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Exploratory Exposure Response (E-R) Analysis of ESK-001, An allosteric oral TYK2 inhibitor, in Patients with Psoriasis

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Introduction & Objectives: ESK-001** is a highly selective, oral, allosteric inhibitor of tyrosine kinase 2 (TYK2) that targets cytokine-mediated signaling in psoriasis (PsO) and other immune-mediated diseases. ESK-001 was tested in multiple Phase 1 trials and in a Phase 2 program in psoriasis consisting of a 12-week, randomized, placebo-controlled trial (STRIDE, NCT05600036) and an ongoing open-label extension trial (OLE, NCT05739435). Data from these trials were used to develop a population pharmacokinetic (popPK) model to characterize the ESK-001 PK and an exploratory E-R analysis to understand the relationship between exposure and skin improvements (PASI) as well as severity reduction (sPGA) to inform Phase 3 dose selection.

Materials & Methods: The popPK analysis incorporated data from 127 healthy volunteers (HV) and 185 patients with PsO. A limited set of covariates (body weight, fed status) were evaluated for their effects on ESK-001 exposure. The popPK model derived the 24-hour average concentration (Cavg) values for each patient, enabling exploration of the E-R relationship between ESK-001 exposure (Cavg) and efficacy outcomes PASI and sPGA. The Cavg of ESK-001 was categorized into four groups (referred to as bins), where the first bin represented subjects receiving placebo (0 exposure), and the remaining 3 bins were based on tertiles of exposure from low to high. Visual predictive graphs were used to assess this correlation. For each group, the proportion of patients with PASI or sPGA was plotted over time and extended to evaluate the effects of longer-term administration up to 40.

Results: The collected data was best fitted to a two-compartment model with first-order absorption and linear elimination. Body weight had a significant effect on PK. The E-R analysis revealed a strong, positive relationship between exposure and improvement in PASI and sPGA scores. For a given exposure level, there was also a clear positive relationship between time on treatment and PASI and sPGA improvement.

Conclusion: The popPK analysis indicated similar exposures and linear PK in both HV and patients with PsO. The E-R analysis revealed a strong positive correlation between exposure and the key efficacy endpoints. Also, there was a positive correlation between time on treatment and the key efficacy endpoints. The maximum response occurred at the highest dose of 40 mg BID.