A Phase 2, Randomized, Multicenter, Double-Blind, Active- and Vehicle- Controlled Parallel-group Study Evaluating the Efficacy, Safety, and Tolerability of Products TWIN High and TWIN Low for the Treatment of Acne Vulgaris for 12 Weeks

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Introduction: Current acne guidelines recommend both retinoids and benzoyl peroxide (BPO) as first line agents. Previously, all-trans-retinoic-acid (ATRA) and benzoyl peroxide (BPO) have not been able to be combined because of incompatibility. TWIN is a cream containing encapsulated BPO (E-BPO) and encapsulated ATRA (E-ATRA), which we have shown in prior studies to be stable and compatible. TWIN was developed as a fixed-dose combination in a single container closure system, having one strength of BPO and two strengths of ATRA (E-ATRA High and E-ATRA Low).

Objective: The primary objective of this study was to determine numerical superiority in efficacy of Products TWIN High and TWIN Low as compared to their respective active components and the vehicle. The co-primary efficacy endpoints were Success rate at week 12 (defined as 'clear' or 'almost clear' on a 5-point Investigator's Global Assessment [IGA]) and an absolute change from baseline in inflammatory and non-inflammatory facial lesion counts at week 12.

Study Design: This was a randomized, double-blind, multicenter, parallel group, active- and vehicle-controlled study of the efficacy, tolerability, and safety of TWIN High and TWIN Low for the treatment of acne vulgaris. 726 subjects randomized, age 9 and older, with moderate to severe facial acne (rated 3 or 4 on IGA) in ratio of 1:1:1:1:1:1 to receive once daily treatment with TWIN High, TWIN Low, E-ATRA High, E-ATRA Low, E-BPO and vehicle cream. Efficacy assessments included facial lesion counts, IGA and Patient Reported Outcomes (PRO) including Patient-Reported Evaluation of Facial Acne (PRE-FACE). Safety assessments included reported adverse events, an investigator cutaneous safety assessment (pigmentation, erythema and scaling) and a local tolerability assessment (itching, burning, and stinging).

Results: TWIN Low was numerically more successful than E-ATRA Low and E-BPO for all three co-primary efficacy endpoints and TWIN High was numerically more successful than E-ATRA High and E-BPO in IGA and in reducing inflammatory lesions. TWIN High achieved unprecedented success in getting patients to the state of 'clear' or 'almost clear' at week 12 (39.7% for TWIN High, 27,4% for TWIN Low and 12.3% for the vehicle). Both TWIN High and TWIN Low exhibited statistically significant improvements ($p \leq 0.006$) in all pre-defined co-primary efficacy endpoints, in comparison to the vehicle. The decreases from baseline in mean inflammatory lesions count at week 8 (absolute and percent change) was statistically significantly greater for both TWIN concentrations than for the vehicle ($p<0.003$). PRO of facial acne showed a clear trend for improvement over time with TWIN High and TWIN Low treatments compared to vehicle. Both combinations were safe and well-tolerated with expected dermal incidences of application site dryness, exfoliation (scaling) and pain (mild burning and stinging) typical for the individual components of the two formulations.

Conclusions: Both encapsulated ATRA and encapsulated BPO contributed to the efficacy of TWIN Low and TWIN High. Both TWIN Low and TWIN High are good candidates for pivotal clinical studies with onset as early as week