Rapid and Early Onset of Itch Relief with Tapinarof Cream 1% Once Daily in Two Pivotal Phase 3 Trials in Adults and Children Down to Two Years of Age with Atopic Dermatitis

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INTRODUCTION

- Pruritus is the most bothersome symptom for patients with atopic dermatitis (AD), and has a significant negative impact on health-related quality of life[1–4]
  - Pruritus can negatively affect physical activity, school attentiveness and learning, sleep, and psychological well-being
- Relief from core AD symptoms, such as pruritus, with sustained efficacy is a key factor in disease management
- Tapinarof (VTAMA®, Dermavant Sciences, Inc.) is a first-in-class, non-steroidal, topical aryl hydrocarbon receptor agonist approved by the Food and Drug Administration for the treatment of plaque psoriasis in adults,[5] and under investigation for the treatment of psoriasis in children down to 2 years of age
- Tapinarof cream 1% once daily (QD) demonstrated significant improvements in pruritus from the earliest visit at Week 2 through Week 12 in adults with mild to severe plaque psoriasis in the pivotal phase 3 trials, PSOARING 1 and 2[6]
- In a phase 2 trial in adults and adolescents with AD, tapinarof cream 1% QD demonstrated efficacy versus vehicle and was well tolerated[7,8]
- In ADORING 1 and 2 (NCT05014568, NCT05032859), two pivotal identical phase 3, double-blind, randomized, vehicle-controlled trials, tapinarof cream 1% QD demonstrated highly statistically significant efficacy and was well tolerated in adults and children down to 2 years of age with AD[9]
- The Peak Pruritus Numerical Rating Scale (PP-NRS) is a well-defined and reliable patient-reported outcome measure for evaluating the intensity of pruritus in the past 24 hours[10]
  - In the PSOARING and ADORING trials, the minimal clinically important difference for improvement in PP-NRS (reduction in pruritus) was 4 points; however, a 2-point difference may also be considered clinically meaningful[10–12]

OBJECTIVE

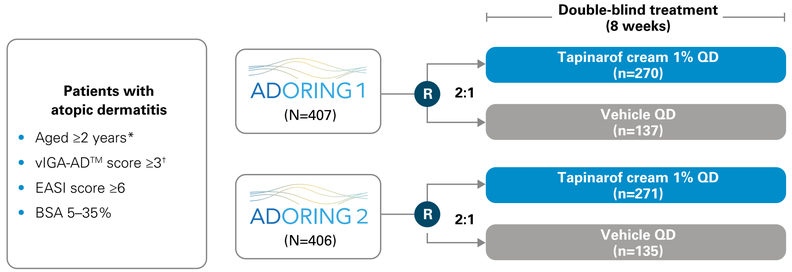
- To evaluate time to onset of itch relief in the pivotal phase 3 trials with tapinarof cream 1% QD in the treatment of adults and children down to 2 years of age with AD

MATERIALS AND METHODS

Trial Design

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

Figure 1. 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 (≥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

- Itch relief was evaluated as mean change in PP-NRS score (daily and by visit [Weeks 1, 2, 4, and 8]) from baseline through Week 8
  - The PP-NRS score is evaluated using an 11-point scale, where 0 indicates "no itch" and 10 indicates "worst imaginable itch" within the last 24 hours
  - Daily PP-NRS scores were recorded in diaries
  - Patients aged ≥12 years self-completed the PP-NRS, while caregivers completed it for children aged <12 years
- Safety assessments included the 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

- The analyses included 541 tapinarof-treated and 272 vehicle-treated patients (**Table 1**):
  - Mean baseline PP-NRS scores were similar across treatment groups in ADORING 1 and 2

Table 1. Baseline Demographics and Disease Characteristics

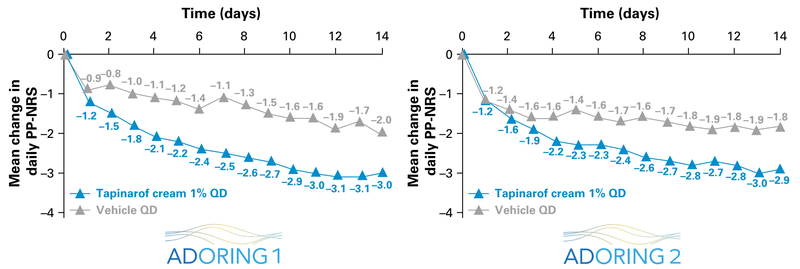
	ADORING 1		ADORING 2	
	Tapinarof cream 1% QD (n=270)	Vehicle QD (n=137)	Tapinarof cream 1% QD (n=271)	Vehicle QD (n=135)
Age, years, mean (SD)	15.6 (16.6)	15.6 (16.5)	16.4 (16.2)	16.7 (16.1)
Male, n (%)	130 (48.1)	66 (48.2)	117 (43.2)	58 (43.0)
Weight, kg, mean (SD)	46.7 (27.3)	47.7 (27.7)	51.5 (29.1)	54.0 (32.0)
BMI, kg/m^2, mean (SD)	21.4 (6.3)	22.1 (6.6)	22.7 (7.5)	23.3 (8.3)
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)

BMI, body mass index; 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™.

Mean Change in Daily PP-NRS Score from Baseline

- Greater reductions in mean (standard deviation) daily PP-NRS scores were observed with tapinarof cream versus vehicle as early as Day 1, 24 hours after initial application in ADORING 1 (–1.2 [2.2] vs –0.9 [2.0]) and Day 2 in ADORING 2 (–1.6 [2.4] vs –1.4 [2.1]) (**Figure 2**)
  - The 95% confidence intervals for the daily mean difference in PP-NRS scores excluded 0 starting at Day 2 in ADORING 1 (–1.1, –0.2) and Day 4 in ADORING 2 (–1.2, –0.2)
- Improvements in daily PP-NRS scores with tapinarof cream versus vehicle continued through the first 2 weeks (Day 14; –3.0 [2.8] vs –2.0 [2.4] and –2.9 [2.7] vs –1.8 [2.6]), and through Week 8 for both trials

Figure 2. Rapid Reduction in Pruritus with Tapinarof Cream 1% QD as Early as 24 Hours After First Application, the First Assessment

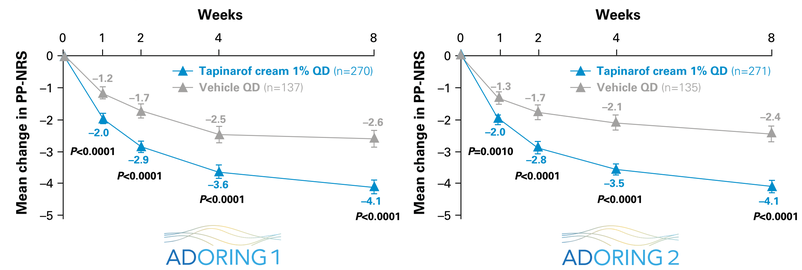


Intention-to-treat, observed cases. Time is days after first application.
PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

Mean Change in PP-NRS Score from Baseline at Weeks 1, 2, 4, and 8

- Statistically significant reductions in mean PP-NRS scores were demonstrated with tapinarof cream versus vehicle as early as Week 1 (–2.0 vs –1.2 [P<0.0001] and –2.0 vs –1.3 [P=0.0010]), the earliest measured time point, in ADORING 1 and 2, respectively (**Figure 3**)
- Significant improvements in mean PP-NRS scores with tapinarof versus vehicle were observed for all visits through Week 8 (ADORING 1, –4.1 vs –2.6 and ADORING 2, –4.1 vs –2.4; both P<0.0001),
  - The minimal clinically important difference of a ≥4-point reduction in mean PP-NRS score from baseline was surpassed in the tapinarof groups at Week 8

Figure 3. Rapid and Significant Reduction in Pruritus with Tapinarof Cream 1% QD from Baseline Through End of Trial

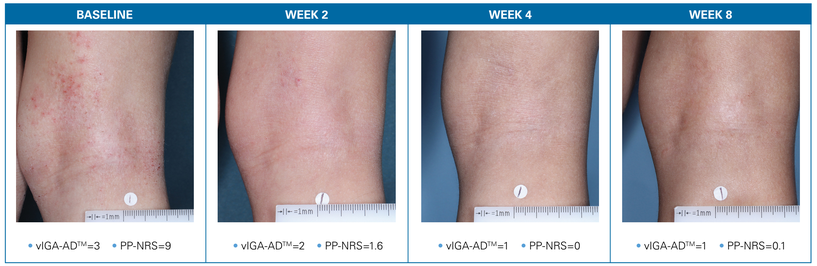


Intention-to-treat, observed cases. Least squares mean (standard error).
PP-NRS, Peak Pruritus Numerical Rating Scale, QD, once daily.

Patient who Achieved the Primary Endpoint and an Itch-free State at Week 4

- The patient (aged 3 years) in **Figure 4** had moderate AD (Validated Investigator Global Assessment for Atopic Dermatitis™ [vIGA-AD™]=3) affecting the back of the leg at baseline. At Week 4, the primary endpoint (vIGA-AD™ score of clear [0] or almost clear [1] and ≥2-grade improvement) was achieved
- Severe itch was reported by the patient at baseline (PP-NRS=9); reduction in itch surpassed the minimal clinically important ≥4-point improvement by Week 2, and continued to improve to a PP-NRS score of 0 (an itch-free state) at Week 4

Figure 4. Achievement of Primary Endpoint and Complete Resolution of Itch by Week 4 in a 3-Year-Old Patient with AD 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.
AD, atopic dermatitis; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Safety

- Most TEAEs were mild or moderate, and consistent with previous trials
- Trial discontinuation rates due to TEAEs were lower with tapinarof versus vehicle (ADORING 1: 1.9% vs 3.6%; ADORING 2: 1.5% vs 3.0%, respectively)

CONCLUSIONS

- Tapinarof cream 1% QD demonstrated rapid pruritus relief from 24 hours after initial application, with improvements increasing through Week 8 in both trials in adults and children down to 2 years with AD
  - Significant improvements in pruritis versus vehicle were seen as early as Week 1 and continued through Week 8
  - The minimal clinically important difference of ≥4 points was exceeded in the tapinarof groups at Week 8
- Tapinarof was well tolerated; TEAEs were consistent with those seen in previous trials, and trial discontinuation rates were lower with tapinarof versus vehicle
- Tapinarof is a non-steroidal topical medication with the potential to be used for the treatment of patients down to 2 years of age with AD, without restrictions on duration, extent, or sites of application

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ACKNOWLEDGMENTS

This trial was funded by Dermavant Sciences, Inc. The authors thank the participating investigators, patients and their families, and colleagues involved in the conduct of the trial.
E.S. reports grants and fees for participation as a consultant and principal investigator from Eli Lilly and Company, LEO Pharma, Pfizer, and Regeneron; grants for participation as a principal investigator from Galderma and Merck & Co.; and fees for consultant services from AbbVie, Boehringer Ingelheim, Dermavant Sciences, Inc., Incyte, Forte Bio, Pierre Fabre Dermo, and Sanofi Genzyme. J.I.S. has received honoraria as a consultant and/or advisory board member for AbbVie, Alamar, Aldena, Amgen, AOBiome, Arcutis, Arena, Asana, Aslan, BioMX, Biosion, Bodewell, Boehringer Ingelheim, Bristol Myers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant Sciences, Inc., Dermira, Dermtech, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, LEO Pharma, Menlo, Novartis, Optum, Pfizer, RAPT, Recludix, Regeneron, Sanofi-Genzyme, Shaperon, TARGET-RWE, Union, and UpToDate; speaker for AbbVie, Eli Lilly, LEO Pharma, Pfizer, Regeneron, and Sanofi-Genzyme; and institution received grants from Galderma, Incyte, and Pfizer. R.B. has served as a consultant/investigator/advisory board member for AbbVie, Alumis, Almirall, Amgen, AnaptysBio, Arcutis, Aristea, Bausch Health, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, Escalier, Janssen, Kyowa Kirin, LEO Pharma, Nimbus, Novartis, Pfizer, Regeneron, Sienna, and UCB Biopharma; and is an employee and shareholder of Innovaderm Research. L.S.G. has served as a consultant, and/or has received payment for the development of educational presentations, and/or has received grants from Amgen, Arcutis, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, LEO Pharma, Ortho Dermatologics, Pfizer, and UCB Biopharma. A.W.A. has served as a research investigator and/or scientific advisor for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant Sciences, Inc., Dermira, EPI, Incyte, Janssen, LEO Pharma, Eli Lilly, Modmed, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sun Pharma, Sanofi, and UCB Biopharma. A.A.H. has received research support paid to the medical school from AbbVie, Arcutis, Dermavant Sciences Inc., and Pfizer; and honoraria received from Arcutis, Dermavant Sciences, Inc., Galderma, GSK, Incyte, LEO Pharma, Novan, Ortho Dermatologics (as part of a Data Safety Monitoring Board), Pfizer, Sanofi Regeneron, Sun Pharma, and Verrica. R.T.S. has served as a consultant and/or has received payment for the development of educational presentations, and/or has received grants from Abbott, AbbVie, Arcutis, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, Incyte, Janssen, Pfizer, Regeneron, and Sanofi Genzyme. J.R.J. is a clinical investigator for the ADORING trials; an employee of SUNY Downstate Health Sciences University, which received compensation from Dermavant Sciences, Inc. for trial participation; and an investigator, advisor, and/or consultant for Amgen, Arcutis, Galderma, Incyte, Pfizer, Regeneron, and Verrica. P.M.B., D.S.R., S.C.P., and A.M.T. are employees of Dermavant Sciences, Inc., with stock options. L.F.E. has served as a consultant, advisor, or investigator for AbbVie, Amgen, Arcutis, Aslan, Castle Biosciences, Dermavant Sciences, Inc., Eli Lilly, Forté, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Target, and UCB Pharma.

Editorial and medical writing support under the guidance of the authors was provided by ApotheCom, UK, and was funded by Dermavant Sciences, Inc., in accordance with Good Publication Practice (GPP) guidelines (*Ann Intern Med.* 2022;175:1298–1304).

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