Achievement of No-to-minimal Itch and Sleep Improvement with Tapinarof Cream 1% Once Daily in Two Pivotal Phase 3 Trials in Adults and Children Down to 2 Years of Age with Atopic Dermatitis

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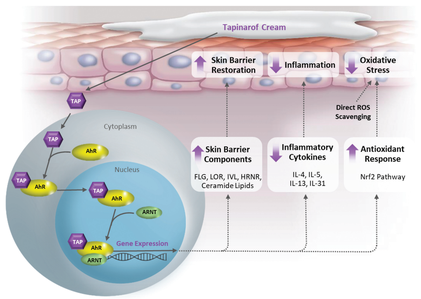
INTRODUCTION

- Pruritus (itch) is the most burdensome symptom for patients with atopic dermatitis (AD), and has a substantial impact on health-related quality of life[1–4]
  - Pruritus can negatively affect physical activity, school attentiveness and learning, sleep, and psychological well-being
- The impact of AD on sleep is largely mediated through pruritus and scratching[3]
- 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,[6] with no warnings, contraindications, drug–drug interactions, or restrictions on duration, location, or extent of use
- Tapinarof binds to and activates AhR to restore the skin barrier through upregulation of skin barrier components, to downregulate pro-inflammatory cytokines associated with AD, and to reduce oxidative stress (**Figure 1**)[7]
- In two phase 3 trials, ADORING 1 and 2 (NCT05014568, NCT05032859), tapinarof cream 1% once daily (QD) demonstrated superior efficacy versus vehicle and was well tolerated in adults and children down to 2 years of age with AD[8]
  - Tapinarof demonstrated rapid itch relief from 24 hours after initial application (the first assessment), with improvements through Week 8 in both trials[9]
- The gold-standard Peak Pruritus Numerical Rating Scale (PP-NRS) improvement from baseline is 4 points,[10] however, more stringent outcomes include achieving mean weekly no-to-minimal itch (PP-NRS score of ≤1) and PP-NRS <2

Figure 1. Proposed Mechanism of Action of Tapinarof[7]



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

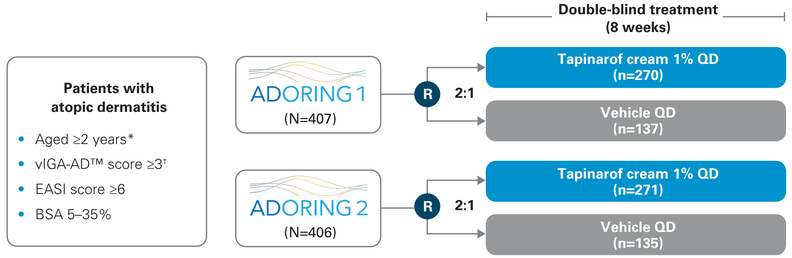
- To present highly stringent itch outcomes and sleep improvement with tapinarof cream 1% QD from ADORING 1 and 2

METHODS

Trial Design

- In ADORING 1 and 2, two identical pivotal phase 3, double-blind, randomized, vehicle-controlled trials, patients with moderate to severe AD were randomized 2:1 to tapinarof cream 1% or vehicle QD for 8 weeks (**Figure 2**)
- Following the double-blind period, patients could enroll in an open-label, long-term extension trial (ADORING 3, NCT05142774) or complete a follow-up visit, 1 week after the end of treatment (Week 9)

Figure 2. ADORING 1 and 2 Trial Design



Copyright ©2017 Eli Lilly and Company – Used with the permission of Eli Lilly and Company under a Creative Commons Attribution-NoDerivatives 4.0 International License. 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; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Endpoints and Statistical Analysis

- Post hoc analyses:
  - The proportion of patients who achieved no-to-minimal itch, defined as a mean weekly PP-NRS score of ≤1
    - Where mean weekly PP-NRS score = mean of daily PP-NRS scores for 7 days
  - The proportion of patients who achieved a mean weekly PP-NRS score of <2
  - PP-NRS scores are assessed on an 11-point scale, where 0 indicates "no itch" and 10 is "worst imaginable itch"[10]
  - Improvement in Patient Oriented Eczema Measure (POEM) Question (Q)2, evaluating sleep disturbance over the past week
    - POEM question scores are assessed on a 5-point scale, where 0 indicates "no days" and 4 is "every day"
  - The PP-NRS and POEM were proxy-completed by parents/caregivers for patients aged 2–11 years, and self-completed by patients aged ≥12 years
- Safety assessments included incidence and frequency 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 in ADORING 1 and 2, respectively, at 106 sites in the US and 12 in Canada (**Table 1**)
  - Pediatric patients (aged 2–17 years) comprised 80.4% (n=654/813) of the trial population
- Mean baseline PP-NRS scores indicated moderate to severe itch, and were similar across treatment groups regardless of patient age (**Table 1**)
- Patients' mean pooled POEM sleep disturbance question scores were 2.0 (aged ≥12 years) and 2.4 (<12 years)

Table 1. Baseline Demographics and Disease Characteristics

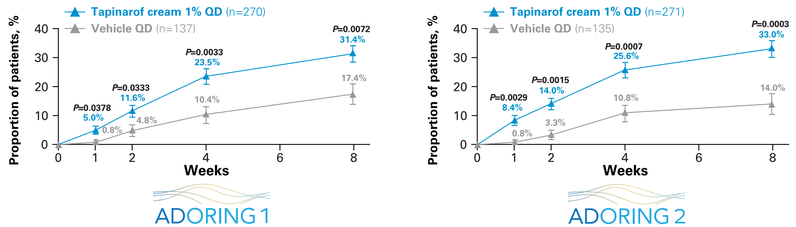
	ADORING 1		ADORING 2	
	Tapinarof cream 1% QD (n=270)	Vehicle QD (n=137)	Tapinarof cream 1% QD (n=271)	Vehicle QD (n=135)
vIGA-AD™, n (%)				
3 – Moderate	244 (90.4)	122 (89.1)	228 (84.1)	113 (83.7)
4 – Severe	26 (9.6)	15 (10.9)	43 (15.9)	22 (16.3)
EASI, mean (SD)	12.2 (5.0)	12.9 (5.6)	13.5 (5.6)	13.1 (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)

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 No-to-minimal Itch (Mean Weekly PP-NRS ≤1)

- The proportion of patients achieving no-to-minimal itch (PP-NRS ≤1) was significantly higher in tapinarof groups compared with vehicle as early as Week 1 (the first assessment) in both ADORING 1 and 2: 5.0% vs 0.8% (P=0.0378) and 8.4% vs 0.8% (P=0.0029) (**Figure 3**)
  - Statistically significant achievement of no-to-minimal itch continued through Week 8: 31.4% vs 17.4% (P=0.0072) and 33.0% vs 14.0% (P=0.0003) (**Figure 3**)

Figure 3. Rapid and Statistically Significant Achievement of No-to-minimal Itch (Mean Weekly PP-NRS ≤1) with Tapinarof Cream 1% QD

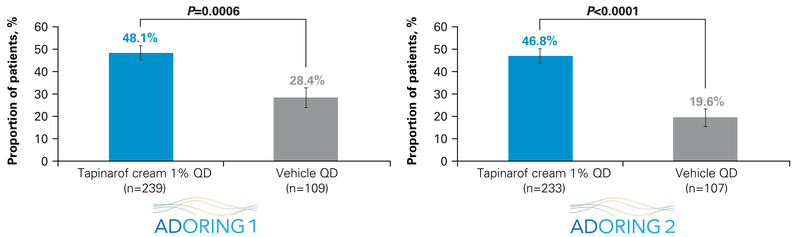


Intention-to-treat, observed cases. Percentage (standard error). PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

Achievement of Mean Weekly PP-NRS <2

- A PP-NRS <2 was achieved by a significantly higher proportion of patients in tapinarof groups versus vehicle as early as Week 1, the first assessment
- At Week 8, a PP-NRS <2 was achieved by 48.1% vs 28.4% (P=0.0006) in ADORING 1 and 46.8% vs 19.6% (P<0.0001) in ADORING 2 (**Figure 4**)

Figure 4. Statistically Significant Achievement of PP-NRS <2 with Tapinarof Cream 1% QD at Week 8

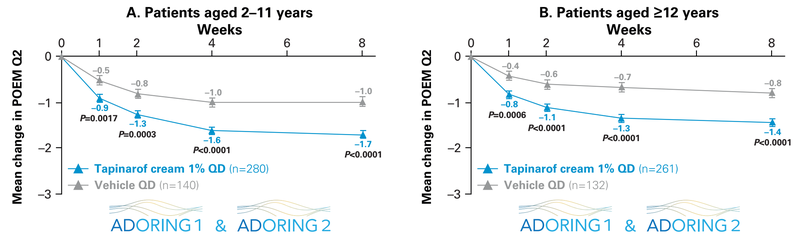


Intention-to-treat, observed cases. Percentage (standard error). PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

Improvements in Sleep as Measured by POEM Question 2

- Improvements in sleep (POEM Q2) for patients aged 2–11 years reached statistical significance with tapinarof compared with vehicle at Week 1, the earliest assessment, in ADORING 1 and 2 (pooled): –0.9 versus –0.5 (P=0.0017) (**Figure 5A**)
  - Improvements continued through Week 8: –1.7 versus –1.0 (P<0.0001)
- For patients aged ≥12 years, significant improvement in sleep (POEM Q2) was also reported with tapinarof versus vehicle as early Week 1, the earliest assessment: –0.8 versus –0.4 (P=0.0006) (**Figure 5A**)
  - Improvements continued through Week 8: –1.4 versus –0.8 (P<0.0001)

Figure 5. Rapid and Continued Improvement in Sleep with Tapinarof Cream 1% QD, Measured by POEM Q2



Intention-to-treat, observed cases (pooled data). Least squares mean (standard error). POEM, Patient Oriented Eczema Measure; Q, question; QD, once daily.

3-year-old Patient who Achieved No-to-minimal Itch at Week 4 and the Primary Endpoint at Week 8

- The Asian patient (aged 3 years) in **Figure 6** had moderate AD (vIGA-AD™=3) affecting the ankle at baseline. He achieved the primary endpoint (vIGA-AD™ score of clear [0] or almost clear [1] and ≥2-grade improvement) at Week 8
- Moderate to severe itch was reported by the parent/caregiver at baseline (PP-NRS=7); reduction in itch surpassed the minimal clinically important ≥4-point improvement by Week 2, and no-to-minimal itch (PP-NRS ≤1) was achieved at Week 4
- His overall POEM score (moderate AD severity at baseline) improved to clear or almost clear AD at Weeks 2, 4, and 8

Figure 6. Achievement of No-to-minimal Itch at Week 4 and the Primary Endpoint at Week 8 in a 3-year-old 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 clinical trial. Individual results may vary.
EASI, Eczema Area and Severity Index; IDQOL, Infants' Dermatitis Quality of Life Index; POEM, Patient Orientated Eczema Measure; 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 than vehicle (ADORING 1: 1.9% vs 3.6%; ADORING 2: 1.5% vs 3.0%, respectively)

CONCLUSIONS

- Tapinarof cream 1% QD monotherapy demonstrated early, significant, and meaningful achievement of stringent mean weekly itch outcomes of no-to-minimal itch (PP-NRS ≤1) and PP-NRS <2, and improvement in sleep in adults and children down to 2 years of age with AD and moderate to severe itch at baseline (mean PP-NRS of ~7)
- Adverse events were mostly mild to moderate and led to low rates of trial discontinuation, demonstrating the predictable safety profile of tapinarof cream 1% QD
- Tapinarof is a once-daily, non-steroidal cream that rapidly improves itch and sleep in patients down to 2 years of age with AD, and has the potential to be used without restrictions on duration of use, extent of body surface area treated, or sites of application

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