Tapinarof Cream 1% Once Daily is Efficacious for the Treatment of Atopic Dermatitis in Patients with Skin of Color Down to 2 Years of Age in Two Pivotal Phase 3 Trials

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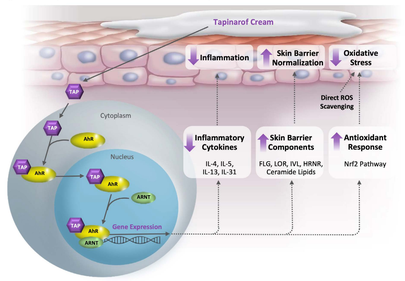
INTRODUCTION

- Racial/ethnic variations in the prevalence, clinical characteristics, and the burden of atopic dermatitis (AD) have been reported[1]
  - There are few data on AD treatment in patients with skin of color (a diverse range of populations with Fitzpatrick skin types IV–VI, who self-identify as non-White)
- Pigment changes are a distinct feature of AD in patients with skin of color, and xerosis may be more stigmatizing due to greater visibility in dark skin[1]
- There is a need for efficacious and well tolerated, non-steroidal, topical therapies that can be used without restrictions relating to duration or extent of use, or site of application by people with skin of color
- Tapinarof (VTAMA®, Dermavant Sciences, Inc.) is a non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist, approved by the FDA for the treatment of plaque psoriasis in adults,[2] 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 binds to and activates AhR to downregulate proinflammatory cytokines associated with AD (interleukin [IL]-4, IL-5, IL-13, and IL-31), normalize the skin barrier through upregulation of skin barrier components (filaggrin, loricrin, hornerin, involucrin, and ceramide lipids), and increase cytoprotective antioxidant responses to reduce oxidative stress (**Figure 1**)[3]
- In ADORING 1 and 2, two pivotal phase 3, randomized, double-blind, vehicle-controlled trials, tapinarof cream 1% once daily (QD) demonstrated highly statistically significant efficacy and was well tolerated in adults and children down to 2 years of age with AD[4]

Figure 1. Proposed Mechanism of Action of Tapinarof[3]



AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; HRNR, hornerin; IL, interleukin; IVL, involucrin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof.

OBJECTIVE

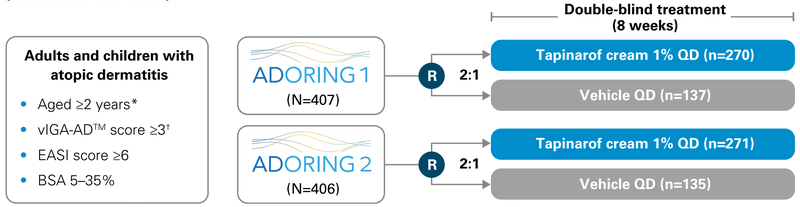
- To report analyses of efficacy by skin color based on patient self-reported race and investigator-assessed Fitzpatrick skin type, in two pivotal phase 3 trials of tapinarof cream 1% QD (ADORING 1 and ADORING 2) in the treatment of AD in adults and children down to 2 years of age

METHODS

Trial Design

- In ADORING 1 (NCT05014568) and 2 (NCT05032859), two identically designed, randomized, double-blind, vehicle-controlled trials, patients with AD were randomized 2:1 to tapinarof cream 1% or vehicle QD for 8 weeks (**Figure 2**)

Figure 2. 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 endpoint was the vIGA-AD™ response at Week 8, defined as a score of 0 or 1 and ≥2-grade improvement from baseline
- The secondary endpoint was EASI75 response (≥75% improvement in Eczema Area and Severity Index score from baseline)
  - Patients could also provide their self-identified ethnicity as Hispanic or Latino, or Not Hispanic or Latino
- Efficacy was stratified by self-identified race categories (where demographic categories except White and "not reported" represented patients with skin of color), and investigator-assessed Fitzpatrick skin type categories[5] (where categories IV–VI are most representative of populations with skin of color)
- Efficacy analyses were based on the intention-to-treat population, evaluated using a multiple imputation approach

RESULTS

Baseline Patient Demographics and Disease Characteristics

- 407 and 406 patients were enrolled in ADORING 1 and 2, respectively (**Table 1**):
  - Patients' mean age was 15.6–16.5 years, and 43.1–48.2% were male across trials
  - Disease characteristics were similar across treatment groups
- Across both ADORING 1 and 2, approximately 50% of patients had skin of color (**Table 1**):
  - 8.8–15.3% were Asian, 26.5–35.0% were Black/African American, 2.7–5.2% were other groups (including American Indian, Alaska Native, Native Hawaiian, Pacific Islander, or other/multiple races), and 44.8–56.8% were White
  - Patients with Fitzpatrick skin types IV, V, and VI represented 23.8–25.1%, 20.6–22.2%, and 7.6–8.9% of patients, respectively, across trials

Table 1. Baseline Demographics and Disease Characteristics

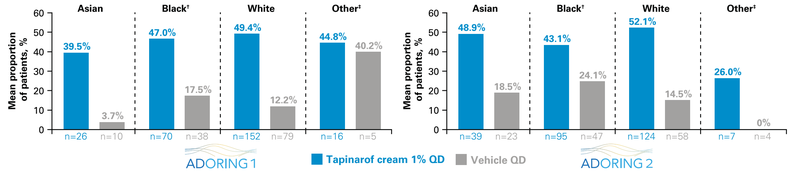
	ADORING 1		ADORING 2	
	Tapinarof cream 1% QD (n=270)	Vehicle QD (n=137)	Tapinarof cream 1% QD (n=271)	Vehicle QD (n=135)
Race, n (%)				
Asian	26 (9.6)	10 (7.3)	39 (14.4)	23 (17.0)
Black or African American	70 (25.9)	38 (27.7)	95 (35.1)	47 (34.8)
White	152 (56.3)	79 (57.7)	124 (45.8)	58 (43.0)
American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; multiple races	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)
Fitzpatrick skin type, n (%)				
I	9 (3.3)	7 (5.1)	11 (4.1)	4 (3.0)
II	66 (24.4)	22 (16.1)	52 (19.2)	28 (20.7)
III	60 (22.2)	31 (22.6)	50 (18.5)	33 (24.4)
IV	67 (24.8)	30 (21.9)	71 (26.2)	31 (23.0)
V	44 (16.3)	40 (29.2)	63 (23.2)	27 (20.0)
VI	24 (8.9)	7 (5.1)	24 (8.9)	12 (8.9)
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)

EASI, Eczema Area and Severity Index score; QD, once daily; SD, standard deviation; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Primary Efficacy Endpoint of vIGA-AD™ Response at Week 8

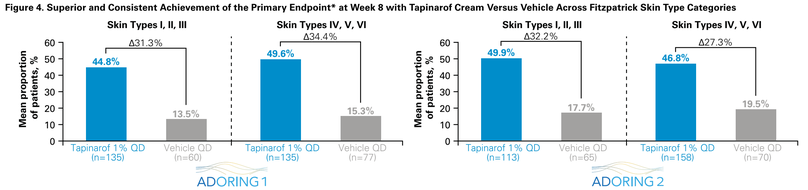
- As previously reported, overall, the primary efficacy endpoint of a vIGA-AD™ response at Week 8 was met with high statistical significance in ADORING 1 and 2; 45.4% vs 13.9% and 46.4% vs 18.0% (both $P<0.0001$), for tapinarof versus vehicle, respectively[4]
- Consistently high efficacy was achieved with tapinarof cream versus vehicle for the primary endpoint across race categories (**Figure 3**) and Fitzpatrick skin type category groups (**Figure 4**) in both trials

Figure 3. Superior and Consistent Achievement of the Primary Endpoint* at Week 8 with Tapinarof Cream Versus Vehicle Across Race Categories



*vIGA-AD™ score of 0 or 1 and ≥2-grade improvement from baseline. †Includes Black or African American. ‡Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiple races.
Intention-to-treat, multiple imputation. QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Figure 4. Superior and Consistent Achievement of the Primary Endpoint* at Week 8 with Tapinarof Cream Versus Vehicle Across Fitzpatrick Skin Type Categories

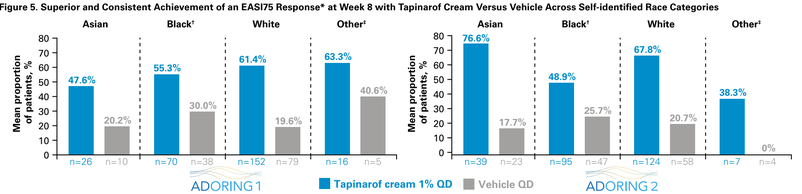


*vIGA-AD™ score of 0 or 1 and ≥2-grade improvement from baseline at Week 8 by Fitzpatrick skin type category groups, where categories IV–VI indicate patients with skin of color.
Intention-to-treat, multiple imputation. QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

EASI75 Response at Week 8

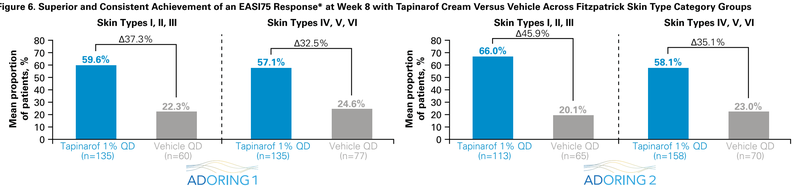
- Overall, the secondary efficacy endpoint of an EASI75 response was met with high statistical significance in ADORING 1 and 2; 55.8% vs 22.9% and 59.1% vs 21.2% (both $P<0.0001$) for tapinarof versus vehicle, respectively[4]
- Tapinarof cream demonstrated consistently high achievement of EASI75 response versus vehicle across race categories (**Figure 5**) and Fitzpatrick skin type category groups (**Figure 6**) in both trials

Figure 5. Superior and Consistent Achievement of an EASI75 Response* at Week 8 with Tapinarof Cream Versus Vehicle Across Self-identified Race Categories



*≥75% improvement in Eczema Area and Severity Index score from baseline (EASI75).
†Includes Black or African American. ‡Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiple races.
Intention-to-treat, multiple imputation. QD, once daily.

Figure 6. Superior and Consistent Achievement of an EASI75 Response* at Week 8 with Tapinarof Cream Versus Vehicle Across Fitzpatrick Skin Type Category Groups



*≥75% improvement in Eczema Area and Severity Index score from baseline (EASI75) by Fitzpatrick skin type category groups, where categories IV–VI indicate patients with skin of color.
Intention-to-treat, multiple imputation. QD, once daily.

Safety

- Treatment-emergent adverse events (TEAEs) were mostly mild or moderate; the most frequent (≥5% in any group) were folliculitis, headache, and nasopharyngitis
- No hypopigmentation was reported
- Trial discontinuation rates due to TEAEs were lower with tapinarof cream versus vehicle (1.9% vs 3.6% and 1.5% vs 3.0%, for all patients in ADORING 1 and ADORING 2, respectively)

Patient who Achieved the Primary and Secondary Efficacy Endpoints by Week 2

- The patient (aged 5 years) in **Figure 7** had moderate disease with a Validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) score of 3 at baseline and achieved almost clear skin (vIGA-AD™=1) by Week 2, and through the end of trial at Week 8, with no hypo- or hyperpigmentation

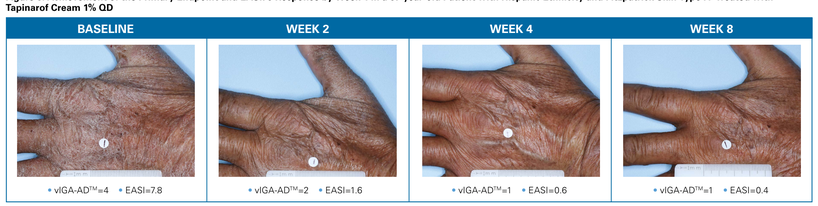
Figure 7. Achievement of the Primary Endpoint and EASI75 Response as Early as Week 2 in a 5-year-old Black or African-American Patient with Fitzpatrick Skin Type V Treated with Tapinarof Cream 1% QD

Example of one representative target lesion in a tapinarof-treated patient from the ADORING 1 trial. Individual results may vary.
EASI, Eczema Area and Severity Index score; EASI75, ≥75% improvement in Eczema Area and Severity Index score from baseline; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Patient who Achieved the Primary and Secondary Efficacy Endpoints by Week 4

- The patient (aged 67 years) in **Figure 8** had severe disease (vIGA-AD™=4) and xerosis evident at baseline. They achieved almost clear skin (vIGA-AD™=1) by Week 4, which was maintained through the end of trial at Week 8, with no hypo- or hyperpigmentation

Figure 8. Achievement of the Primary Endpoint and EASI75 Response by Week 4 in a 67-year-old Patient with Hispanic Ethnicity and Fitzpatrick Skin Type IV Treated with Tapinarof Cream 1% QD



Example of one representative target lesion in a tapinarof-treated patient from the ADORING 2 trial. Individual results may vary.
EASI, Eczema Area and Severity Index score; EASI75, ≥75% improvement in Eczema Area and Severity Index score from baseline; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

CONCLUSIONS

- As previously reported, 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 moderate to severe AD, in a diverse population comprising approximately 50% of patients with skin of color
- In this analysis, tapinarof was consistently highly efficacious across the range of self-identified racial categories and investigator-assessed Fitzpatrick skin types
- Adverse events were mostly mild or 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, including patients with skin of color, without restrictions on duration, extent, or sites of application

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