Tapinarof Cream 1% Once Daily: Significant Efficacy in the Treatment of Atopic Dermatitis in Two Pivotal Phase 3 Trials in Adults and Children Down to 2 Years of Age

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INTRODUCTION

- Atopic dermatitis (AD) is a chronic, relapsing and remitting inflammatory skin disease characterized by pruritus that can substantially impact sleep and quality of life[1–4]
- Topical agents form the mainstay of treatment in patients with AD[5]
  - Topical corticosteroids (TCSs) are efficacious but are also associated with adverse events (AEs) that can limit their use[5,6]
  - The effectiveness of TCSs may also be limited by the potential for tachyphylaxis (loss of response), and recurrence of symptoms associated with reduced frequency of use or cessation of treatment; in addition, TCSs have restrictions relating to patients' age, as well as duration and extent of use, and locations used[6,7]
- Consequently, use of TCSs is often limited or restricted, especially in sensitive skin areas (e.g., the face, and skin flexures or intertriginous areas), and in infants and younger children who are at increased risk of systemic absorption and potential AEs[5,8,9]
- A need remains for efficacious non-steroidal topical therapies that can be used without restrictions relating to duration or extent of use, or site of application
- Tapinarof (VTAMA®, Dermavant Sciences, Inc.) is a non-steroidal, topical aryl hydrocarbon receptor agonist, approved by the Food and Drug Administration for the treatment of plaque psoriasis in adults,[10] and under investigation for the treatment of psoriasis in children down to 2 years of age and for AD in adults and children down to 2 years of age
- Tapinarof cream 1% once daily (QD) demonstrated statistically significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two pivotal phase 3 trials, PSOARING 1 and 2[11]
- Efficacy continued to improve in the long-term extension trial, PSOARING 3, with a high rate of complete disease clearance (Physician Global Assessment [PGA]=0; 40.9% [n=312/763]), an approximately 4-month remittive effect off therapy after first achieving a PGA score of 0, and durability of response both on treatment or with intermittent therapy for up to 52 weeks[12]
- In a phase 2 trial in adults and adolescents with AD, tapinarof cream 1% QD demonstrated efficacy versus vehicle and was well tolerated[13]

OBJECTIVE

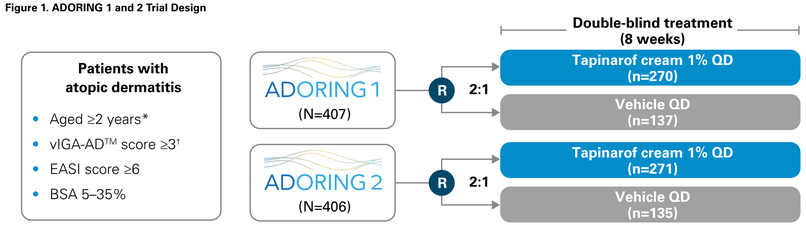
- To report the efficacy and safety of tapinarof cream 1% QD in the treatment of adults and children down to 2 years of age with AD in two pivotal phase 3 trials, ADORING 1 and 2 (NCT05014568, NCT05032859)

MATERIALS AND METHODS

Trial Design

- In ADORING 1 and 2, two identically designed phase 3, double-blind, randomized, vehicle-controlled trials, patients with AD were randomized 2:1 to tapinarof cream 1% or vehicle QD for 8 weeks (**Figure 1**)
- Following the double-blind period, patients could enroll in an open-label, long-term extension trial (ADORING 3) or complete a follow-up visit, 1 week after the end of treatment (Week 9)

Figure 1. ADORING 1 and 2 Trial Design



A minimum of ~15% of patients were enrolled into the following age groups: 2–6 years, 7–11 years, 12–17 years, and ≥18 years. Adults (aged ≥18 years) comprised a maximum of approximately 20% of enrolled patients. †Patients with a vIGA-AD™ score of 4 (severe) represented a minimum of ~10% of the total randomized population; the remainder had a vIGA-AD™ score of 3 (moderate).
BSA, body surface area; EASI, Eczema Area and Severity Index; QD, once daily; R, randomized; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Endpoints and Statistical Analysis

- The primary efficacy endpoint was Validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) response, defined as a score of clear (0) or almost clear (1) and ≥2-grade improvement from baseline at Week 8
- Secondary efficacy endpoints included ≥75% improvement in Eczema Area and Severity Index score (EASI75), and proportion of patients (aged ≥12 years) with a baseline Peak Pruritus Numerical Rating Scale (PP-NRS) score of ≥4 who achieved a ≥4-point reduction at Week 8
- Safety assessments included the incidence, frequency, and duration of treatment-emergent adverse events (TEAEs)
- Efficacy endpoints were based on the intention-to-treat population

RESULTS

Baseline Patient Demographics and Disease Characteristics

- 407 and 406 patients were enrolled (at 106 sites in the US and 12 in Canada) in ADORING 1 and 2, respectively (**Table 1**):
  - Overall, patients' mean age was 15.6–16.7 years, and 43.0–48.2% were male across groups and trials
  - Across trials, approximately 50% of patients had skin of color; patients with Fitzpatrick skin types IV, V, and VI represented 23.8–25.1%, 20.6–22.2%, and 7.6–8.9%, respectively

Table 1. Baseline Demographics and Disease Characteristics

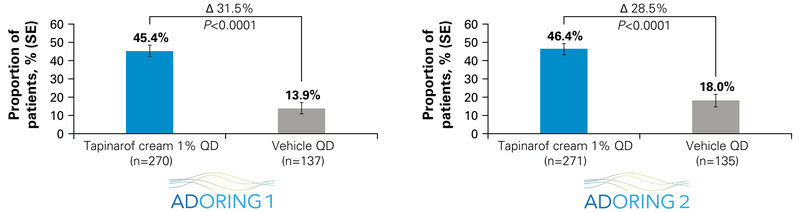
	ADORING 1		ADORING 2	
	Tapinarof cream 1% QD (n=270)	Vehicle QD (n=137)	Tapinarof cream 1% QD (n=271)	Vehicle QD (n=135)
Age, years, mean (SD)	15.6 (16.6)	15.6 (16.5)	16.4 (16.2)	16.7 (16.1)
Male, n (%)	130 (48.1)	66 (48.2)	117 (43.2)	58 (43.0)
BMI, kg/m², mean (SD)	21.4 (6.3)	22.1 (6.6)	22.7 (7.5)	23.3 (8.3)
Race, n (%)				
Asian	26 (9.6)	10 (7.3)	39 (14.4)	23 (17.0)
Black or African American	70 (25.9)	38 (27.7)	95 (35.1)	47 (34.8)
White	152 (56.3)	79 (57.7)	124 (45.8)	58 (43.0)
Other*	16 (5.9)	5 (3.6)	7 (2.6)	4 (3.0)
Not reported	6 (2.2)	5 (3.6)	6 (2.2)	3 (2.2)
vIGA-AD™, n (%)				
3 – Moderate	244 (90.4)	122 (89.1)	228 (84.1)	113 (83.7)
4 – Severe	26 (9.6)	15 (10.9)	43 (15.9)	22 (16.3)
EASI, mean (SD)	12.2 (5.0)	12.9 (5.6)	13.5 (5.6)	13.1 (4.7)
BSA affected, (%), mean (SD)	16.5 (8.7)	17.7 (9.5)	17.1 (8.7)	15.8 (7.9)
PP-NRS (all), mean (SD)	6.8 (2.3)	6.5 (2.4)	6.7 (2.4)	6.9 (2.1)
PP-NRS (≥12 years), mean (SD)	6.5 (2.4)	6.3 (2.3)	6.3 (2.4)	6.5 (2.2)
PP-NRS (<12 years), mean (SD)	7.0 (2.3)	6.6 (2.5)	7.1 (2.3)	7.4 (1.8)

*Other comprised American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or Multiple races checked. BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; SD, standard deviation; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Achievement of vIGA-AD™ Response at Week 8

- The primary endpoint of vIGA-AD™ response (score of 0 or 1 and ≥2-grade improvement from baseline) was highly statistically significant in the tapinarof cream 1% QD group versus the vehicle group in both ADORING 1 and 2: 45.4% vs 13.9% and 46.4% vs 18.0% (both *P*<0.0001), respectively (**Figure 2**)

Figure 2. Proportion of Patients who Achieved a vIGA-AD™ Response* at Week 8

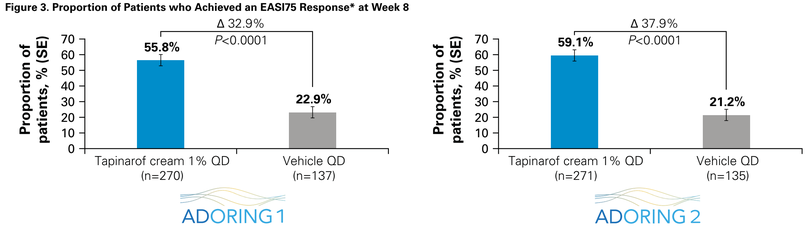


*vIGA-AD™ score of 0 or 1 and ≥2-grade improvement from baseline.
Intention-to-treat, multiple imputation.
QD, once daily; SE, standard error; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Achievement of EASI75 Response and ≥4-point reduction in PP-NRS at Week 8

- The secondary efficacy endpoint of an EASI75 response was met with statistical significance with tapinarof cream versus vehicle: 55.8% vs 22.9% and 59.1% vs 21.2% (both *P*<0.0001) (**Figure 3**)
- A ≥4-point reduction in PP-NRS (patients aged ≥12 years) was achieved by 55.8% vs 34.2% (*P*=0.0366) and 52.8% vs 24.1% (*P*=0.0015), in ADORING 1 and 2, respectively

Figure 3. Proportion of Patients who Achieved an EASI75 Response* at Week 8

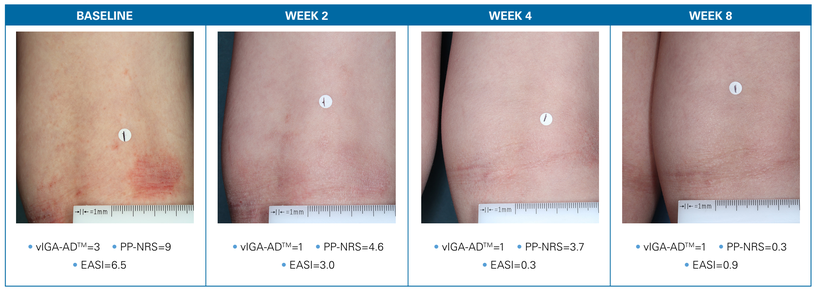


*≥75% improvement in Eczema Area and Severity Index score from baseline.
Intention-to-treat, multiple imputation.
EASI75, ≥75% improvement in Eczema Area and Severity Index score; QD, once daily; SE, standard error.

Patient who Achieved Almost Clear Skin (vIGA-AD™=1) at Week 2

- The patient (aged 8 years) in **Figure 4** had moderate disease (vIGA-AD™=3) at baseline and achieved almost clear skin (vIGA-AD™=1) by Week 2
- The patient also had severe itch (PP-NRS=9) at baseline, achieving a clinically meaningful ≥4-point reduction in PP-NRS by Week 2, with improvement to an itch-free state by Week 8 (PP-NRS=0.3)

Figure 4. Achievement of the Primary Endpoint as Early as Week 2 and Complete Resolution of Itch by Week 8 in an 8-Year-Old Patient with Moderate AD Treated with Tapinarof Cream 1% QD



Example of one representative target lesion in a tapinarof-treated patient from the ADORING 2 clinical trial. Individual results may vary.
AD, atopic dermatitis; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Safety

- TEAEs were mostly mild or moderate; the most frequent (≥5% in any group) were folliculitis, headache, and nasopharyngitis
- Trial discontinuation rates due to TEAEs were lower with tapinarof cream versus vehicle (1.9% vs 3.6% and 1.5% vs 3.0% in ADORING 1 and ADORING 2, respectively) (**Table 2**)

Table 2. Safety Overview

	ADORING 1		ADORING 2	
	Tapinarof cream 1% QD (n=270)	Vehicle QD (n=137)	Tapinarof cream 1% QD (n=271)	Vehicle QD (n=135)
Any TEAE	118 (43.7)	33 (24.1)	95 (35.1)	24 (18.0)
AESI (treatment emergent)				
Contact dermatitis	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Follicular event	27 (10.0)	1 (0.7)	24 (8.9)	2 (1.5)
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Treatment-related TEAE	34 (12.6)	9 (6.6)	32 (11.8)	9 (6.8)
TEAE leading to treatment discontinuation	6 (2.2)	6 (4.4)	4 (1.5)	5 (3.8)
TEAE leading to trial discontinuation	5 (1.9)	5 (3.6)	4 (1.5)	4 (3.0)
Serious TEAE, non-fatal	3 (1.1)	0	2 (0.7)	0
Treatment-related serious TEAE	0	0	0	0

AE, adverse event; AESI, adverse event of special interest; QD, once daily; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Tapinarof cream 1% QD demonstrated statistically significant efficacy compared with vehicle for primary and secondary efficacy endpoints in adults and children down to 2 years of age with AD
- Tapinarof was well tolerated, with no new safety or tolerability signals
- AEs were mostly mild to moderate and led to low rates of trial discontinuation (lower with tapinarof versus vehicle), demonstrating the predictable safety profile of tapinarof cream 1% QD
- Tapinarof is a non-steroidal topical medication with the potential to be used for the treatment of AD in patients down to 2 years of age without restrictions on duration, extent, or sites of application

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