Title: Tapinarof Cream 1% Once Daily for the Treatment of Moderate to Severe Atopic Dermatitis in Children and Adults: the Pivotal Phase 3 ADORING Clinical Program

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Abstract

Introduction: There is a need for efficacious non-steroidal topical therapies for atopic dermatitis (AD) without restrictions on duration, extent of use, or application site. Tapinarof is a novel therapeutic aryl hydrocarbon receptor modulating agent (TAMA) in development for the treatment of psoriasis and AD. Tapinarof specifically binds to and activates the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor. This leads to the downregulation of inflammatory Th2 cytokines (including IL-4, IL-5 and IL-13), increase in skin barrier proteins related to keratinocyte differentiation, including filaggrin, loricrin, and involucrin, and increased antioxidant activity. In a 12-week Phase 2b trial, tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle and was well tolerated in adolescents and adult patients with moderate to severe AD. Furthermore, efficacy was generally maintained through the last study visit, 4 weeks after completing treatment, warranting further investigation of a potential remittive effect.

Objective: To assess the efficacy and safety of tapinarof cream 1% QD in children and adults with moderate to severe AD in two pivotal Phase 3 trials (ADORING 1 and 2) and a long-term extension Phase 3 trial (ADORING 3).

Methods: ADORING 1 and 2 are two identical, Phase 3, multicenter, double-blind, vehicle-controlled, randomized trials aiming to recruit 800 patients overall (Figure 1). Male or female patients aged ≥2 years, with a clinical diagnosis of AD, a validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD) score ≥3, and body surface area (BSA) involvement ≥5% and ≤35% (excluding the scalp) are randomized 2:1 to tapinarof cream 1% or vehicle cream QD for 8 weeks. The primary efficacy endpoint of ADORING 1 and 2 is the proportion of patients with a vIGA-AD score of clear (0) or almost clear (1) and ≥2-grade improvement from baseline at Week 8. Secondary efficacy endpoints include assessments on Eczema Area and Severity Index (EASI75 and EASI90), %BSA affected, and Peak Pruritus-Numeric Rating Scale scores from baseline at Week 8.

Patients who complete ADORING 1 or 2 will have the option to enroll in the 48-week, open-label, long-term extension trial, ADORING 3 (Figure 2). In ADORING 3, patients entering with vIGA-AD score ≥1 will receive tapinarof until complete disease clearance (vIGA-AD=0). Patients entering with, or achieving, vIGA-AD=0 will discontinue treatment and be monitored for duration of remittive effect: off-therapy maintenance of vIGA-AD score of clear (0) or almost clear (1). Patients with disease
worsening (vIGA-AD≥2) are re-treated with tapinarof until vIGA-AD=0. Patients will be followed for durability of response off-therapy (absence of tachyphylaxis).

Across all trials, safety assessments include adverse events and patient- and investigator-rated local tolerability.

**Discussion:** This comprehensive Phase 3 clinical trial program will assess the efficacy, safety, tolerability, durability, and potential remittive effect of tapinarof cream 1% QD for the treatment of moderate to severe AD in more than 800 patients down to 2 years of age.

**Figure 1. Trial Design: ADORING 1 and 2**

*Patients with moderate to severe atopic dermatitis (N=800)*
- Aged ≥2 years*
- vIGA-AD™ score ≥3†
- BSA ≥5% – ≤35%

* A minimum of approximately 15% of patients will be enrolled into each of the following age groups: 2–6 years, 7–11 years, 12–17 years, and ≥18 years. Adults (≥18 years) will comprise a maximum of approximately 20% of enrolled patients. † Patients with a vIGA-AD score of 4 (severe) will represent a minimum of approximately 10% of the total randomized population; the remainder of the population will have a vIGA-AD score of 3 (moderate).

**BSA, body surface area; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis™; QD, once daily; R, randomized.**

**Figure 2. Trial Design: ADORING 3**

*N=up to ~960*
- Eligible patients from ADORING 1 and ADORING 2*
- Eligible patients from Maximal Use PK trial
- ~125 additional patients aged 2 to <18 years enrolling directly into ADORING 3*

*Patients electing not to participate in ADORING 3 will attend follow-up visit 1 week after completion of the treatment period in ADORING 1 or 2. * Patients with a vIGA-AD score of ≥3 (moderate) and %BSA affected ≥40% at screening and baseline (pre-randomization), or patients with a vIGA-AD score of 2 (mild) at screening and baseline (pre-randomization) regardless of %BSA affected, who were screened for ADORING 1 or 2 but did not meet vIGA-AD and/or BSA requirements.

vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis™; PK, pharmacokinetics; QD, once daily.