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Pharmacokinetics, Safety, and Tolerability of ESK-001, an Allosteric TYK2 Inhibitor for Plaque Psoriasis: Evaluation in Asian Populations Compared to Caucasians

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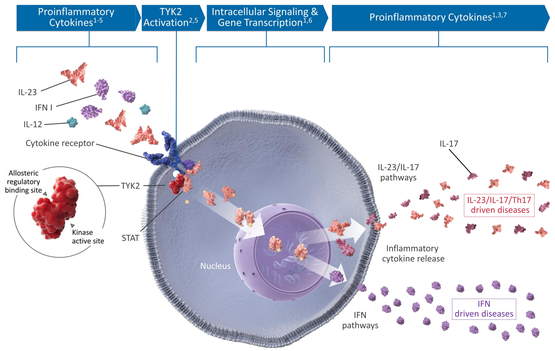
Background



- **ESK-001 is an oral, next-generation tyrosine kinase 2 (TYK2) inhibitor** that delivers maximal target inhibition and reduces off-target effects to correct immune dysregulation across the spectrum of diseases driven by proinflammatory mediators, including IL-23, IL-17, and IFN I.[1,8]
- Combining convenient oral administration with highly selective targeting, it delivers maximal inhibition while minimizing off-target binding and associated adverse effects.[1]
- ESK-001 is currently being investigated for the treatment of plaque psoriasis and systemic lupus erythematosus. Potential future indications include psoriatic arthritis, inflammatory bowel disease, and other chronic inflammatory conditions.[9-11]

Objectives

- **Primary objective:** To evaluate the **pharmacokinetics (PK) of ESK-001** in Japanese, Chinese, and Caucasian healthy participants following single and multiple doses.
- **Secondary objective:** To assess the **safety and tolerability of ESK-001** in Japanese, Chinese, and Caucasian healthy participants following single and multiple doses.

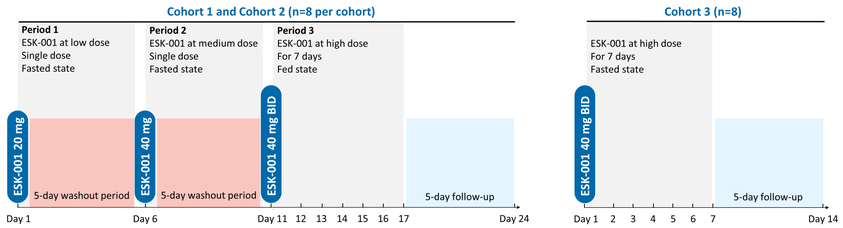
Methods

Study Design

- ***This Phase I, single-center, open-label study*** enrolled a total of 24 healthy participants (8 per cohort) into 1 of 3 cohorts.
  ESK-001 was administered as film-coated immediate-release tablets containing 20 mg of ESK-001.
  - ***Cohort 1 and Cohort 2***
    - ✓ 3 sequential treatment periods (**Period 1:** 20 mg single dose on Day 1; **Period 2:** 40 mg single dose on Day 6; **Period 3:** 40 mg BID for 7 days), each separated by 5-day washout periods.
    - ✓ Blood samples collected on Days 1 and 2 for Period 1, on Days 6 and 7 for Period 2, and from Day 11 to Day 19 for Period 3.
    - ✓ Enrolled participants of Japanese and Chinese ancestry in Cohort 1 and Cohort 2, respectively.
  - ***Cohort 3 (reference)***
    - ✓ 1 treatment period (40 mg BID for 7 days). *Note: Several previous ESK-001 studies (ClinPharm, STRIDE) have provided Caucasian data. Therefore, Cohort 3 was directly given the expected therapeutic dose (ie, 40 mg BID).*
    - ✓ Blood samples collected from Day 1 to Day 9.
    - ✓ Enrolled participants of Caucasian ancestry.

PK Analyses

- ***PK parameters*** were calculated from concentrations of ESK-001 (and its main metabolite) in plasma using noncompartmental analysis methods.



Conclusions

No clinically relevant differences in PK parameters, safety, or tolerability were observed across ethnicities, supporting the conclusion that **the same therapeutic dosing regimen can be safely used for psoriasis treatment in Asian populations**.

Results

Demographics

	Cohort 1: Japanese (n=8)	Cohort 2: Chinese (n=8)	Cohort 3: Caucasian (n=8)	Overall (n=24)
Age (years), mean (SD)	42.6 (9.3)	38.4 (8.2)	45.5 (11.8)	42.2 (9.9)
Sex, n (%)				
Female/male	1 (12.5)/7 (87.5)	0 (0.0)/8 (100.0)	5 (62.5)/3 (37.5)	6 (25.0)/18 (75.0)
Ethnicity, n (%)				
Hispanic or Latino	0 (0.0)	0 (0.0)	2 (25.0)	2 (8.3)
Not Hispanic or Latino	8 (100.0)	8 (100.0)	6 (75.0)	22 (91.7)
Height (cm), mean (SD)	170.2 (8.2)	170.0 (3.0)	168.6 (7.7)	169.6 (6.4)
Weight (kg), mean (SD)	66.4 (10.2)	72.6 (9.7)	80.4 (8.1)	73.1 (10.7)

PK evaluation

PK evaluation of ESK-001 and its main metabolite following 7th day of BID 40 mg oral administration of ESK-001

	Cohort 1: Japanese (n=8)	Cohort 2: Chinese (n=8)	Cohort 3: Caucasian (n=8)
$C_{max,\ ss}$ (ng/mL), GMean (CV%)	502 (25.1)	586 (24.3)	531 (11.1)
$AUC_{0\text{-}\tau,\ ss}$ (hr*ng/mL), GMean (CV%)	3,410 (22.7)	4,580 (18.3)	3,530 (9.5)
$T_{max,\ ss}$ (hr), Median (min, max)	2.8 (2.0, 4.0)	3.0 (1.0, 6.0)	1.0 (1.0, 2.0)
$t_{1/2,\ ss}$ (hr), GMean (CV%)	7.6 (20.4)	8.4 (13.4)	9.1 (17.0)
CL/F (L/hr), GMean (CV%)	10.8 (22.7)	8.0 (18.3)	10.4 (9.5)
V_d/F (L), GMean (CV%)	118.0 (35.9)	97.4 (26.5)	138.0 (17.7)
BWC_{max} (ng/mL/mg/kg), GMean (CV%)	895 (32.5)	1,140 (14.3)	1,140 (12.6)
$BWAUC_{0\text{-}\tau,\ ss}$ (hr*ng/mL/mg/kg), GMean (CV%)	6,080 (26.9)	8,950 (9.8)	7,540 (11.4)
R_{ac}, GMean (CV%)	2.10 (96.3)	2.48 (38.0)	2.09 (34.7)
MRC_{max} main metabolite, GMean (CV%)	2.65 (33.6)	2.91 (23.1)	2.60 (24.9)
MRAUC main metabolite, GMean (CV%)	3.56 (30.3)	3.69 (24.9)	3.73 (15.8)

$C_{max,ss}$ = maximum plasma concentration on Day 7 at steady state; $AUC_{0\text{-}\tau,\ ss}$ = area under the concentration-time curve for the dosing interval at steady state; $T_{max,ss}$= time needed to reach C_{max} postdose on Day 7 at steady state; $t_{1/2,ss}$ = terminal elimination half-life on Day 7 at steady state; CL/F = apparent clearance; V_d/F = volume of distribution; BWC_{max} = body weight normalized C_{max}; BWAUC = body weight normalized AUC; R_{ac} = accumulation ratio; MRC_{max} = metabolite to parent ratio based on C_{max}; MRAUC = metabolite to parent ratio based on AUC; GMean = geometric mean; CV% = coefficient of variance as percentage.
The descriptive statistics shown are not log-transformed.

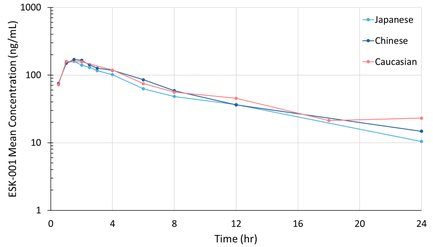
PK profiles of ESK-001 were similar across different ethnicities

- Rapid absorption, steady elimination, and dose-proportional exposure across all ethnicities.
- Food slightly delayed T_{max} but did not significantly affect exposure.
- In general, plasma exposures (as C_{max} and AUC) of ESK-001 and its main metabolite were comparable across ethnicities, as were elimination half-lives ($t_{1/2}$), clearance (CL/F), and volume of distribution (V_d/F).

PK profiles

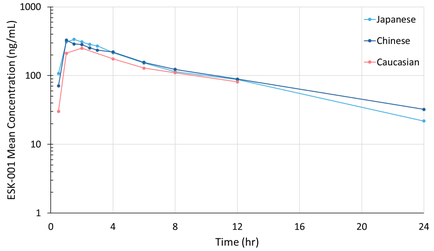
Plasma ESK-001 concentration-time profiles following single oral administration of ESK-001 (semi-log scale)

20 mg single dose (fasted state)

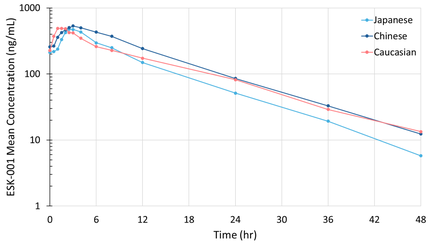


Note: In 20 mg & 40 mg single dose graphs, Caucasian data was plotted with the data from another study (ie, ESK-001-003 20 mg QD/40 mg BID multiple dosing study).

40 mg single dose (fasted state)



Plasma ESK-001 concentration-time profiles following 7th day of BID 40 mg oral administration of ESK-001 (semi-log scale)



Note: Japanese & Chinese BID Day 7 PK profile is fed state and Caucasian BID Day 7 PK profile is fasted state dosing data.

Safety and tolerability

	ESK-001 20 mg		ESK-001 40 mg		ESK-001 40 mg BID		
	Cohort 1: Japanese (n=8)	Cohort 2: Chinese (n=8)	Cohort 1: Japanese (n=8)	Cohort 2: Chinese (n=8)	Cohort 1: Japanese (n=8)	Cohort 2: Chinese (n=8)	Cohort 3: Caucasian (n=8)
Any TEAE, n (%)	1 (12.5)	2 (25.0)	5 (62.5)	1 (12.5)	4 (50.0)	5 (62.5)	6 (75.0)
At least 1 TEAE Grade 2, n (%)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	1 (12.5)	0 (0.0)	4 (50.0)
At least 1 TEAE Grade ≥3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE related to study medication	1 (12.5)	1 (12.5)	5 (62.5)	1 (12.5)	4 (50.0)	4 (50.0)	6 (75.0)
TEAEs leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)*
TEAEs leading to study medication discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)*

*Moderate headache that resolved with routine treatment (paracetamol) within 4 days of discontinuation of ESK-001; ** Dizziness postural.

Safety profiles of ESK-001 were similar across different ethnicities

- ESK-001 was generally well tolerated at all evaluated doses.
- Most treatment-emergent adverse events (TEAEs) were mild, with some instances of moderate TEAEs.
- TEAEs related to ESK-001 were generally limited to expected TEAEs also observed during earlier clinical studies with ESK-001.
- Most common TEAEs were:
  - Headache (Cohort 1: n=6; Cohort 2: n=3; Cohort 3: n=6)
  - Somnolence (Cohort 1: n=4; Cohort 2: n=0; Cohort 3: n=0)
  - Dizziness (Cohort 1: n=1; Cohort 2: n=2; Cohort 3: n=1**)
- No severe, life-threatening, or fatal TEAEs.
- No serious TEAEs or deaths.

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