Investigator- and patient-rated local tolerability in phase 3 trials of topical roflumilast in patients with psoriasis, seborrheic dermatitis, and atopic dermatitis

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Background: Formulating a topical medication that does not irritate the skin is an important factor contributing to patient treatment adherence and satisfaction. Many topical prescription products use penetration enhancers (including propylene glycol, polyethylene glycol, and ethanol) to overcome barrier properties of the skin. However, these excipients may irritate the skin causing tolerability reactions such as burning and stinging, which can reduce patient treatment adherence. Topical roflumilast is a highly potent (Kd~0.7 nM) phosphodiesterase 4 inhibitor formulated as a water-based cream or foam that does not contain penetration enhancers or fragrances.

Objective: We present prospectively assessed investigator- and patient-rated local tolerability from Phase 3 trials of topical roflumilast for patients with psoriasis (DERMIS-1, DERMIS-2, ARRECTOR), seborrheic dermatitis (SD; STRATUM), and atopic dermatitis (AD; INTEGUMENT-1, INTEGUMENT-2).

Methods: Patients were randomized to apply topical roflumilast (DERMIS: 0.3% cream; ARRECTOR and STRATUM: 0.3% foam; INTEGUMENT: 0.15% cream) or vehicle once daily for 8 weeks (DERMIS, ARRECTOR, and STRATUM) or 4 weeks (INTEGUMENT). Investigators assessed local tolerability on an 8-point scale (0 [no evidence of irritation] to 7 [strong reaction spreading beyond application site]) in the clinic before investigational product (IP) application. Patients reported local tolerability on a 4-point scale (0 [none: no sensation] to 3 [severe: hot, tingling/stinging sensation that has
caused definite discomfort]) in the clinic 10-15 minutes after IP application. Tolerability was also assessed by reviewing documented adverse events.

**Results:** As assessed by investigators, ≥96.5% of patients in the roflumilast-treated groups had no evidence of irritation at the application site across all trials at all timepoints. Patient-rated local tolerability was favorable and improved with treatment: across all trials, 1% of roflumilast-treated patients reported a score of 3 (severe; defined as a “hot tingling/stinging sensation that has caused definite discomfort”) after the first application (day 1) and <1% at each subsequent assessment. Rates of adverse events, including those at the application site, were low for all trials.

**Conclusions:** Roflumilast cream and foam formulations demonstrated favorable local tolerability based on investigator- and patient-rated assessments in patients with psoriasis, SD, and AD, including application to sensitive areas such as the face and intertriginous areas.

**Keywords:** Atopic dermatitis, local tolerability, psoriasis, seborrheic dermatitis, topical roflumilast