6% [61/71]) received tapinarof 1% QD; the remainder of the 0.5% QD (38.9%), 0.5% BID (10.3%), or 1% BID (10.1%) patients were excluded.

Patient Baseline Characteristics (PK Population)

Table 2. Baseline Patient Demographics (PK Population)

Table 3. Baseline Patient Demographics (PK Population)

Exposure–Response Analyses

Pharmacokinetics of Tapinarof

Tapinarof plasma exposure was low overall and below quantifiable limits in the majority (82.6% [343/416]) of samples using a highly sensitive assay.

Mean Cmax (±SD) and C0-24h (±SD) were 216 (123) pg/mL and 345 (167) pg/mL, respectively.

There were no trends observed between tapinarof plasma concentrations and disease (AD or psoriasis), or the concentration of tapinarof cream 0.5% or 1% (Figure 1). In a separate, post hoc analysis of the pharmacokinetic data, no correlation was observed between tapinarof plasma concentration and BSA in patients with psoriasis (ranging from 21%–46%) (Table 2).

To evaluate the hypothesis that there is no relationship between tapinarof exposure and either safety or efficacy, exposure–response analyses were performed in all patients who received ≥1 dose of trial drug (Table 3).

There was no correlation between tapinarof plasma exposure and AESIs of folliculitis, contact dermatitis, or headache in patients with AD or psoriasis.

There was no correlation between tapinarof plasma exposure and PASI response on Day 29 (Figure 2).

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REFERENCES


CONCLUSIONS

Tapinarof cream 1% QD is efficacious and well tolerated, including on intertriginous and sensitive skin areas, in patients with mild to severe plaque psoriasis.

Topical cream of tapinarof 3% QD in patients with psoriasis or AD resulted in minimal systemic exposure.

The maximal-use trial in psoriasis demonstrated that tapinarof plasma exposure declined over time.

Furthermore; tapinarof systemic exposure was also unrelated to %BSA affected for patients with psoriasis.

This exposure–response analysis demonstrates a lack of dependence on systemic activity for the therapeutic efficacy of tapinarof.

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