Tapinarof Cream 1% Once Daily: Maintenance of Low Disease Activity Including Pruritus Through End of the Treatment-free Interval in a Long-term Extension Trial in Patients Down to 2 Years of Age with Atopic Dermatitis

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OBJECTIVE

- To characterize disease activity at the end of treatment-free (remittive) intervals in the ADORING 3 long-term trial

CONCLUSIONS

- **In ADORING 3, after first achieving complete disease clearance (vIGA-AD™=0) and discontinuing treatment, a high proportion of patients demonstrated low disease activity, including itch, after ~80 consecutive days off treatment**
  - **Mean EASI scores at the end of treatment-free intervals were <4, indicating mild disease**
- **Tapinarof monotherapy induced complete disease clearance followed by prolonged treatment-free (remittive) intervals and low disease activity in adults and children down to 2 years of age with AD**
  - **Slow re-emergence of mild symptoms during treatment-free intervals is unlike most topicals, where a rapid disease rebound is often observed[1]**
- **Tapinarof is a once-daily, non-steroidal cream without restrictions on duration, extent, or location of use, and without the need for long-term maintenance therapy[2,5]**

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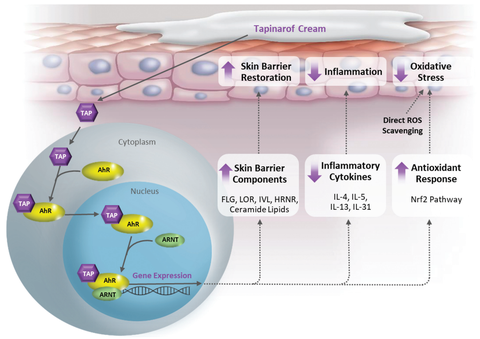
INTRODUCTION

- 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 atopic dermatitis (AD) in adults and children down to 2 years of age, and for the treatment of plaque psoriasis in adults[2]
- Tapinarof binds to and activates AhR to restore the skin barrier by upregulating key barrier components, downregulating pro-inflammatory cytokines associated with AD, and reducing oxidative stress (**Figure 1**)[1]
- Discontinuation of topical therapy for AD may be associated with rapid return of disease[3]
- Preventative maintenance with topicals may be a significant treatment burden for patients and caregivers[1,3,4]
- In the ADORING 3 long-term trial, adults and children with AD received tapinarof cream 1% once daily (QD)[5]
  - Patients entered with or achieved complete disease clearance (51.9%; Validated Investigator Global Assessment for Atopic Dermatitis™ [vIGA-AD™]=0) and clear or almost clear skin (81.6%; vIGA-AD™=0 or 1)[5]
  - After discontinuing tapinarof per protocol, patients maintained clear or almost clear skin for 79.8 (mean) consecutive days (first treatment-free interval)[5]

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



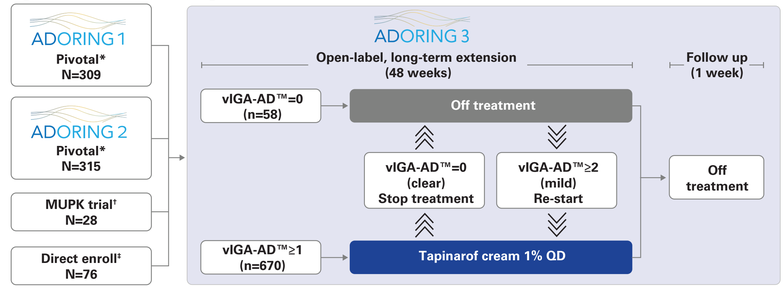
AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; HRNR, hornerin; IL, interleukin; IVL, involucrin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof.

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 (remittive effect, i.e., 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



 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,[6] 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,[6] 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™.

Endpoints

- Treatment-free interval is 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
- Endpoints assessed at the end of treatment-free intervals:
  - Proportion of patients with vIGA-AD™ scores of 0 (clear) to 4 (severe)
  - Mean Eczema Area and Severity Index (EASI) score and mean weekly Peak Pruritus Numerical Rating Scale (PP-NRS) score
- Patients could experience more than one treatment-free interval during ADORING 3
- Safety assessments included the incidence and frequency of treatment-emergent adverse events (TEAEs), including adverse events of special interest (AESI); and investigator- and patient- or parent/caregiver-assessed Local Tolerability Scale (LTS) scores

RESULTS

ADORING 3 Baseline Patient Demographics and Disease Characteristics

- 728 patients enrolled in ADORING 3 (**Table 1**)
  - Pediatric patients (aged 2–17 years) comprised 83.0% of the trial population, including 76 children who enrolled directly
  - ~47% patients were non-white (White, 52.6%; Black/African American, 30.1%; Asian, 11.1%; other races, 4.4%)
- Patients entered with vIGA-AD™ scores ranging from 0 (clear) to 4 (severe) depending on their entry route
  - In the parent pivotal trials, most patients had moderate or severe AD at baseline

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 naive (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)
PP-NRS, mean (SD)	2.5 (2.3)	4.2 (2.8)	3.0 (2.2)	6.2 (2.8)	3.4 (2.8)

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

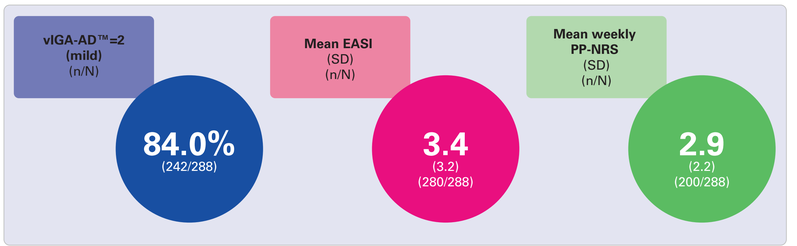
Maintenance of Low Disease Activity at the End of the First Treatment-free Interval

- After achieving complete disease clearance and discontinuing tapinarof, the mean duration of the first treatment-free interval was ~80 consecutive days off therapy
- Low disease activity was maintained at the end of the first treatment-free interval: 84.0% had vIGA-AD™=2; mean EASI=3.4 (standard deviation [SD]±3.2); mean weekly PP-NRS=2.9 (SD±2.2) (**Figure 3**)

Maintenance of Low Disease Activity at the End of all Treatment-free Intervals

- The overall mean duration of all treatment-free intervals was ~75 consecutive days (SD 76.0), demonstrating consistent ability to achieve complete clearance and maintain clear or almost clear skin
  - The mean duration of all treatment-free intervals may be an underestimate, due to the duration of some intervals being truncated prematurely by trial end (right censoring) and not by the need to restart treatment
- Similar low disease activity was seen at the end of subsequent treatment-free intervals

Figure 3. Low Disease Activity at the End of the First Treatment-free Interval with Tapinarof Cream 1% QD



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™.

Tolerability

- Tapinarof cream was well tolerated; the majority of patients or parents/caregivers reported no or minimal burning/stinging and itching with long-term treatment for 48 weeks, even with intermittent treatment[5]
- Investigators assessed that most 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 baseline[5]
- Tapinarof was well tolerated locally, even when applied on sensitive skin across all evaluations for 48 weeks[5]

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%)[5]
- 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)[5]