Exploratory Exposure-response (E-R) Analysis of ESK-001, an Allosteric Oral TYK2 Inhibitor, in Patients with Plaque Psoriasis

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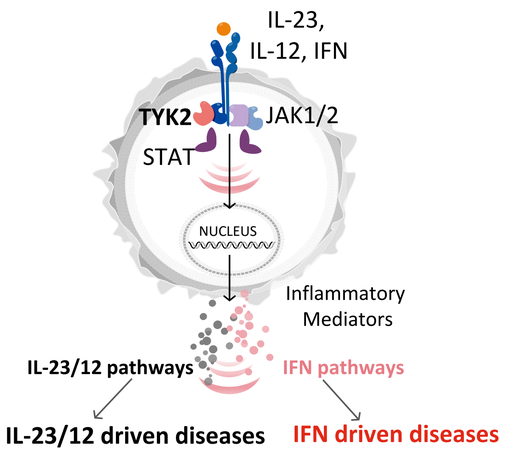
Background

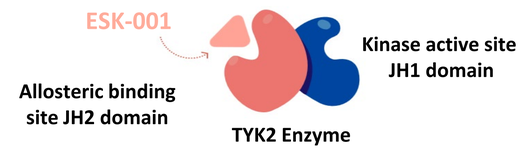
Tyrosine Kinase 2 (TYK2) is central to key pathways in many immune-mediated diseases

- TYK2 mediates signaling from key proinflammatory cytokines, including **IL-23, IL-12, and type I IFN**, through STAT phosphorylation.
- Human TYK2 loss-of-function genetic variants protect from immune-mediated diseases, including plaque psoriasis (PsO). [1]
- TYK2 is an established therapeutic target, with TYK2 inhibitors being recently approved for PsO.[2]



ESK-001 is an oral, highly selective allosteric inhibitor of TYK2 being developed for immune-mediated diseases, including plaque PsO

- Potent and intrinsically selective for TYK2, without observed JAK-related pharmacology.
- Allosterically inhibits TYK2, with maximal target inhibition maintained over 24 hours with 40 mg BID dose (both IC50 and IC90).



Objectives

- To develop a **population pharmacokinetic (popPK) model** to characterize the ESK-001 PK, using data from three Phase I studies and one Phase II study (STRIDE study followed by an open-label extension [OLE] study).
- To perform an **exploratory exposure-response (E-R) analysis** to understand the relationship between ESK-001 exposure and efficacy endpoints: skin improvements (PASI), severity reduction (sPGA), and change in the disease's body surface area (%BSA) through Week 12 (STRIDE study) and through Week 40 (OLE study) **to inform Phase III dose selection**.

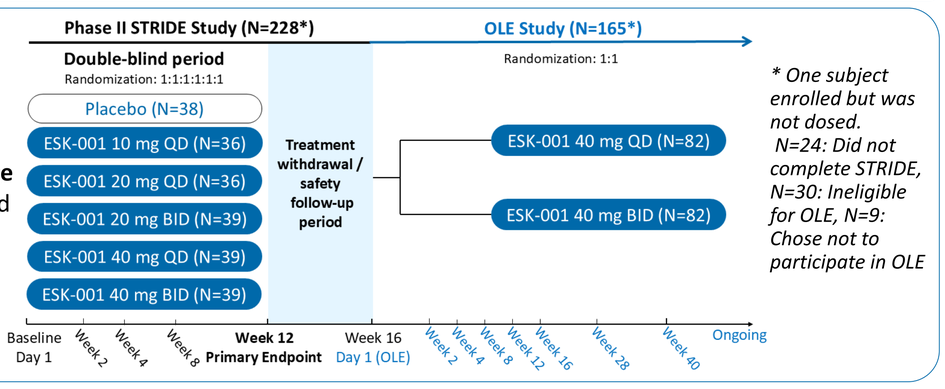
Methods

Study Design

- ***STRIDE study*** = a 12-week randomized, double-blinded, placebo-controlled Phase II study of ESK-001 in adults with moderate-to-severe plaque PsO *(NCT05600036).*
  - *Subjects with plaque PsO were randomized to receive one of the 5 doses of ESK-001 or placebo, given orally for 12 weeks.*
  - *Study design and eligibility criteria were presented previously. [3]*
  - *Efficacy endpoints were assessed at baseline and Week 2, 4, 8, and 12.*
- ***OLE study*** = an ongoing open-label extension study with ESK-001 *(NCT05739435).*
  - *This study enrolled 95% of eligible subjects who completed the STRIDE study.*
  - *Efficacy and safety endpoints were assessed at multiple time points.*

E-R Analysis

- The 24-hour average concentration of ESK-001 **(Cavg)** was used to assess effects on efficacy endpoints.
- Efficacy endpoints were **PASI, sPGA, %BSA change** (% of subjects with <1, <3, and <10% BSA involved with PsO) .
- **Exploratory graphs** visualized the effects of exposure and time on each efficacy endpoint.



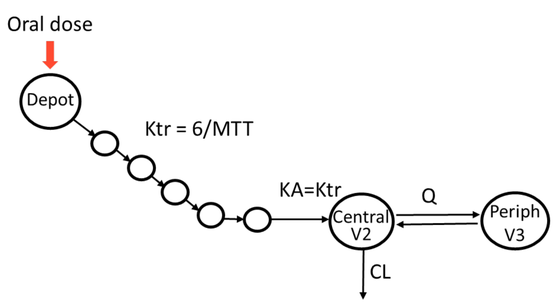
** One subject enrolled but was not dosed. N=24: Did not complete STRIDE, N=30: Ineligible for OLE, N=9: Chose not to participate in OLE*

Results

Development of PopPK model

- Data from 121 healthy subjects and 185 subjects with PsO.
- Developed and verified using data from three Phase I studies and one Phase II study:
  - *Phase I studies: single- (SAD) and multiple-ascending dose (MAD) (ACTRN12621000011886)[4], multiple dose (MD) (NCT05431634)[4], relative bioavailability and food effect study (NTC05330858).*
  - *Phase II study: STRIDE study.*
- The collected data best fit a **two-compartment model** with first-order absorption and linear elimination.
- Absorption was represented as a series of five transit compartments with relatively rapid transitions.
- The model accurately reflected the observed data, showing both the overall trend and the differences between individuals.

The PopPK modeling diagram



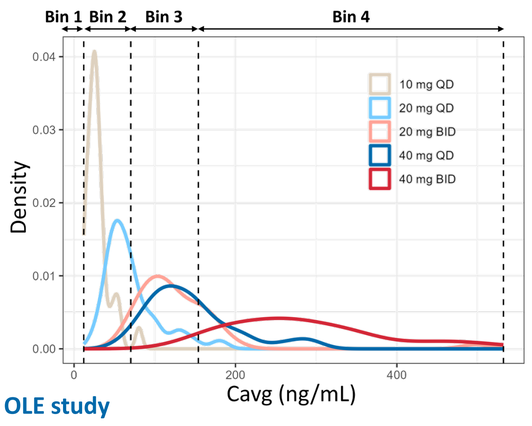
Ktr = transition rate constant; KA = absorption rate constant; Q = intercompartmental clearance; MTT = mean transit time, V = volume of distribution, CL = clearance

- PopPK model was used to derive the 24-hour **Cavg** values for each subject in the STRIDE study.

Cavg as matrix to assess the exploratory E-R analysis

- Cavg of ESK-001 was categorized into four exposure groups or **bins** (Bin 1 = placebo, Bin 2-4 = tertiles of exposure from low to high; number of subjects is about equal for each bin).
- STRIDE Week 12 Cavg probability distribution by exposure bins showed that **40 mg BID had substantially higher exposures** overall and thus, would be expected to have the strongest efficacy.

STRIDE Week 12 Cavg probability distribution by bins



Efficacy

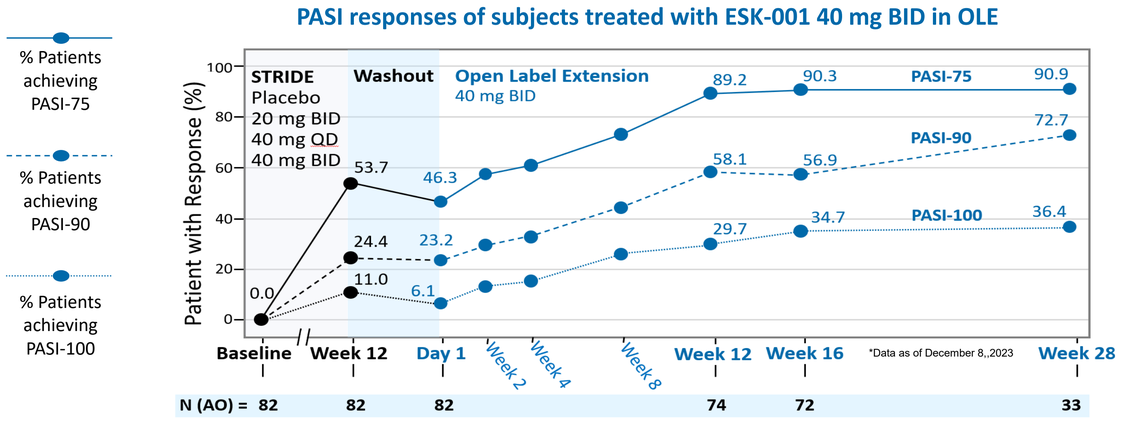
STRIDE study

- Primary and all secondary endpoints (PASI, sPGA, %BSA) were met at 40 mg BID dose.
- Clear dose-dependent effect was observed.
- Maximal TYK2 inhibition was achieved at the highest dose (40 mg BID) at Week 12.
- Well tolerated with no concerning safety signals.

OLE study

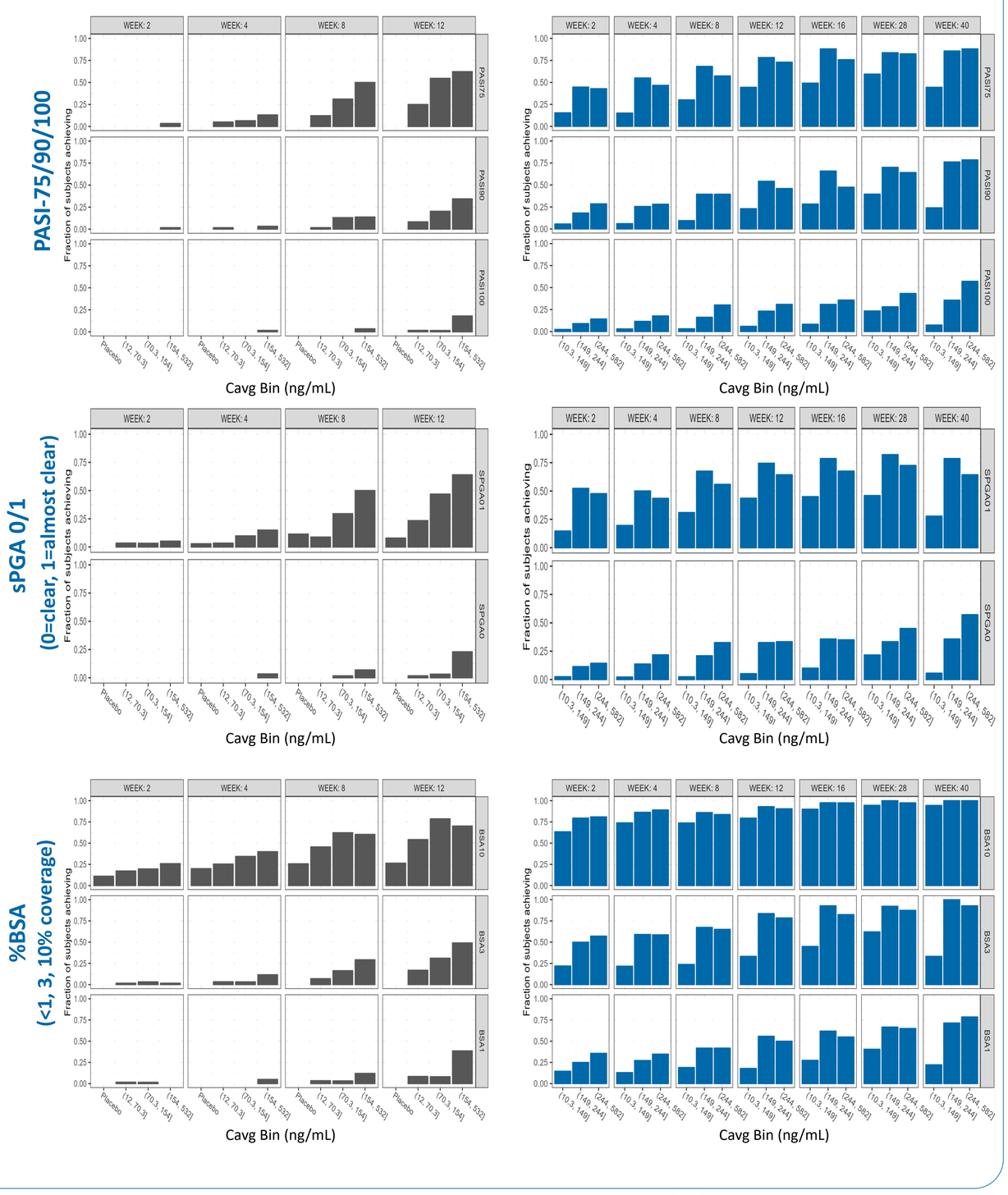
- Continued ESK-001 exposure achieved substantial increases in efficacy responses.

PASI responses of subjects treated with ESK-001 40 mg BID in OLE



E-R analysis revealed a strong, positive relationship between exposure and efficacy endpoints

- The exploratory E-R analyses demonstrated an **exposure-dependent increase in key efficacy endpoints** PASI-75, sPGA 0/1, and %BSA change responses.
- The **PASI, sPGA, and %BSA scores continued to improve during the OLE** compared to Week 12 STRIDE results, indicating that **longer treatment periods at the highest dose led to better responses** with the same drug exposure.
- The **maximal response** was observed **at the highest dose of 40 mg BID**.



Conclusions

- The PopPK model
  - The model **accurately reflected the observed data**, indicated similar ESK-001 exposures and linear PK in both healthy subjects and subjects with plaque PsO.
- The E-R analysis
  - Showed a **strong correlation between ESK-001 exposure and key efficacy endpoints**.
  - **Prolonged exposure** at the same dose **substantially improved efficacy responses.**
  - **Maximal therapeutic response** was achieved **at 40 mg BID dose**, which maintained **a safety profile comparable to lower tested doses**. Hence, 40 mg BID dose **was selected** for the upcoming **Phase III studies in subjects with moderate-to-severe plaque PsO**.
  - Additional information on the efficacy, safety, and tolerability of STRIDE and OLE studies are available at this congress: **Poster P1004,** and **Presentation at Free Communication 6, Section 5769**, respectively.

References

1) Dendrou et al. Sci Transl Med, 2016
2) Jensen et al. EBioMedicine, 2023
3) AAD 2024 Annual Meeting, S026 – Late-Breaking Research: Session 1; Efficacy and Safety of ESK-001, a highly selective oral TYK2 inhibitor, in a Phase 2 study in adults with moderate-to-severe plaque psoriasis (STRIDE) by Kim A Papp, MD, FAAD
4) https://aad-eposters.s3.amazonaws.com/AM2024/poster/53968/Pharmacokinetic+and+Pharmacodynamic+Characteristics+of+ESK-001+an+Oral+Allosteric+TYK2+Inhibitor+in+Phase+1+Healthy+Volunteer+Trials.pdf