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Safety, Tolerability, and Pharmacokinetics of A-005: A Selective Brain-Penetrant TYK2 Inhibitor for CNS Inflammatory Diseases in Healthy Volunteers Following Single and Multiple Ascending Doses

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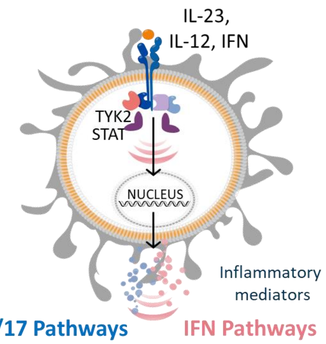
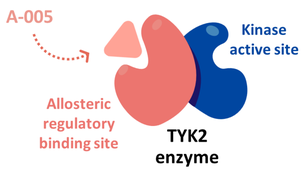
Background

- **Tyrosine kinase 2 (TYK2)** mediates signaling from key proinflammatory cytokines, including **IL-23, IL-12, IL-17 downstream of IL-23, and type I interferons (IFNs)**.
- Loss-of-kinase function TYK2 genetic variants are protective for an array of immune-mediated diseases, including multiple sclerosis (MS).[1,2]
- Clinical validation of TYK2 inhibitors has been established in peripheral autoimmune conditions — with recent approval for psoriasis— and trials are ongoing in other indications.[3]
- **TYK2 inhibition** may, therefore, represent a **novel approach to treat central nervous system (CNS) inflammation** that is associated with neurodegeneration and consequent disability in MS.





- **A-005 is an allosteric TYK2 inhibitor** that has shown to efficiently cross the blood-barrier and achieve pharmacologically relevant brain exposures preclinically.[4]

Objectives

This Phase 1 Study of oral administered A-005 in healthy volunteers was performed to support dose selection for future studies in the MS patient populations or other neuroinflammatory and neurodegenerative conditions.

Objectives

- Evaluate **safety, tolerability, and PK** of single and multiple oral A-005 dosages.
- Evaluate **PK/PD relationship** using phosphorylated Signal Transducer and Activator of Transcription 3 (pSTAT3) marker in SAD and MAD cohorts.
- Evaluate **CSF levels** of A-005 over time postdose.

Methods

Study design

Single Ascending Dose (SAD) Study

- Dose cohorts: 1, 2, 4, 8, 15, 30, 60, 120, 240, 360 mg once daily (QD).
  - N per cohort=8 (Placebo n=2, A-005 n=6), except for 15 mg Cohort (Placebo n=2, A-005 n=12).
  - Liquid formulation under fasting conditions.
- Food effect and tablet formulation evaluated as cross-over study in 15 mg QD cohort (A-005 n=14).

Multiple Ascending Dose (MAD) Study

- Dose cohorts: 10, 30, 60, 120 mg QD, and 120 mg twice daily (BID).
  - N per cohort=8 (Placebo n=2, A-005 n=6).
  - Tablet formulation under fasting conditions for 14 days.

Single Dose Study for cerebrospinal fluid (CSF) exposure

- Dose cohort: 120 mg QD evaluated at 1, 2, 9h postdose.
  - N=9 (n per timepoint=3).
  - Liquid formulation under fasting conditions.

Results

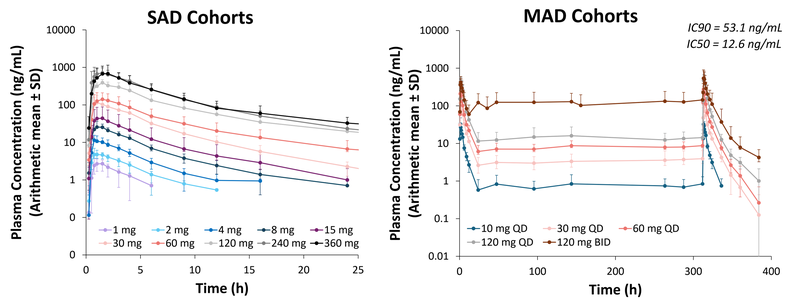
Study demographics and safety summary

	SAD		MAD		CSF
	Pooled Placebo (N = 20)	Pooled A-005 Active (N = 66)	Pooled Placebo (N = 10)	Pooled A-005 Active (N = 30)	Pooled A-005 Active (N = 9)
Sex, n (%)					
Female	5 (25)	20 (30)	3 (30)	10 (33)	2 (22)
Male	15 (75)	46 (70)	7 (70)	20 (67)	7 (78)
Age (yr), mean (SD)	30 (8)	36 (9)	43 (6)	37 (8)	36 (11)
Body Mass Index (kg/m²), mean (SD)	25 (3)	27 (4)	28 (3)	26 (3)	26 (2)

A-005 was generally well tolerated at all dosages

- No serious, severe, or fatal TEAEs were observed.
- Most common TEAEs were headache, medical device site reactions, and constipation.
- All TEAEs were mild to moderate and none led to study drug discontinuation.
- No clinically relevant trends in lab abnormalities or vital signs were observed.

A-005 plasma concentrations over time in SAD and MAD Cohorts



Samples from 24h to 312h (Day 2-Day 13) in MAD Cohorts were collected as predose.

PK Summary of A-005 in SAD and MAD Cohorts

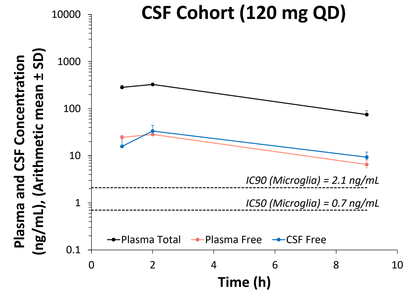
- A-005 liquid and tablet formulation showed rapid absorption (T_{max} ~ 1.5h), independent of dose.
- A-005 plasma exposure (C_{max}, AUC) increased proportional to dose, in the range of 1 to 240 mg QD dose.
- Steady state achieved within 2 days with minimal accumulation.
- Dose-dependent increase of $T_{1/2}$ in both SAD and MAD Cohorts.
- Higher A-005 doses sustained in vitro pSTAT IC90 coverage over 24h.

PK Summary: MAD Cohorts

	$T_{1/2}$ (h)	T_{max} (h)		C_{max} (ng/mL)		AUC_{0-24} (h*ng/mL)		RA AUC_{0-24}
	Day14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	
10 mg QD, mean (SD)	5.5 (1.2)	1.2 (0.3)	1.4 (0.8)	34 (14)	35 (10)	148 (38)	163 (26)	1.1
30 mg QD, mean (SD)	7.6 (3.0)	1.3 (0.3)	1.2 (0.3)	133 (60)	117 (21)	612 (191)	623 (97)	1.1
60 mg QD, mean (SD)	11.3 (6.9)	1.2 (0.3)	1.0 (1.0)	244 (69)	275 (54)	1110 (273)	1300 (231)	1.2
120 mg QD, mean (SD)	21.0 (16.0)	1.8 (0.8)	1.4 (0.5)	498 (123)	556 (171)	2500 (590)	2840 (908)	1.1
120 mg BID, mean (SD)	17.6 (8.1)	1.5 (0.3)	1.4 (0.4)	430 (166)	580 (325)	4117[a] (2058)	3020[b] (1940)	1.6

[a] AUC_{0-24} extrapolated from AUC_{0-12} and calculated as 2 x AUC_{0-12}, [b] Final dose is administered in the morning.

In both CSF and periphery, A-005 achieved high exposure and maintained IC90 coverage for maximal target inhibition throughout the dosing period

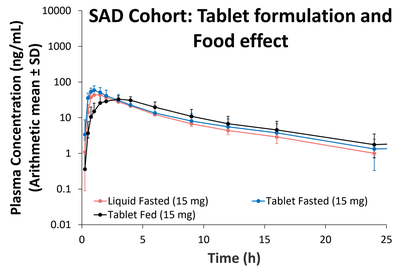


- CSF_{free} ≥ $Plasma_{free}$ exposure for all timepoints from 1h postdose.
- A-005 concentration in CSF 9h postdose was >4 times higher than IC90 measured in microglia cells in vitro.

PK Summary: CSF Cohort (120 mg QD)

	T_{max} (h)	C_{max} (ng/mL)	C_{9h} (ng/mL)
$Plasma_{Total}$, mean (SD)	1.5 (NA)	327 (0.6)	75 (16)
$Plasma_{Free}$, mean (SD)	1.5 (NA)	29 (0.1)	7 (1.4)
CSF_{Free}, mean (SD)	2.0 (NA)	34 (10.9)	9 (2.7)
Ratio (CSF_{free}/$Plasma_{free}$)	NA	1.2	1.4

Similar exposures observed between liquid and tablet formulations with minimal effect of food intake

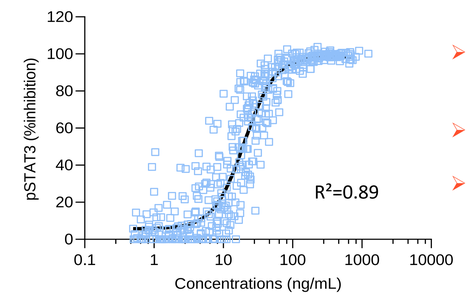


- Liquid and tablet formulations had comparable exposures, eliminating the need for dose adjustments.
- Food had minimal effect on AUC, with peak exposure (C_{max}) reduced by approximately 38% and slightly delayed T_{max}.

PK Summary: SAD Cohort 15 mg QD

	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	AUC_{inf} (h*ng/mL)
Liquid (Fasted), mean (SD)	5.5 (0.8)	1.2 (0.3)	47 (11)	227 (43)	235 (46)
Tablet (Fasted), mean (SD)	5.6 (1.0)	0.9 (0.1)	60 (18)	272 (130)	285 (144)
Tablet (Fed), mean (SD)	5.6 (1.1)	2.5 (1.0)	37 (8)	263 (103)	280 (126)

A-005 showed a strong PK/PD correlation in SAD and MAD Cohorts



- A strong PK/PD correlation was observed (R^2=0.89) for IFNα-induced pSTAT3 in T cells from whole blood.
- Maximum inhibition was achieved at 30 mg dose and above.
- Higher doses sustained inhibition throughout the dosing period.

Conclusions

- A-005 was **generally safe and well tolerated** at dosages up to 360 mg QD.
- A-005 PK data showed rapid absorption, dose-proportional linear exposure up to 240 mg dose, and limited accumulation after multiple doses for 14 days.
- A-005 demonstrated a **strong PK/PD correlation** for the TYK2 PD marker (pSTAT3) in both SAD and MAD cohorts.
- A-005 **effectively crossed the blood-to-brain barrier**, with equal to even higher free drug exposures in CSF compared to plasma and maintained exposure for maximum target inhibition within CNS and periphery.
- This Phase 1 study supports dose range selection for future clinical treatment development in MS and additional neuroinflammatory and neurodegenerative diseases.

References

[1] *Couturier et al. Brain, 2011.*
[2] *Ban et al. Eur J Hum Genet, 2009.*
[3] *Jensen et al. EBioMedicine, 2023.*
[4] *Graham et al. ACTRIMS Forum 2024, Poster No. P400*