Tapinarof Cream 1% Once Daily for the Treatment of Extensive Atopic Dermatitis in Adolescents and Children: 4-Week Maximal-Use Trial

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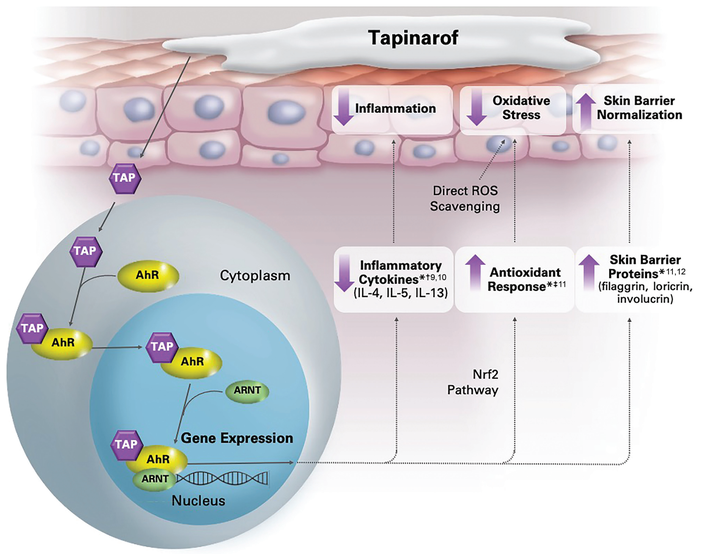
INTRODUCTION

- Atopic dermatitis (AD) is a chronic, relapsing and remitting inflammatory skin disease, characterized by intense pruritus and eczematous lesions. AD can substantially impact patients' sleep and quality of life[1–4]
- There is a need for efficacious, non-steroidal topical therapies for AD, without restrictions relating to duration, extent of use, and application sites
- Tapinarof (VTAMA®; Dermavant Sciences, Inc., USA) is a first-in-class, non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist approved by the Food and Drug Administration for the treatment of plaque psoriasis in adults, and under investigation for the treatment of plaque psoriasis in children down to 2 years of age and for AD in adults and children down to 2 years of age[5]
- Tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two identical, 12-week, phase 3 trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980)[6]
  - Efficacy continued to improve beyond the 12-week trials in PSOARING 3 (NCT04053387), the long-term extension trial[7]
- Tapinarof specifically binds to and activates the AhR, a ligand-dependent transcription factor. This leads to downregulation of inflammatory Th2 cytokines (including interleukin [IL]-4, IL-5, and IL-13), increase in expression of skin barrier proteins related to keratinocyte differentiation (including filaggrin, loricrin, and involucrin), and antioxidant activity[8–12] (**Figure 1**)

Figure 1. Potential Mechanisms of Action of Tapinarof in Atopic Dermatitis



*Demonstrated *in vitro*. †Demonstrated in mouse models. ‡Demonstrated *ex vivo*.
AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; IL, interleukin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof.

- Tapinarof cream 1% QD demonstrated significant efficacy versus vehicle and was well tolerated in adults and adolescents with moderate to severe AD in a 12-week phase 2b trial (NCT02564055)[13,14]
  - Efficacy was generally maintained through the last trial visit, 4 weeks after completing treatment[13,14]
- In a phase 1 pharmacokinetics (PK) evaluation of tapinarof cream 1% in adults (n=6) with moderate to severe AD, there were low levels of systemic absorption that decreased from baseline to Day 21 of assessment (mean 1.2 ng [10^{-9}]/mL [Day 1] and 0.15 ng/mL [Day 21])[15]
- Tapinarof cream 1% has also been assessed in a 4-week, maximal-use PK trial in adults with extensive plaque psoriasis; tapinarof was well tolerated with limited systemic exposure, even in patients with up to 46% body surface area (BSA) affected[16]

OBJECTIVES

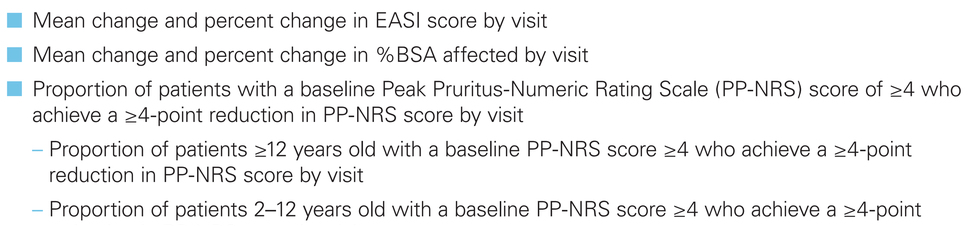
- To present the 4-week, maximal-use AD trial design and patient baseline characteristics
- To assess the safety, tolerability, PK, and efficacy of tapinarof cream 1% QD in adolescents and children with extensive AD in the 4-week, maximal-use trial

METHODS

Trial Design

- In this phase 2a, multicenter, open-label trial (NCT05186805), adolescents and children with extensive AD will receive tapinarof cream 1% QD for 27 days (**Figure 2**)
- Patients or caregivers will be instructed to apply a thin layer of tapinarof cream, sufficient to cover each lesion
- Tapinarof PK will be assessed at Days 1 (baseline) and 28
  - The screening blood sample will be used for baseline pre-dose PK assessment if the patient is enrolled
- Key inclusion and exclusion criteria are shown in **Table 1**
- Eligible patients completing this trial will have the option to enroll in an open-label, long-term extension trial (NCT05142774) to receive up to an additional 48 weeks of tapinarof treatment

Figure 2. Maximal-Use PK Trial Design in Adolescents and Children with AD



AD, atopic dermatitis; PK, pharmacokinetics; QD, once daily.

Table 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Males and females aged 2–17 years	Significant dermatologic or inflammatory condition and concurrent skin lesions in the treatment area or pruritus due to conditions other than AD
A clinical diagnosis of AD by Hanifin and Rajka criteria[17]	Patients who would not be considered suitable for topical therapy
%BSA involvement ≥25% for adolescents (12–17 years) or ≥35% for children (2–11 years)	Use of any prohibited medication or procedure within the indicated period before the baseline visit
A vIGA-AD™ score of ≥3 at screening and baseline (pre-dosing)	History of sensitivity to the trial medications
AD present for ≥6 months for patients aged 6–17 years or 3 months for patients aged 2–5 years	Previous known participation in a clinical trial with tapinarof

AD, atopic dermatitis; BSA, body surface area; vIGA-AD™, validated Investigator Global Assessment for Atopic Dermatitis™.

Primary Endpoints

- Incidence, frequency, and nature of adverse events (AEs) and serious AEs
- Change from baseline in laboratory values and vital signs
- Mean Investigator-assessed Local Tolerability Scale scores by visit (overall and sensitive areas)
- Tapinarof plasma PK parameters on Day 1, including:
  - Area under the plasma concentration versus time curve from baseline to the last quantifiable concentration (AUC_{0-last})
  - Maximum plasma concentration (C_{max})
  - Time to maximum plasma concentration (t_{max})
  - Time of last quantifiable concentration (t_{last})
- Tapinarof plasma concentration on Day 28

Secondary Endpoints

- Change in validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) score by visit
- Proportion of patients with a vIGA-AD™ score of clear (0) or almost clear (1) by visit
- Proportion of patients with ≥50%, ≥75%, and ≥90% improvement in Eczema Area and Severity Index (EASI) score by visit
- Mean change and percent change in EASI score by visit
- Mean change and percent change in %BSA affected by visit
- Proportion of patients with a baseline Peak Pruritus-Numeric Rating Scale (PP-NRS) score of ≥4 who achieve a ≥4-point reduction in PP-NRS score by visit
  - Proportion of patients ≥12 years old with a baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in PP-NRS score by visit
  - Proportion of patients 2–12 years old with a baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in PP-NRS score by visit
  - Mean change in PP-NRS score at each visit by age group

Statistical Analyses

- Safety analyses will include all patients who received at least one application of tapinarof
- Analyses of efficacy endpoints will be based upon the safety population

RESULTS

Baseline Patient Demographics and Disease Characteristics

- Overall, 36 patients were enrolled at nine sites in the US and Canada
- Patients' baseline demographics and disease characteristics are shown in **Table 2**
  - Equal proportions of patients (33.3% [12/36]) were young children (2–6 years), children (7–11 years), and adolescents (12–17 years)
  - Most patients (77.8%) across the three groups had a vIGA-AD™ score of 3 (moderate)
  - Overall mean (standard deviation [SD]) EASI score was 23.8 (9.2), with a range of 8.2–49.6 indicating moderate to severe AD
  - Overall mean (SD) %BSA affected was 42.8% (15.1%), with a range of 26%–90%

Table 2. Baseline Demographics and Disease Characteristics

	Tapinarof cream 1% QD			
	Young children 2–6 years (n=12)	Children 7–11 years (n=12)	Adolescents 12–17 years (n=12)	Overall (N=36)
Age, years, mean (SD)	3.7 (1.4)	8.2 (1.4)	14.8 (1.8)	8.9 (4.9)
Male, n (%)	9 (75.0)	7 (58.3)	8 (66.7)	24 (66.7)
vIGA-AD™ of 3 (moderate), n (%)	8 (66.7)	9 (75.0)	11 (91.7)	28 (77.8)
vIGA-AD™ of 4 (severe), n (%)	4 (33.3)	3 (25.0)	1 (8.3)	8 (22.2)
EASI, mean (SD)	30.2 (8.6)	21.0 (10.0)	20.3 (5.5)	23.8 (9.2)
BSA affected, %, mean (SD)	52.4 (19.1)	42.0 (10.0)	33.9 (8.6)	42.8 (15.1)

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

CONCLUSIONS

- In a phase 2b trial, tapinarof cream 1% QD demonstrated significant efficacy versus vehicle and was well tolerated in adolescents and adults with moderate to severe AD[13,14]
- Tapinarof cream 1% has shown minimal systemic absorption in adults with AD or psoriasis, even with extensive BSA affected of up to 46%[15,16]
- This maximal-use PK trial will assess the safety, tolerability, PK, and efficacy of tapinarof cream 1% QD in 36 adolescents and children down to 2 years of age with extensive, moderate to severe AD
- In addition, tapinarof cream 1% QD is being evaluated for the treatment of AD in adults and children down to 2 years of age in three phase 3 clinical trials (ADORING 1 [NCT05014568], ADORING 2 [NCT05032859], and ADORING 3 [NCT05142774])

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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. A.P. is an investigator (without personal compensation) for AbbVie, AnaptysBio, Dermavant Sciences Inc., Eli Lilly, Incyte, Janssen, Krystal, Regeneron, and UCB Pharma, a consultant (with honoraria) for AbbVie, Acrotech, Almirall, Amgen, Amryt, Arcutis, Arena, Azitra, BioCryst, BiomX, Boehringer Ingelheim, Botanix, Bridgebio, Castle Biosciences, Catawba, Eli Lilly, Exicure, Gilead, Incyte, Janssen, Kamari, Leo, Novartis, Pfizer, Pierre Fabre, RAPT, Regeneron, Sanofi/Genzyme, Seanergy, UCB Pharma, Union, and on the Data Safety Monitoring Board for AbbVie, Abeona, Bausch, Bristol Myers Squibb, Galderma, Inmed, and Novan. A.A.H. has received grants/honoraria/ research support from AbbVie, Almirall, Arcutis, Dermavant Sciences Inc., GSK (as part of a Data Safety Monitoring Board), Incyte, LEO Pharma, Mayne, Novan, and Verrica. J.E.J., P.M.B., D.S.R., and S.C.P. are employees of Dermavant Sciences, Inc., with stock options. 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 (GPP3) guidelines (*Ann Intern Med.* 2015;163:461–464).

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