Skin Clearance, Duration of Treatment-free Interval, 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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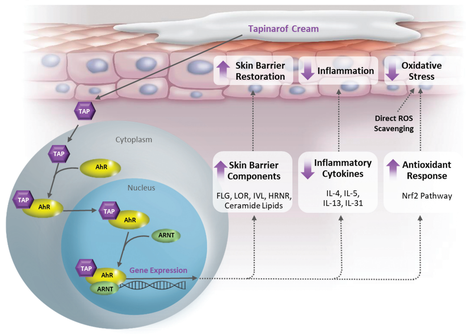
INTRODUCTION

- 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

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.

- Tapinarof (VTAMA®, Dermavant Sciences, an Organon Company) is a non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist, approved by the FDA for the treatment of AD in adults and children down to 2 years of age, and plaque psoriasis in adults, with no restrictions on duration, location, or extent of use[4]
- 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

OBJECTIVE

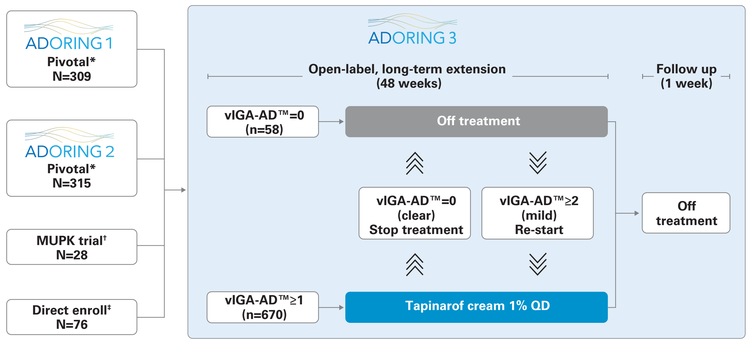
- To present skin clearance rates, treatment response off therapy, safety, and tolerability outcomes from ADORING 3, a 48-week, open-label, long-term extension trial

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

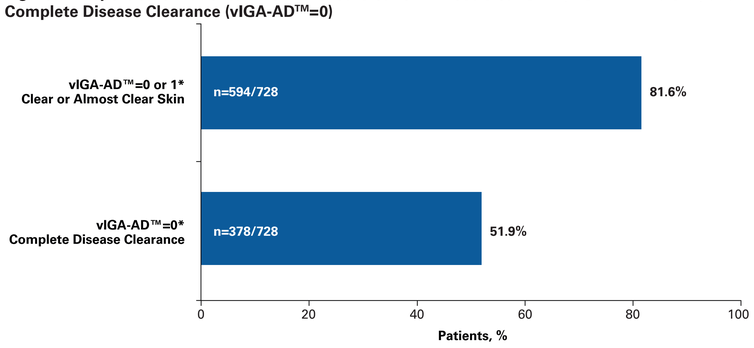
	ADORING 3				
	ADORING 1 and 2 (pivotal trials)		MUPK trial	Direct enroll	Overall
	Tapinarof cream 1% QD (n=431)	Vehicle QD (n=193)	Tapinarof cream 1% QD (n=28)	Tapinarof naïve (n=76)	Total (N=728)
Age, years, mean (SD)	16.1 (16.3)	16.4 (15.8)	8.8 (4.9)	7.9 (4.8)	15.0 (15.3)
Male, n (%)	201 (46.6)	85 (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

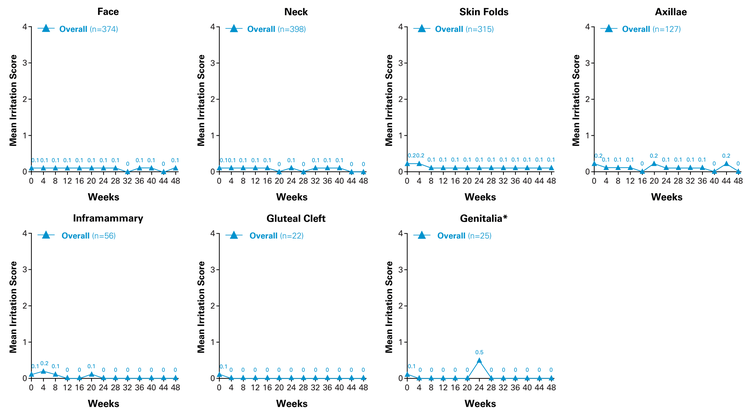
Maintenance of Response (No Tachyphylaxis)

- 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

REFERENCES

1. Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;70:338–351. 2. Eichenfield LF, et al. *J Dermatolog Treat.* 2024;35:2300354. 3. Ruer-Mulard M, et al. *Pediatr Dermatol.* 2009;26:551–558. 4. Dermavant Sciences. VTAMA® (tapinarof) cream, 1%: US Prescribing Information. 2024. Available at: https://www.vtama.com/PI/. Accessed January 2025. 5. Silverberg JI, et al. *J Am Acad Dermatol.* 2024;91:457–465.
6. Paller A, et al. Presentation at the RAD Conference, Washington, DC, USA, April 29-May 1, 2023. 7. Hanifin JM, Rajka G. *Acta Derm Venereol (Stockh).* 1980;92:236.

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