SYNOPSIS

- Atopic dermatitis (AD) is a chronic, relapsing, and remitting inflammatory skin disease characterized by intense pruritus and eczematous lesions that can substantially impact sleep and quality of life.
- In the US, approximately 16.5 million adults and 9.6 million children under the age of 18 years have AD.
- There is a need for efficacious non-steroidal topical therapies for AD without restrictions on duration, extent or site of use.
- Tapinarof is a novel, first-in-class, small-molecule topical therapeutic ary lhydrocarbon receptor modulator associated with TAM formation in development for the treatment of AD and psoriasis. Tapinarof has demonstrated efficacy and a remittive effect in Phase 3 clinical trials for the treatment of plaque psoriasis: PERO 1 (NCT03956355), PERO 2 (NCT03983980), and PERO 3 (NCT04053387).
- 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 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.

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

METHODS

Trial Design: ADORING 1 and 2

- ADORING 1 and ADORING 2 are two identical designed, Phase 3, multicenter (US and Canada), double-blind, vehicle-controlled randomized trials (Figure 2).
- Following a 30-day screening period, patients aged ≥2 years old with a vIGA-AD score ≥3 (moderate to severe) and a percentage body surface area (%BSA) affected of ≥5 – ≤35% will be randomized 2:1 to tapinarof cream 1% QD or vehicle QD for 8 weeks.

Figure 2. Trial Design: ADORING 1 and ADORING 2

**Primary efficacy endpoint** is the proportion of patients with a vIGA-AD score of 0 (clear) or 1 (almost clear) and ≥2-grade improvement from baseline at Week 8.

**Secondary efficacy endpoints** from baseline at Week 8:
- Proportion who achieve ≥75% improvement in Eczema Area and Severity Index (EASI75).
- Mean change in %BSA affected.
- Proportion of patients aged ≥12 years with a baseline Peak Pruritus Numeric Rating Scale (PP-NRS) score ≥4, who achieve a 4-point reduction in the PP-NRS.

**Safety and Tolerability Endpoints**:
- Incidence, frequency, and nature of treatment-emergent adverse events and serious adverse events.
- Laboratory values, vital signs, and electrocardiograms.
- Patient- and investigator-assessed local tolerability.

**Primary efficacy endpoint** requires randomization of a minimum of 150 patients with AD who will be enrolled into each of the following age groups: 2-6 years, 7-11 years, 12-17 years, and ≥18 years. Subjects ≤18 years old will receive a maximum of approximately 20% of enrolled patients. Patients with a vIGA-AD score of 3 labeled will represent a minimum of approximately 10% of the total randomized population; the remainder of the population will have a vIGA-AD score of 0 (clear) or 1 (almost clear).

**Statistical Analysis**

- Efficacy endpoints analyzed from the intention-to-treat (ITT) population using multiple imputation for missing data. Safety endpoints analyzed based on the safety population, defined as all randomized subjects who receive at least 1 application of study drug.

**Objective**

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

**METHODS (continued)**

Trial Design: ADORING 3 (continued)

- If disease worsening occurs (defined as a vIGA-AD score ≥2 [mild]), tapinarof 1% QD will be started and continued until a vIGA-AD score of 0 (clear) is achieved.
- Treatment and re-treatment will continue until the end of the study.

Endpoints and Statistical Analysis: ADORING 3

- **Safety and tolerability endpoints**: Adverse events, patient- and investigator-assessed local tolerability, laboratory values, vital signs, and physical exam.
- **Efficacy endpoints include**: Complete disease clearance (Proportion of patients achieving vIGA-AD of 0 (clear))
- Remittive effect: Duration of efficacy maintenance, vIGA-AD of 0 (clear) or 1 (almost clear) while off therapy, after achieving complete disease clearance (vIGA-AD = 0)
- Response: Proportion of patients who enter the trial with a vIGA-AD ≥2 (mild) and achieve a vIGA-AD of 0 (clear) or almost clear (1)
- Efficacy endpoints will be based on the ITT population using observed case and last observation carried forward analyses. Safety endpoint analysis will be based on the ITT population.

CONCLUSIONS

- 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 patients down to 2 years of age.

REFERENCES

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8. Dermavant DOF (DMV-5151 AD Mouse Model: Oct 2016);

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