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Pharmacokinetic and Pharmacodynamic Characteristics of ESK-001, an Oral Allosteric TYK2 inhibitor, in Phase 1 Healthy Volunteer Trials

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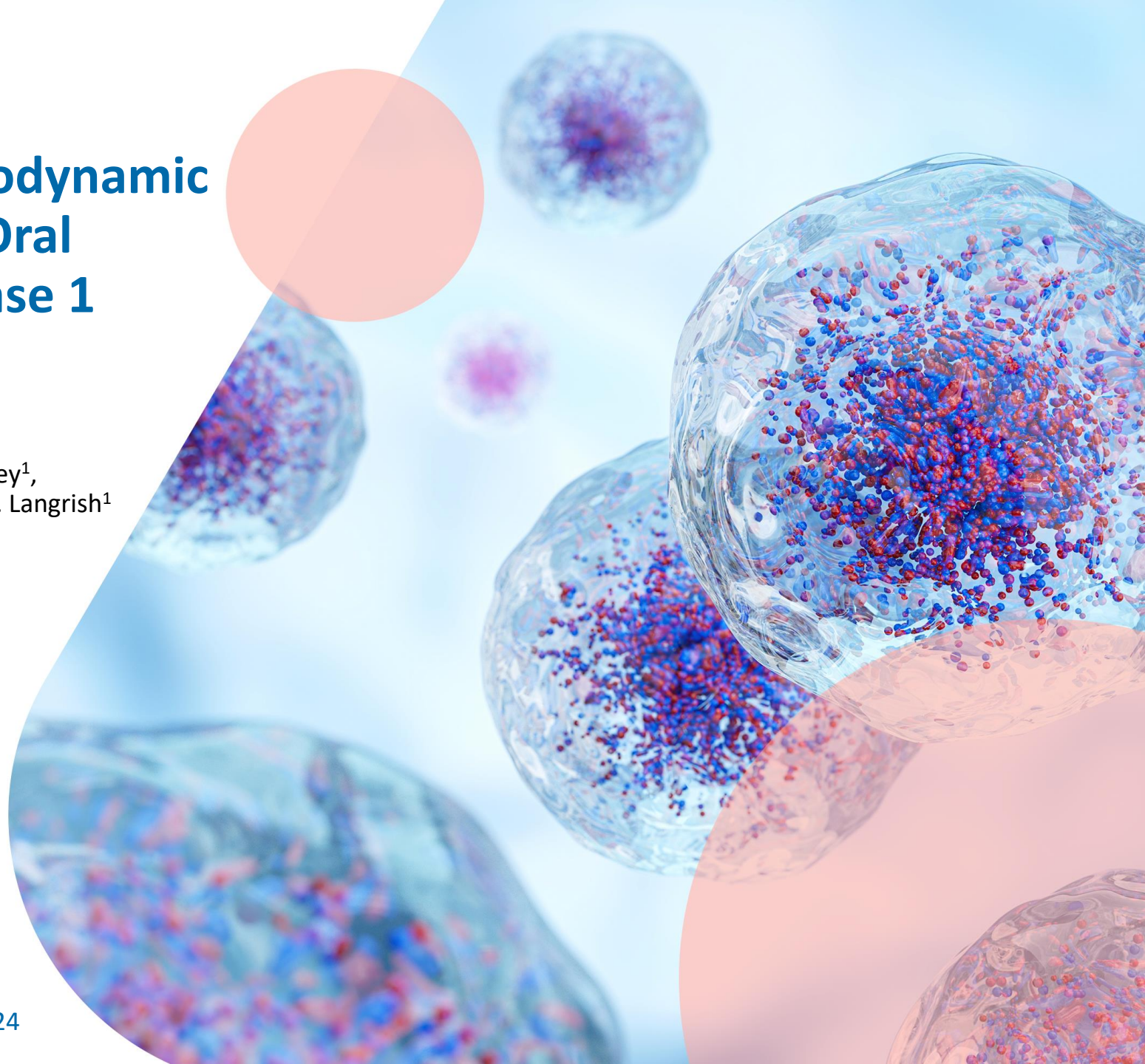

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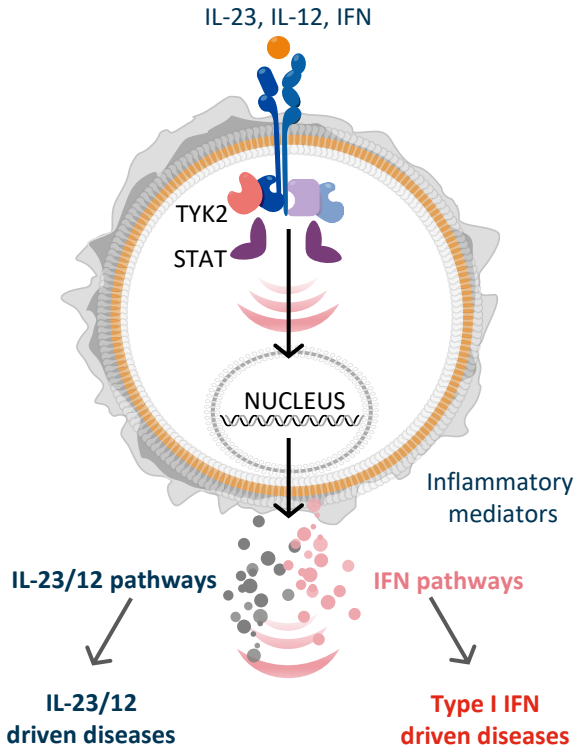
PK and PD Characteristics of ESK-001, an Oral Allosteric TYK2 inhibitor, in Phase 1 Healthy Volunteer Trials

Background

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

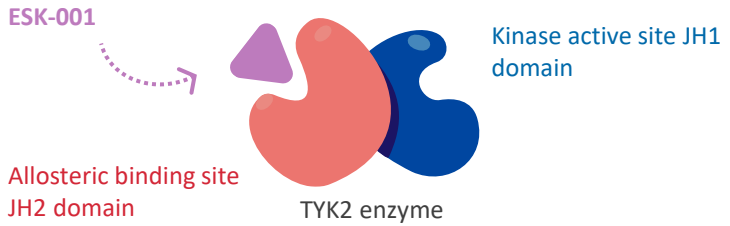
- TYK2 mediates signaling from key proinflammatory cytokines, including IL-23, IL-12, and Type I IFN.
- Human loss-of-function TYK2 genetic variants are associated with protection from immune-mediated diseases.
- Based on these mechanisms, TYK2 inhibition has potential to treat a wide array of diseases with a benign safety profile.



ESK-001 is an oral, highly selective allosteric TYK2 inhibitor

- High intrinsic selectivity for TYK2.
- Exclusive binding of ESK-001 to the JH2 allosteric binding pocket avoids JAK kinase liabilities.
- Highly selective for TYK2: no off-target binding across kinome, no measurable JAK pharmacology.
- ESK-001 is under development for the treatment of immune-mediated inflammatory diseases, including plaque psoriasis.

ESK-001 inhibits TYK2 allosterically



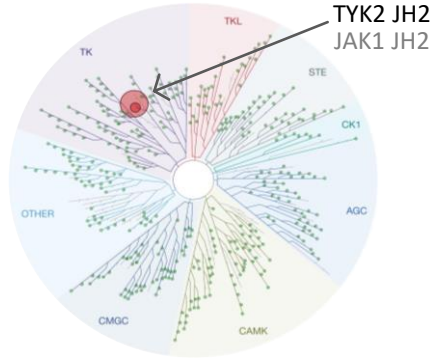
ESK-001 is highly selective for TYK2 with no measurable inhibition of JAKs

Human whole blood IC50 (nM)		ESK-001
IFNα	TYK2	104
IL-12	TYK2	149
IL-2	JAK1/JAK3	>30,000
TPO	JAK2	>30,000

ESK-001 has no off-target effects across kinome

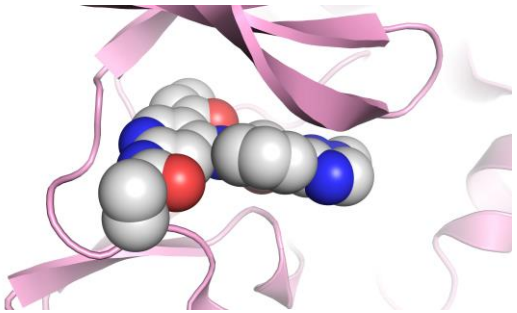
Only 2 of 468 kinases inhibited

- TYK2 JH2 domain
- JAK1 JH2 domain (no functional consequence)



ESK-001 is designed to deliver best-in-class PK properties

- Characteristics:
  - Molecular weight <500 g/mol.
  - Low polar surface area.
- Benefits:
  - Rapid absorption,
  - High permeability with no efflux, and
  - Good penetration into relevant tissues.
- Currently formulated as an immediate-release tablet.



ESK-001 structure

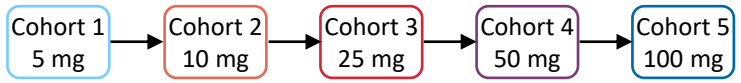
PK and PD Characteristics of ESK-001, an Oral Allosteric TYK2 inhibitor, in Phase 1 Healthy Volunteer Trials

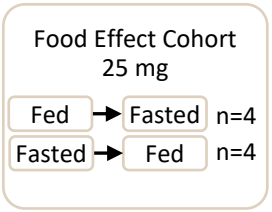
Methods

- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics were measured following oral administration of single ascending doses (SAD) and multiple doses (MD) of ESK-001 to healthy volunteers.
  - Double-blinded (with sponsor unblinded for MD study)
  - Randomized
  - Placebo-controlled
  - ESK-001 liquid formulation (SAD) or tablets (MD)
- Assessments
  - Safety and tolerability *(adverse events, clinical laboratory parameters, vital signs, physical examinations, and electrocardiogram parameters)*
  - Plasma and urine PK parameters
  - PD parameters

Single Ascending Doses (SAD)

Design





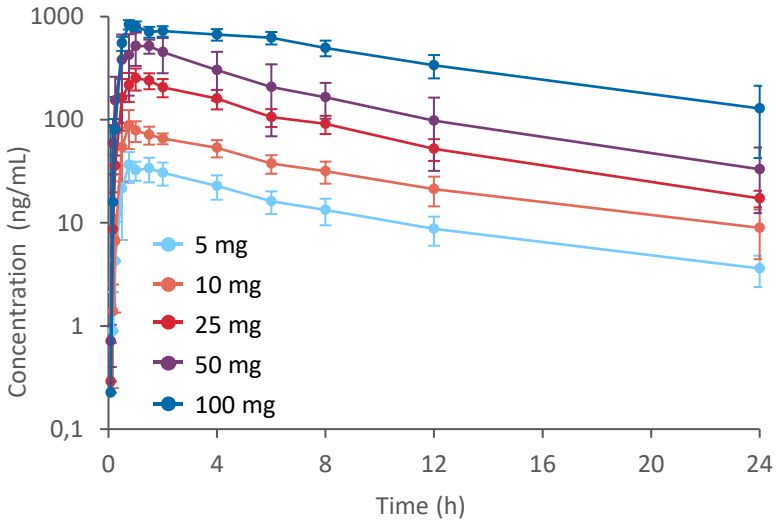
ESK-001: liquid formulation
n=8 per cohort
Cohorts 1 to 5: fasted, active (n=6), placebo (n=2)

Part A from Study ACTRN12621000011886
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380885

Results

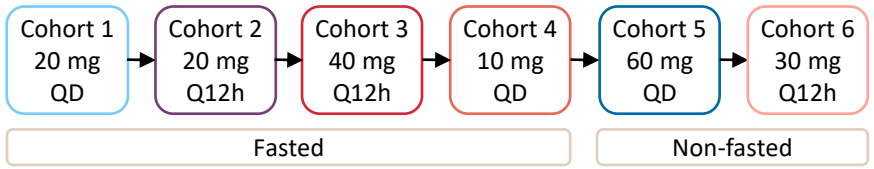
- ESK-001 was generally well tolerated as a single dose across cohorts.
- PK exposure was dose proportional.
- Linear PK with low variability.

Arithmetic mean (±SD) ESK-001 plasma concentration over time



Multiple Dose (MD) Study

Design



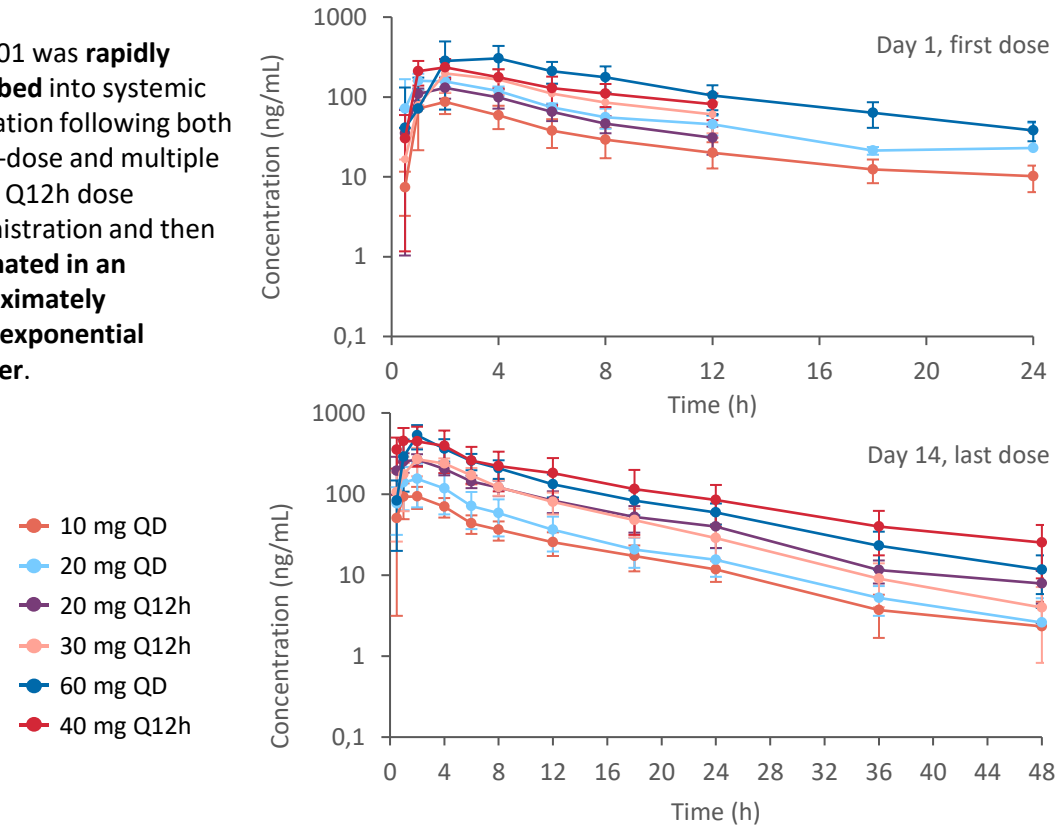
ESK-001: tablets
n=8 per cohort
Active (n=6), placebo (n=2)
Dosing over 14 days
QD = once daily
Q12h = once every 12 hours

Study NCT05431634
https://clinicaltrials.gov/study/NCT05431634

Results

- ESK-001 was **rapidly absorbed** into systemic circulation following both single-dose and multiple QD or Q12h dose administration and then **eliminated in an approximately monoexponential manner**.

Arithmetic mean (±SD) ESK-001 plasma concentration over time



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Summary of Plasma PK Parameters (MD study)

Cohort	Dosing days	$AUC_{0\text{-}tau}$ (h.ng/mL) [a]	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	Rac,AUC
10 mg QD	Day 1 (Fasted)	669.8 (35.1%)	94.25 (38.5%)	2.02 (1.01-2.04)	-	-
	Day 14 (Fasted)	835.2 (30.7%)	105.6 (35.9%)	1.60 (0.50-2.24)	9.419 (23.0%)	1.270 (12.3%)
20 mg QD	Day 1 (Fasted)	1350 (15.1%)	176.5 (27.6%)	1.53 (0.51-2.07)	-	-
	Day 14 (Fasted)	1256 (45.9%)	159.1 (51.7%)	2.10 (1.02-2.16)	9.640 (34.5%)	0.9235 (44.8%)
20 mg Q12h	Day 1 (Fasted)	810.7 (21.4%)	134.5 (19.8%)	2.01 (0.51-2.05)	-	-
	Day 14 (Fasted)	1944 (17.9%)	291.8 (19.7%)	2.06 (0.50-2.14)	9.637 (7.6%)	2.489 (27.5%)
30 mg Q12h	Day 1 (Non-Fasted)	1276 (36.6%)	196.9 (42.3%)	2.09 (2.06-2.19)	-	-
	Day 14 (Non-Fasted)	1943 (26.1%)	288.6 (21.1%)	2.20 (2.12-4.19)	7.664 (14.7%)	1.742 (9.9%)
60 mg QD	Day 1 (Non-Fasted)	3043 (28.8%)	387.8 (42.1%)	3.12 (1.13-4.07)	-	-
	Day 14 (Non-Fasted)	4239 (27.6%)	533.2 (33.4%)	2.09 (2.03-2.12)	9.722 (20.2%)	1.445 (33.2%)
40 mg Q12h	Day 1 (Fasted)	1620 (28.3%)	256.2 (24.0%)	2.06 (1.01-4.01)	-	-
	Day 14 (Fasted)	3569 (49.7%)	477.5 (46.1%)	1.08 (1.04-2.13)	12.87 (30.4%)	2.302 (58.5%)

$AUC_{0\text{-}tau}$ = AUC over the dosing interval; C_{max} = maximum observed concentration; CV = coefficient of variation; Rac,AUC = accumulation ratio calculated by using $AUC_{0\text{-}tau}$ at steady state divided by $AUC_{0\text{-}tau}$ after single dosing; QD = once daily; Q12h = once every 12 hours; T_{max} = time corresponding to occurrence of C_{max}; $t_{1/2}$ = apparent terminal elimination half-life.

All data are reported as arithmetic mean (CV%) except T_{max}, which was reported as median (minimum-maximum).

[a] Day 1 mean $AUC_{0\text{-}tau}$ was reported as $AUC_{0\text{-}12h}$ for Q12h dosing and mean $AUC_{0\text{-}24h}$ for QD dosing.

PK Results Summary (MD study)

- ESK-001 demonstrated **rapid absorption** with a median T_{max} of 1 to 3 hours post-dose on Day 1 (single dose) and Day 14 (steady states).
- Following multiple doses, ESK-001 exposure ($AUC_{0\text{-}tau}$) increased in general in a **dose-proportional manner**.
- The **mean $t_{1/2}$** ranged **from 8 to 13 hours**.
- No to minimal accumulation of ESK-001 was observed after multiple doses.
- Steady state was reached by Day 3.
- The **primary elimination route was through liver metabolism**, with <1% renal excretion.

Safety Summary (MD study)

- **ESK-001 was generally well tolerated across cohorts.** No deaths or serious treatment-emergent adverse events (TEAEs) were observed. One participant receiving ESK-001 (30 mg Q12h) discontinued the study drug and the study due to a TEAE (rash morbilliform, Grade 1).
- The majority of TEAEs (90.1% [82/91]) were mild in severity; all other TEAEs were moderate in severity. There was no dose-dependent increase in the number of overall TEAEs or significant change in the severity levels observed.
- The most frequently reported TEAEs by preferred term were erythema* and headache. (*Events of erythema were secondary to skin taping.)
- No major adverse cardiovascular events, malignancies, venous thromboembolism events or adverse trends in laboratory parameters occurred.

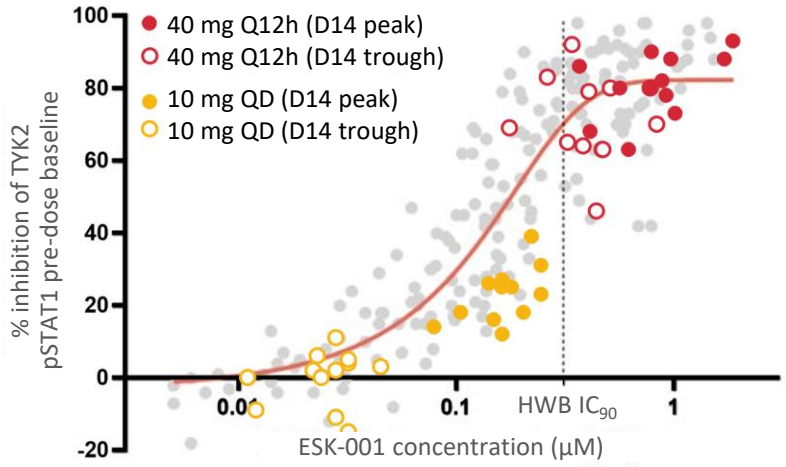
PK and PD Characteristics of ESK-001, an Oral Allosteric TYK2 inhibitor, in Phase 1 Healthy Volunteer Trials

Clear PK/PD Relationship

Methods The PK/PD relationship was determined by correlating exposure data and PD readouts from the MD study.

Results

- Maximal TYK2 pathway inhibition, aligned with human whole blood (HWB) 90% inhibitory concentration (IC_{90}) for ESK-001.
- **Strong PK/PD dose-relationship** with high predictability and low variability.
- PK/PD relationship guided selection of high and low dose for the STRIDE Phase 2 study (NCT05600036, https://clinicaltrials.gov/study/NCT05600036) in plaque psoriasis.
- **Clear dose-dependence** was reflected in clinical outcomes in participants.



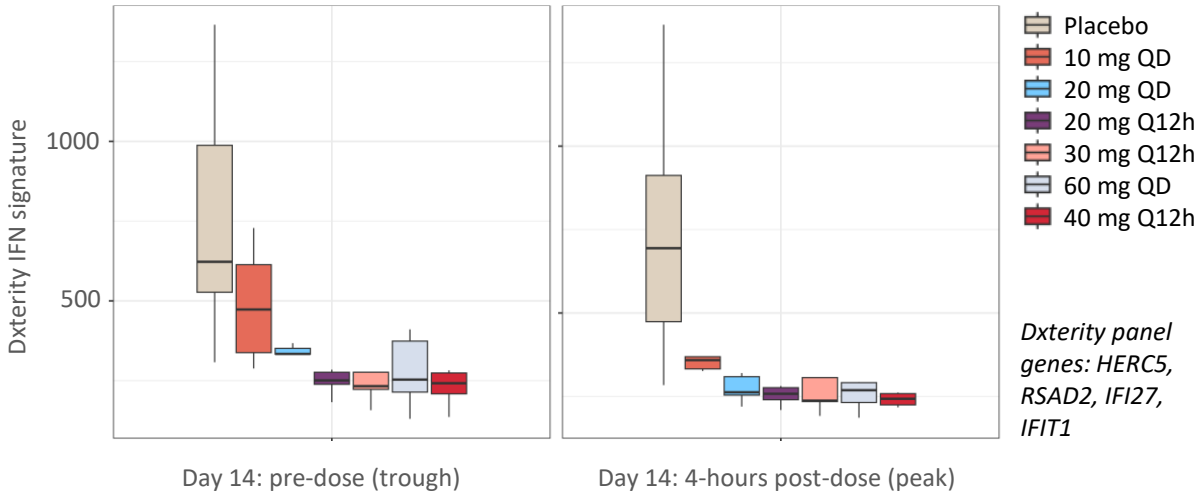
- PK exposure versus % change from pre-dose baseline IFNα induced pSTAT1 in whole blood T cells.
- Healthy participants MD study, Day 14 timepoint, peak 2 to 4 hours and trough 12 hours (Q12h) or 24 hours (QD) post-dose.
- In-vitro IFNα HWB IC_{90}.

Full TYK2 Pathway Inhibition

Methods TYK2 pathway PD markers including IFNα and IL-12-induced phosphorylated pSTATs, downstream cytokines and transcriptomic analysis were evaluated in whole blood.

Results

- Confirmation of
  - Robust ESK-001 pharmacologic activity;
  - Maximal TYK2 pathway inhibition;
  - Downstream pathway inhibition of IFNα induced CXCL10 and IL-12/IL-18 induced IFNγ production.
- ESK-001 blood RNA-sequencing showed dose-dependent inhibition of Type 1 IFN gene signature suppression, and full target inhibition at higher doses:



Conclusions

- In healthy volunteers, ESK-001 was generally well tolerated at doses up to 100 mg.
- ESK-001 showed
  - Linear dose-dependent PK characteristics;
  - Maximal inhibition of IL-12/IL-23 and Type I IFN pathways;
  - A predictable concentration-dependent PK/PD relationship.
- Data were used to select the dose range for the STRIDE Phase 2 study in plaque psoriasis to include minimal to maximal TYK2 inhibition.
- The PK/PD characteristics support further clinical development of ESK-001 as treatment for plaque psoriasis and other immune-mediated inflammatory diseases.