Exposure–Response Analysis Demonstrates Response to 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 down to 2 years of age and for atopic dermatitis (AD) in adults and children down to 2 years of age[1]
- 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, pivotal phase 3 trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980)[2]
- In the long-term extension trial, PSOARING 3 (NCT04053387), tapinarof was well tolerated and demonstrated a high rate of complete disease clearance, ~4-month remittive effect off therapy, and durability on therapy for up to 52 weeks[3]
- 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 trial, topical application of tapinarof cream 1% QD under maximal use conditions in patients with extensive psoriasis (up to 46% body surface area [BSA] involvement) resulted in minimal systemic exposure[4]

OBJECTIVE

- To evaluate the hypothesis that there is no relationship between tapinarof 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**)

Table 1. Clinical Trials Included in Tapinarof Exposure–Response Analyses

	Patients with AD	Patients with Plaque Psoriasis		
	Phase 2b Dose-finding Trial (N=247)[5]	Phase 2a Maximal-use Trial (N=21)[4]	Pivotal Phase 3 Trials[2]	
			PSOARING 1 (N=510)	PSOARING 2 (N=515)
Trial design	Randomized, double-blind, vehicle-controlled	Open-label	Randomized, double-blind, vehicle-controlled	
Eligibility criteria				
Patient population	AD with IGA score ≥3	Plaque psoriasis with PGA score ≥3	Plaque psoriasis with PGA score ≥2	
Age	12–65 years	18–75 years	18–75 years	
BSA involvement	5%–35%	≥20%	3%–20%	
Trial drug	**Tapinarof cream:** 0.5% QD, 0.5% BID, 1% QD, 1% BID **Vehicle cream:** QD or BID	**Tapinarof cream:** 1% QD	**Tapinarof cream:** 1% QD **Vehicle cream:** QD	
PK sampling	Weeks 1, 2, 4, 8, and 12	Days 1, 15, and 29	Weeks 4 and 12	

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

Pharmacokinetic Sampling and Exposure Parameters

- Tapinarof plasma concentrations were measured using a highly sensitive assay that permitted assessment of drug levels to picogram (pg [10^{-12} g])/mL level
  - The lower limit of quantitation (LLOQ) was 50 pg/mL in the psoriasis trials and 40 pg/mL in the AD trial
- Because most samples were below the LLOQ (BLQ), the exposure–response analysis used imputed concentration values for BLQ samples that assumed an exposure level of approximately half of the LLOQ
- PK parameters were the minimum and maximum plasma concentrations (C_{min} and C_{max}) of tapinarof

Endpoints and Statistical Analysis

- Tapinarof plasma concentrations were evaluated for relationships with disease (AD or plaque psoriasis), tapinarof dose (0.5% or 1%), and application frequency (QD or twice daily [BID])
- A separate analysis of the maximal-use trial in psoriasis investigated whether tapinarof exposure correlated with percentage BSA affected at baseline
- To investigate any relationship between tapinarof exposure and safety endpoints, tapinarof exposure (C_{min} and C_{max}) was categorized as follows:
  - '0' (patients randomized to vehicle)
  - '≤BLQ' (patients with undetectable tapinarof exposure)
  - '>BLQ' (patients with measurable tapinarof concentrations)
  - The >BLQ group 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
- The relationship between tapinarof exposure and efficacy was not assessed in patients with AD
- Demographics and PK concentrations were assessed in patients who received ≥1 dose of trial drug and had ≥1 PK sample (PK population)
- Efficacy–response analyses were assessed in all patients who received ≥1 dose of trial drug (safety population)

RESULTS

Patient Baseline Characteristics

- The majority of patients (58.9% [346/587]) had plaque psoriasis; 53.8% overall were male; and the mean age was 41.8 years (**Table 2**)
- Overall, 67.8% (398/587) of patients received tapinarof and 32.2% (189/587) received vehicle
  - Among patients in the tapinarof groups, most (69.8%) received tapinarof 1% QD; the remainder received tapinarof 0.5% QD (9.8%), 0.5% BID (10.3%), or 1% BID (10.1%)

Table 2. Baseline Patient Demographics (PK Population)

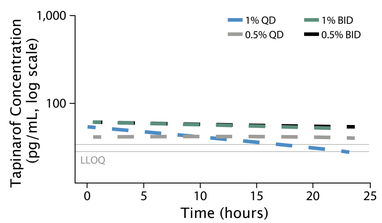
	Patients with AD	Patients with Plaque Psoriasis			Overall (N=587)
	Phase 2b Trial (N=241)[5]	Phase 2a Maximal-use Trial (N=21)[4]	Pivotal Phase 3 Trials[2]		
			PSOARING 1 (N=139)	PSOARING 2 (N=186)	
Age, years, mean (SD)	29.5 (14.9)	51.8 (13.9)	47.9 (13.4)	52.1 (12.4)	41.8 (17.2)
Male, n (%)	122 (50.6)	13 (61.9)	70 (50.4)	111 (59.7)	316 (53.8)
Weight, kg, mean (SD)	76.8 (24.0)	97.5 (24.6)	94.1 (25.2)	93.0 (23.1)	86.8 (25.4)
BMI, kg/m^2, mean (SD)	27.5 (7.6)	33.1 (7.9)	32.2 (8.5)	31.8 (7.4)	30.1 (8.1)

AD, atopic dermatitis; BMI, body mass index; PK, pharmacokinetic; SD, standard deviation.

Pharmacokinetics of Tapinarof

- Tapinarof plasma exposure was low overall and below quantifiable limits in the majority (62.6% [1243/1985]) of samples using a highly sensitive assay
- Mean (SD) C_{min} and C_{max} were 27.6 (23.3) pg/mL and 340 (6270) 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%, 1%), or frequency (QD, BID) of application (**Figure 1**)
- In a separate, post hoc analysis of the psoriasis maximal-use trial, there was also no correlation between tapinarof plasma concentration and BSA in patients with psoriasis (ranging from 21%–46%) (**Figure 2**)
- In the maximal-use trial in patients with psoriasis, tapinarof plasma exposure declined over time, and was approximately 10-fold lower on Day 29 than on Day 1[4]

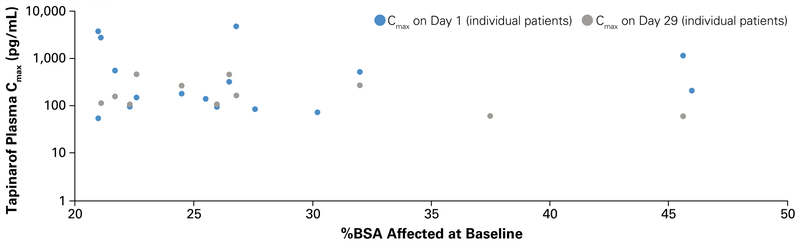
Figure 1. Tapinarof Plasma Concentrations Over Time Remained Low in AD and Psoriasis Trials, Regardless of Dose or Application Frequency



Tapinarof dose and application frequency	Patient Population and Trials		N
1% QD	Psoriasis	Phase 2a maximal-use trial PSOARING 1 trial PSOARING 2 trial	278
	AD	Phase 2b trial	
1% BID	AD	Phase 2b trial	40
0.5% QD	AD	Phase 2b trial	39
0.5% BID	AD	Phase 2b trial	41

*Horizontal lines indicate the LLOQ for the assays used in the psoriasis trials (50 pg/mL) and the AD trial (40 pg/mL). Dashed lines indicate median trend lines.
AD, atopic dermatitis; BID, twice daily; LLOQ, lower limit of quantitation; QD, once daily.

Figure 2. No Correlation Between Tapinarof Exposure (C_{max} on Days 1 and 29) and Baseline %BSA Affected in the Psoriasis Maximal-Use Trial

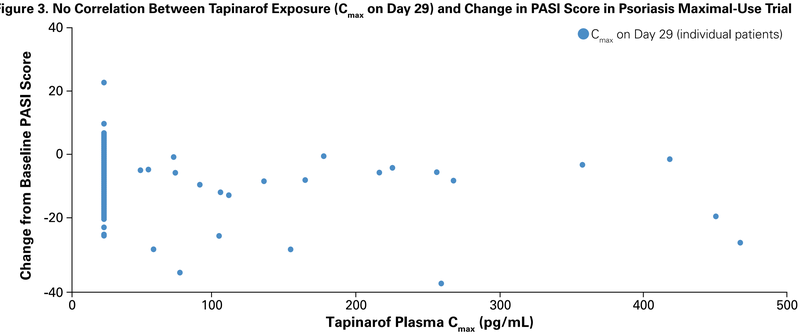


BSA, body surface area; C_{max} maximum plasma concentration.

Exposure–Response Analyses

- In the phase 2a maximal-use trial, there was no relationship between tapinarof plasma exposure and efficacy in patients with psoriasis, including improvements in PGA score and change from baseline in PASI score
- There was no relationship between tapinarof exposure and AESIs of folliculitis, contact dermatitis, or headache in patients with AD or psoriasis across all trials
- There was no correlation between tapinarof plasma exposure and PASI response on Day 29 (**Figure 3**)

Figure 3. No Correlation Between Tapinarof Exposure (C_{max} on Day 29) and Change in PASI Score in Psoriasis Maximal-Use Trial



C_{max} maximum plasma concentration; PASI, Psoriasis Area and Severity Index.

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 application of tapinarof cream 1% 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 cream

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ACKNOWLEDGMENTS

This trial was funded by Dermavant Sciences, Inc. The authors thank the participating investigators, patients and their families, and colleagues involved in the conduct of the trial. J.D.R. serves as a consultant/advisor and clinical research investigator for Dermavant Sciences, Inc. S.G. is a speaker for AbbVie, Aclaris, Janssen, Pfizer, and Sun Pharma. H.C.H. has received consultancy fees, honorarium, and speaker fees from Dermavant Sciences, Inc. J.E.J., P.M.B., D.S.R., and S.C.P. are employees of Dermavant Science, Inc. with stock options. Editorial and medical writing 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).

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