Tapinarof Cream 1% Once Daily for the Treatment of Extensive Atopic Dermatitis in Adolescents and Children: Outcomes from the 4-Week Maximal Usage Trial

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INTRODUCTION

- Tapinarof (VTAMA®, Dermavant Sciences, Inc.) is a first-in-class, non-steroidal, topical, aryl hydrocarbon receptor agonist approved by the Food and Drug Administration in May 2022 for the treatment of plaque psoriasis in adults,[1] and under investigation for the treatment of psoriasis in children down to 2 years of age, and for atopic dermatitis (AD) in adults and children down to 2 years of age
- Tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle and was well tolerated in adults and adolescents with AD in a 12-week phase 2 trial[2,3]
  - Efficacy was generally maintained through the last trial visit, 4 weeks after completing treatment[2,3]
- Tapinarof cream 1% 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, PSOARING 1 and 2[4]
  - Efficacy continued to improve beyond the 12-week trials in PSOARING 3, the long-term extension trial, with an ~4-month remittive effect off therapy (maintenance of PGA of 0 or 1), a high rate (41%; n=312/763) of complete disease clearance (PGA=0), and durability of response (no tachyphylaxis) for up to 52 weeks of treatment[5]
- The pharmacokinetic (PK) profile of tapinarof cream across psoriasis and AD trials is characterized by minimal-to-no systemic absorption and decreasing plasma concentrations over the course of treatment[6,7]
- This was the first trial evaluating tapinarof cream 1% QD in children with AD under 12 years of age

OBJECTIVE

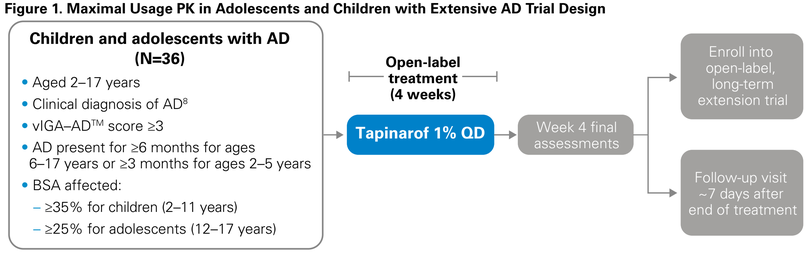
- To assess the PK, safety, and tolerability of tapinarof cream 1% QD in adolescents and children with extensive AD in the 4-week maximal usage trial

MATERIALS AND METHODS

Trial Design

- In this phase 2, multicenter, open-label maximal usage trial, adolescents and children with extensive AD received tapinarof cream 1% QD for 4 weeks (**Figure 1**)
- Tapinarof PK was assessed at Days 1 (baseline) and 28
  - Tapinarof was measured in plasma with a highly sensitive assay (lower limit of quantitation=50 pg [10^{-12} g]/mL [0.05 ng/mL])
- Patients returned to the clinic on Days 8 and 28 for trial assessments
  - Additionally, patients were contacted by phone at Day 15 to assess adverse events (AEs) and concomitant medications
- Eligible patients completing this trial had the option to enroll in an open-label, long-term extension trial (ADORING 3) to receive up to an additional 48 weeks of tapinarof treatment

Figure 1. Maximal Usage PK in Adolescents and Children with Extensive AD Trial Design



AD, atopic dermatitis; BSA, body surface area; PK, pharmacokinetics; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Endpoints and Statistical Analyses

Endpoints:

- The incidence and frequency of treatment-emergent adverse events (TEAEs)
- Mean Investigator-assessed Local Tolerability Scale scores by visit (overall and sensitive areas)
- Tapinarof plasma PK parameters on Day 1, including:
  - Maximum plasma concentration (C_{max})
  - Time to maximum plasma concentration (T_{max})
- Tapinarof plasma concentration on Day 28

Statistical Analyses

- The PK population included all patients who underwent PK sampling and had concentration–time data
- Tapinarof was measured in plasma with a highly sensitive assay (lower limit of quantitation=50 pg [10^{-12} g]/mL)
- Safety analyses included all patients who received at least 1 application of tapinarof

RESULTS

Baseline Patient Demographics and Disease Characteristics

- Overall, 36 patients were enrolled at eight sites in the US and one site in Canada (**Table 1**):
  - There were equal proportions (33.3% [12/36]) of children in the three groups (ages 2–6, 7–11, and 12–17 years)
  - Most patients (77.8%) across the three groups had a Validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) score of 3 (moderate)
  - Overall mean (standard deviation [SD]) Eczema Area and Severity Index (EASI) score was 23.8 (9.2), with a range of 8.2–49.6 indicating moderate to severe AD
  - Overall mean (SD) percent body surface area (%BSA) affected was 42.8% (15.1%), with a range of 26–90%

Table 1. Baseline Demographics and Disease Characteristics

	Tapinarof cream 1% QD			
	Children aged 2–6 years (n=12)	Children aged 7–11 years (n=12)	Adolescents aged 12–17 years (n=12)	Overall (N=36)
Age, years, mean (SD)	3.7 (1.4)	8.2 (1.4)	14.8 (1.8)	8.9 (4.9)
Male, n (%)	9 (75.0)	7 (58.3)	8 (66.7)	24 (66.7)
vIGA-AD™ of 3 (moderate), n (%)	8 (66.7)	9 (75.0)	11 (91.7)	28 (77.8)
vIGA-AD™ of 4 (severe), n (%)	4 (33.3)	3 (25.0)	1 (8.3)	8 (22.2)
EASI, mean (SD); min–max	30.2 (8.6); 19.4–46.3	21.0 (10.0); 8.2–49.6	20.3 (5.5); 12.8–31.3	23.8 (9.2); 8.2–49.6
BSA affected, %, mean (SD); min–max	52.4 (19.1); 36.0–90.0	42.0 (10.0); 35.0–72.0	33.9 (8.6); 26.0–54.5	42.8 (15.1); 26.0–90.0

BSA, body surface area; EASI, Eczema Area and Severity Index; max, maximum; min, minimum; QD, once daily; SD, standard deviation; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Tapinarof Pharmacokinetics

- There was minimal-to-no tapinarof plasma exposure, with 25% of post-treatment plasma samples below the quantifiable limit of the highly sensitive assay (<50 pg [10^{-12}]/mL)
- On Day 1, the mean (SD) C_{max} was 2.4 (3.9) ng/mL, median (range) T_{max} was 2.9 (1.0–5.0) hours, and the mean (SD) AUC_{0-t} was 4.7 (5.6) ng*h/mL
- There was no correlation between tapinarof exposure (C_{max} on Day 1) and baseline %BSA affected
- Overall, 75.9% of PK samples on Day 28 had concentrations that were below the quantifiable limit

Table 2. Safety Overview

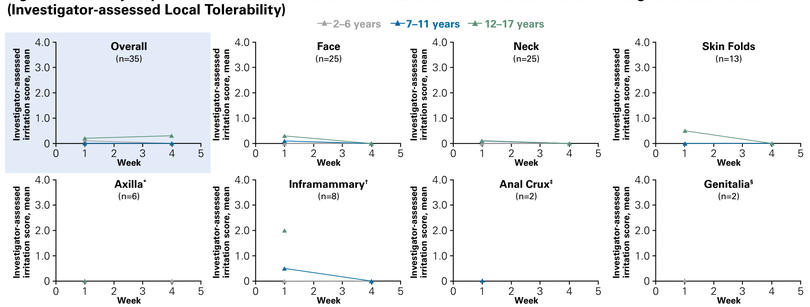
Adverse event category	Tapinarof cream 1% QD			
	Children aged 2–6 years (n=12)	Children aged 7–11 years (n=12)	Adolescents aged 12–17 years (n=12)	Overall (N=36)
Any TEAE, n (%)*	2 (16.7)	4 (33.3)	2 (16.7)	8 (22.2)
Treatment-related TEAE	0	2 (16.7)	1 (8.3)	3 (8.3)
TEAE leading to trial drug discontinuation	0	1 (8.3)	0	1 (2.8)
TEAE leading to trial discontinuation†	0	1 (8.3)	0	1 (2.8)
TEAE of special interest, n (%)*				
Contact dermatitis	0	0	0	0
Folliculitis	0	1 (8.3)	0	1 (2.8)
Headache	0	2 (16.7)	1 (8.3)	3 (8.3)

*Patients could experience ≥1 TEAE; this could result in trial drug discontinuation or trial discontinuation. †One patient experienced one event of vomiting and one event of headache that led to trial discontinuation.
QD, once daily; TEAE, treatment-emergent adverse event.

Local Tolerability

- Mean overall Investigator-assessed Local Tolerability Scale score was 0.1 (no irritation) at Week 1 and Week 4 (**Figure 2**)
- Investigators assessed that the majority of patients had no irritation (0), including on sensitive and intertriginous skin areas (**Figure 2**)

Figure 2. The Majority of Patients had No Irritation Overall, and Across Sensitive and Intertriginous Skin Areas (Investigator-assessed Local Tolerability)



Investigator-assessed irritation scores (0–4) evaluate the presence and overall degree of irritation at the application sites according to the Local Tolerability Scale (dryness, erythema, and peeling) score – no irritation (0), mild (1), moderate (2), severe (3), very severe (4). Sensitive area evaluations include ≥1 patient from each age group at Weeks 1 and 4 unless otherwise stated: *age group 7–11 years n=0 at Week 1; age groups 7–11 and 12–17 years n=0 at Week 4; †age group 12–17 years n=0 at Week 4; ‡age group 12–17 years n=0 at Week 1, and no Week 4 data; §age groups 7–11 and 12–17 years n=0 at Week 1, and no Week 4 data. Safety population.

Safety

- TEAEs were reported by 8 patients (22%) and were all mild or moderate (**Table 2**)
  - One patient discontinued the trial due to two TEAEs that were unrelated to the trial drug
- One case of mild folliculitis and no contact dermatitis occurred during the trial
  - There were no trial discontinuations due to folliculitis

CONCLUSIONS

- This trial is the first report of tapinarof use in children below 12 years of age, and uses the same dosing regimen (1% QD) as that approved for adults with plaque psoriasis
- Tapinarof cream 1% QD demonstrated minimal-to-no systemic exposure in adolescents and children down to 2 years of age with extensive AD, even when measured with a highly sensitive assay (<50 pg [10^{-12} g]/mL)
- Even with extensive application over a large BSA, tapinarof was associated with a low incidence of AEs in patients with up to 90% BSA affected (mean 42.8%)
  - There were no discontinuations due to trial drug-related AEs
- Tapinarof was well tolerated overall, including on sensitive and intertriginous skin areas
- The phase 3 ADORING clinical trial program is ongoing, comprising two double-blind, randomized controlled trials (ADORING 1 and 2) that are complete, an open-label, long-term extension trial, ADORING 3, and this maximal usage trial
  - Results from ADORING 1 and 2 will be available in 2023

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