Skin Clearance, Treatment Response Off-therapy, and Safety of Tapinarof Cream 1% Once Daily: Results from ADORING 3, a 48-week Phase 3 Trial in Adults and Children Down to 2 Years of Age with Atopic Dermatitis

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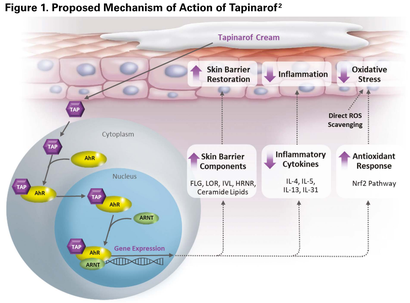
INTRODUCTION

- Topical therapies remain the cornerstone of atopic dermatitis (AD) treatment, regardless of disease severity or age[1,2]
  - However, there can be a significant treatment burden due to requirements for frequent application (e.g., twice daily) or preventative long-term treatment (e.g., twice weekly) due to rapid loss of response after stopping therapy[1–3]
  - Continuous, long-term therapy may also increase the risk of adverse events[1,2]
- There is a need for well-tolerated, efficacious, non-steroidal topicals suitable for all patients, with less frequent application, both for acute and long-term treatment, including as maintenance and with treatment-free intervals with a sustained response
- 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,[4] with no 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, and to reduce oxidative stress (**Figure 1**)[2]
- In two phase 3 AD trials, ADORING 1 and 2, 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[5]
  - The primary efficacy endpoint of Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) score of 0 or 1 and ≥2-grade improvement from baseline was highly statistically significant with tapinarof versus vehicle in both trials: 45.4% vs 13.9% and 46.4% vs 18.0% (both *P*<0.0001)
- In a 4-week maximal usage pharmacokinetics (MUPK) trial, tapinarof cream 1% QD was well tolerated with no-to-minimal systemic exposure in children aged 2–17 years, even with extensive AD (up to 90% body surface area [BSA]; mean 42.8%)[6]
- The ADORING phase 3 program in patients down to 2 years of age with AD evaluated the same dose and frequency as the adult psoriasis trials

Figure 1. Proposed Mechanism of Action of Tapinarof[2]



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

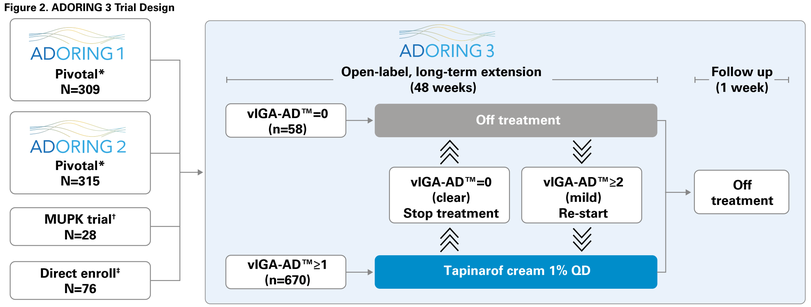
- To present skin clearance rates, treatment response off therapy, safety, and tolerability outcomes from ADORING 3, a 48-week, open-label, long-term extension trial

METHODS

Trial Design

- In the long-term extension trial, ADORING 3, eligible patients from ADORING 1 and 2, from a 4-week maximal usage pharmacokinetics trial, and tapinarof-naive patients with mild AD, or moderate or severe AD, that did not meet inclusion criteria for ADORING 1 or 2, received up to 48 weeks of open-label tapinarof cream 1% QD, followed by a 1-week follow-up period off-treatment (**Figure 2**)
- Patients were treated with tapinarof based on their vIGA-AD™ score:
  - **Complete disease clearance**: Patients entering ADORING 3 with any disease activity (vIGA-AD™≥1) were treated with tapinarof until complete disease clearance (vIGA-AD™=0 [clear])
  - **Treatment-free interval**: After achieving complete disease clearance, patients discontinued therapy and were monitored to determine the duration of the treatment-free interval (maintenance of clear or almost clear skin off treatment)
  - **Recapture of response and absence of tachyphylaxis**: Patients whose AD returned to mild (vIGA-AD™≥2) were re-treated until complete clearance was achieved again

Figure 2. ADORING 3 Trial Design



The vIGA-AD™ scale is copyright ©2017 Eli Lilly and Company – Used with the permission under a Creative Commons Attribution-NoDerivatives 4.0 International License. Patients could use moisturizers but only on non-lesional skin. *Patients were adults and children down to 2 years of age with a clinical diagnosis of AD by Hanifin and Rajka criteria,[7] a vIGA-AD™ score of ≥3 (moderate or severe), an EASI score of ≥6, and BSA involvement of 5–35% at screening and baseline. †Patients were adolescents and children aged 2–17 years with a clinical diagnosis of AD by Hanifin and Rajka criteria,[7] a vIGA-AD™ score of ≥3 (moderate or severe) and BSA involvement of ≥35% for children aged 2–11 years or ≥25% for adolescents aged 12–17 years. ‡Pediatric patients aged 2–17 years with mild AD (vIGA-AD™=2), or moderate or severe AD, that did not meet inclusion criteria for ADORING 1 and 2.
AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; MUPK, maximal usage pharmacokinetics; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Outcome Measures

Efficacy

- **Complete disease clearance**: The proportion of patients entering with or achieving complete disease clearance (vIGA-AD™=0)
- **Clear or almost clear skin**: The proportion of patients entering with or achieving a vIGA-AD™ score of 0 (clear) or 1 (almost clear)
- **Treatment-free interval**: Mean duration of the treatment-free interval, defined as maintenance of clear or almost clear skin (vIGA-AD™=0 or 1) off treatment, after first achieving complete disease clearance (vIGA-AD™=0) and discontinuing treatment
- **Maintenance of response**: Maintenance of clear or almost clear skin (vIGA-AD™=0 or 1) on either continuous or intermittent treatment (absence of tachyphylaxis) over 48 weeks

Safety and Tolerability

- Safety assessments included the incidence and frequency of treatment-emergent adverse events (TEAEs)
- Adverse events of special interest (AESI)
- Investigator- and patient- or parent/caregiver-assessed Local Tolerability Scale (LTS) scores

Statistical Analyses

- Efficacy endpoints were summarized descriptively using observed cases in the intention-to-treat population
- Safety assessments were summarized descriptively for the intention-to-treat population

RESULTS

ADORING 3 Baseline Patient Demographics and Disease Characteristics

- 728 patients enrolled in ADORING 3; this included 76 children who enrolled directly (**Table 1**)
  - Pediatric patients (aged 2–17 years) comprised 83.0% of the trial population
  - ~47% patients were non-white (White, 52.6%; Black or African American, 30.1%; Asian, 11.1%; other race categories, 4.4%)
- Patients had a wide spectrum of AD at baseline, from clear (vIGA-AD™=0) to severe (vIGA-AD™=4), depending on their route into ADORING 3 (**Table 1**)
- Tapinarof-treated patients from ADORING 1 and 2 had less severe disease at ADORING 3 baseline than vehicle-treated patients or patients from the other arms

Table 1. ADORING 3 Baseline Patient Demographics and Disease Characteristics

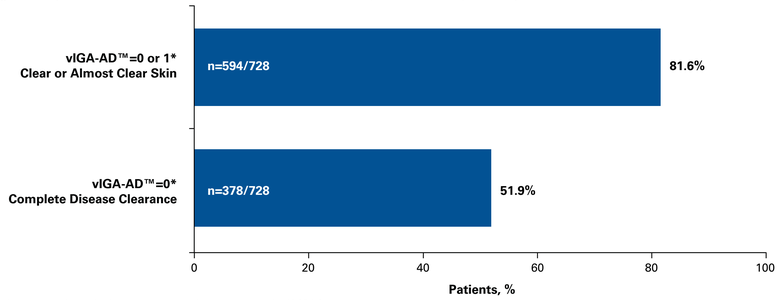
	ADORING 3				
	ADORING 1 and 2 (pivotal trials)		MUPK trial	Direct enroll	Overall
	Tapinarof cream 1% QD (n=431)	Vehicle QD (n=193)	Tapinarof cream 1% QD (n=28)	Tapinarof naïve (n=76)	Total (N=728)
Age, years, mean (SD)	16.1 (16.3)	16.4 (15.8)	8.8 (4.9)	7.9 (4.8)	15.0 (15.3)
Male, n (%)	201 (46.6)	85 (44.0)	19 (67.9)	34 (44.7)	339 (46.6)
vIGA-AD™, n (%)					
0 – Clear	51 (11.8)	6 (3.1)	1 (3.6)	0 (0.0)	58 (8.0)
1 – Almost clear	157 (36.4)	26 (13.5)	6 (21.4)	0 (0.0)	189 (26.0)
2 – Mild	153 (35.5)	63 (32.6)	12 (42.9)	40 (52.6)	268 (36.8)
3 – Moderate	69 (16.0)	88 (45.6)	9 (32.1)	16 (21.1)	182 (25.0)
4 – Severe	1 (0.2)	10 (5.2)	0 (0.0)	20 (26.3)	31 (4.3)
EASI, mean (SD)	3.3 (3.5)	8.2 (6.7)	9.2 (5.6)	17.6 (16.3)	6.3 (8.2)
BSA, %, mean (SD)	5.7 (6.5)	12.4 (10.7)	18.0 (11.7)	31.6 (27.8)	10.6 (14.3)

BSA, body surface area; EASI, Eczema Area and Severity Index; MUPK, maximal usage pharmacokinetics; QD, once daily; SD, standard deviation; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Patients Achieving Complete Disease Clearance (vIGA-AD™=0) and Clear or Almost Clear Skin (vIGA-AD™=0 or 1)

- Overall, 51.9% (n=378/728) of patients achieved complete disease clearance (vIGA-AD™=0 [clear]) at least once during the trial (**Figure 3**)
- In addition, 81.6% (n=594/728) achieved a vIGA-AD™ score of 0 (clear) or 1 (almost clear) at least once during the trial (**Figure 3**)

Figure 3. Proportion of Patients who Achieved Clear or Almost Clear Skin (vIGA-AD™=0 or 1) and Complete Disease Clearance (vIGA-AD™=0)



*Patients entering with or achieving the outcome at any time at least once during ADORING 3.
Intention-to-treat, observed cases.
QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Treatment-free Interval After Complete Disease Clearance

- After first achieving complete clearance and discontinuing treatment (n=378), the mean duration of the first treatment-free interval was 79.8 consecutive days off therapy (standard deviation [SD], 81.4 days)
- Recapture of response was demonstrated
  - After achieving vIGA-AD™=0 and discontinuing tapinarof, patients whose vIGA-AD™ score returned to ≥2 (mild) off treatment could regain vIGA-AD™=0 when re-treated
  - The overall mean duration of treatment-free intervals across the trial was 74.7 consecutive days (SD, 76.0 days), demonstrating the ability for a patient to achieve complete disease clearance repeatedly and experience almost 3 months off therapy

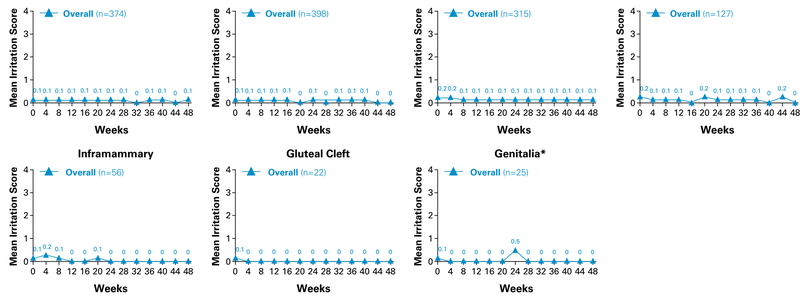
Maintenance of Response (No Tachyphylaxis)

- Tapinarof demonstrated maintenance of clear or almost clear skin (vIGA-AD™=0 or 1) on either continuous or intermittent therapy, with no tachyphylaxis, for up to 48 weeks

Tolerability

- Tapinarof cream was well tolerated, with mean patient or parent/caregiver evaluations indicating no or minimal burning/stinging and itching with long-term treatment for 48 weeks, even with intermittent treatment
- Mean investigator evaluations indicated that patients had no or minimal irritation (LTS=0) at all visits over the 48-week trial, with improvements in tolerability scores compared with ADORING 3 pre-treatment baseline
- Tapinarof was well tolerated locally, even when applied on sensitive skin across all evaluations for 48 weeks (**Figure 4**)
  - At baseline in ADORING 3, 72.5% of patients had AD affecting the head and neck region

Figure 4. Excellent Tolerability Across Sensitive Skin Areas in ADORING 3



Irritation (dryness, erythema, and peeling) at application sites was assessed by investigators at each trial visit on a 5-point scale ranging from 0 (no irritation) to 4 (very severe). Local Tolerability Scale scores were reported pre-dose at baseline and within 2 hours post dose at subsequent weeks.
*A mean irritation score of 0.5 was observed at Week 24 (mean of scores for all affected patients); this was due to one patient who had molluscum contagiosum affecting the genitalia, which the investigator determined was unrelated to treatment. QD, once daily.

Safety

- The most frequent TEAEs included folliculitis (12.1%), nasopharyngitis (6.9%), and upper respiratory tract infection (6.9%); trial discontinuations due to TEAEs were low (2.6%)
- AESI of follicular events, contact dermatitis, and headache were mostly mild or moderate and associated with low discontinuation rates (1.0%, 0.4%, and 0%, respectively)

CONCLUSIONS

- Tapinarof cream 1% QD monotherapy demonstrated a high rate of complete disease clearance (51.9%) in a diverse population of adults and children down to 2 years of age with AD
- After discontinuing tapinarof, patients maintained clear or almost clear skin for almost 3 consecutive months (~80 days)
- Clinical response did not decline over time with continuous or intermittent use of tapinarof monotherapy
- There were no new safety signals and low rates of trial discontinuations due to TEAEs
- Long-term application of tapinarof cream demonstrated favorable local tolerability, even on sensitive skin areas including the face and neck and on either continuous or intermittent therapy
- Tapinarof is a once-daily non-steroidal cream that is efficacious and well tolerated with long-term use in AD, and has the potential to be used without restrictions on duration of use, extent of BSA treated, or sites of application

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