Pharmacokinetics, Pharmacodynamics, and CNS Penetration of A-005: A Novel TYK2 Inhibitor for MS

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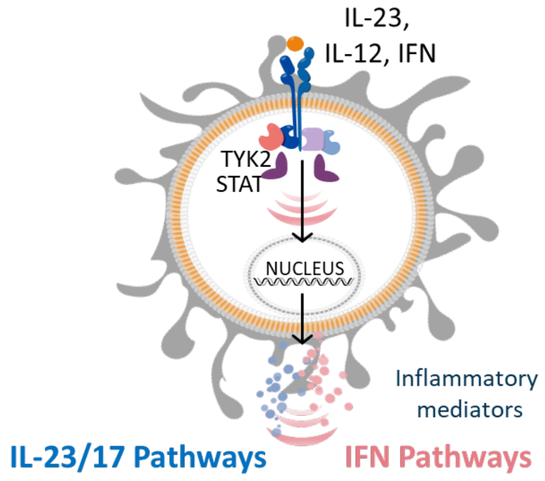
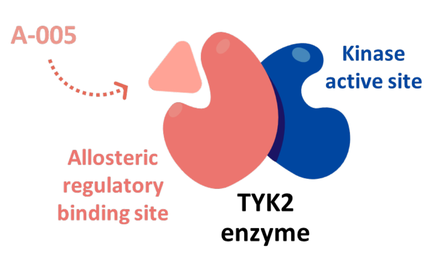
Introduction

- **Tyrosine kinase 2 (TYK2)** mediates signaling from key proinflammatory cytokines, including **interleukin (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 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-brain barrier and achieve pharmacologically relevant brain exposures preclinically.[4]

Objectives

This study evaluated Phase 1 data describing A-005's Pharmacokinetic (PK)/Pharmacodynamic (PD), biomarker relationships, and cerebrospinal fluid (CSF) exposures to guide dose selection for potential future MS trials.

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.

Multiple Ascending Dose (MAD) Study

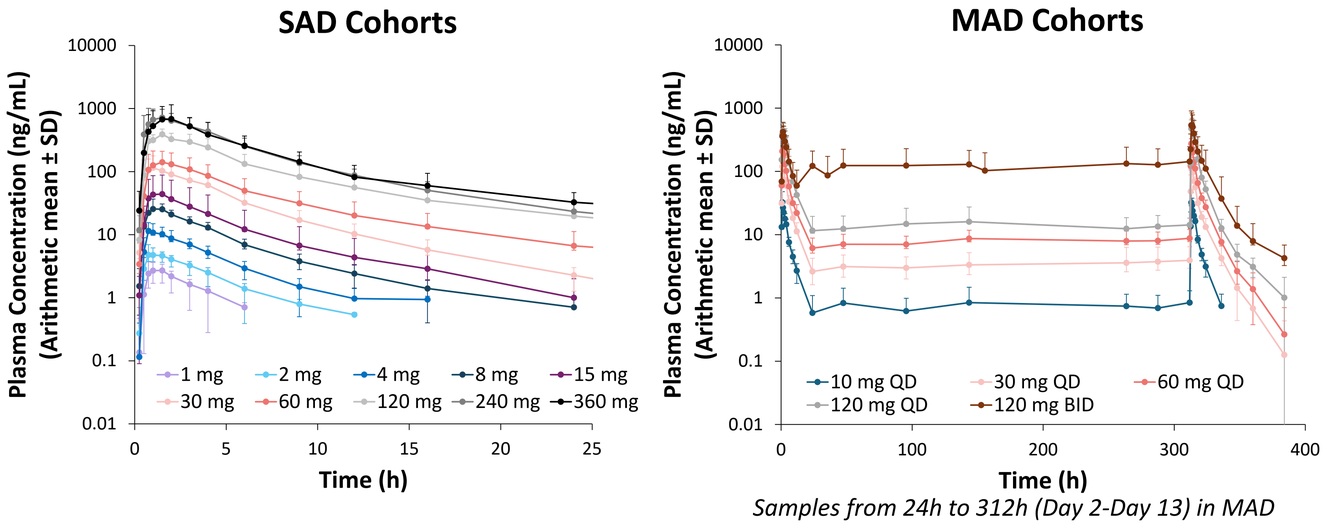
- Dose cohorts: 10, 30, 60, 120 mg QD, and 120 mg twice daily (BID).
  - N per cohort=8 (Placebo n=2, A-005 n=6).
  - Tablet formulation under fasting conditions for 14 days.

Single Dose Study for CSF exposure

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

Results

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

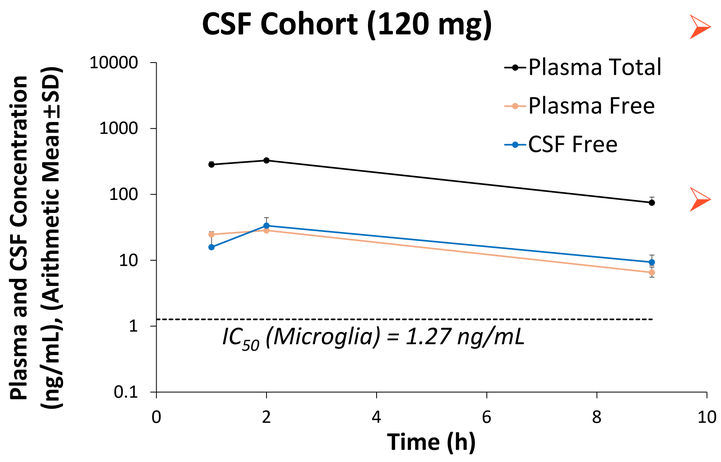


Samples from 24h to 312h (Day 2-Day 13) in MAD Cohorts were collected as predose.

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 whole blood pSTAT IC_{90} coverage over 24h (IC_{90} = 53.1 ng/mL).

In both CSF and periphery, A-005 achieved high exposure and maintained IC_{50} coverage throughout the dosing period



- CSF_{free} ≥ $Plasma_{free}$ exposure for all timepoints from 1h postdose.
- A-005 CSF concentration at 9h is >5x the IFNα-stimulated pSTAT3 IC_{50} in microglia.

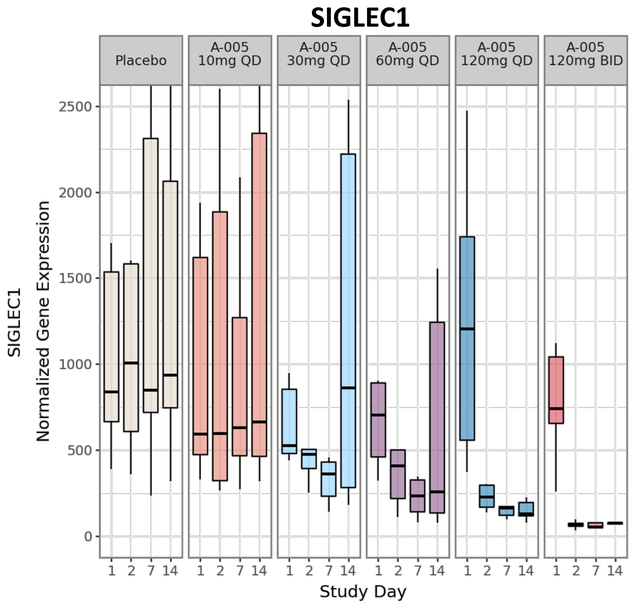
PK Summary: CSF Cohort (120 mg)

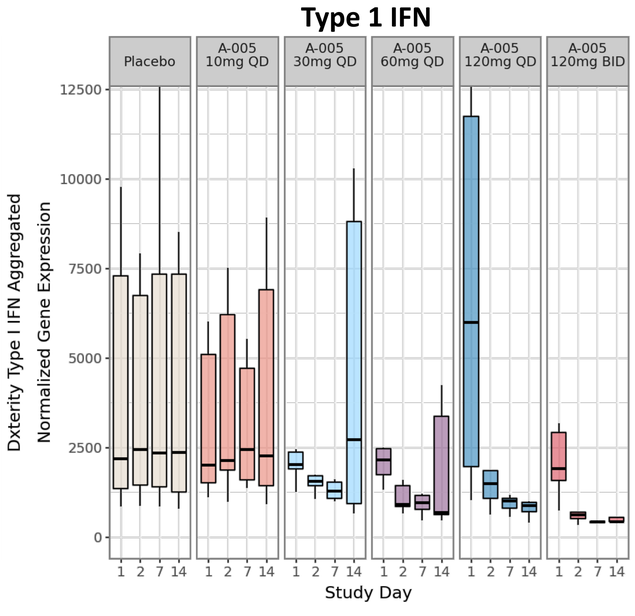
	T_{max}* (h)	C_{max} (ng/mL)	C_{9h} (ng/mL)
$Plasma_{total}$, mean (SD)	1.0 (0.75 – 3.0)	327 (0.6)	75 (16)
$Plasma_{free}$, mean (SD)	1.0 (0.75 – 3.0)	29 (0.1)	7 (1.4)
CSF_{free}, mean (SD)	2.0 (2.0 – 2.0)	34 (10.9)	9 (2.7)
Ratio (CSF_{free}/$Plasma_{free}$)	NA	1.2	1.4

**T_{max} was reported as median (range).*

Whole blood PD biomarker results of A-005

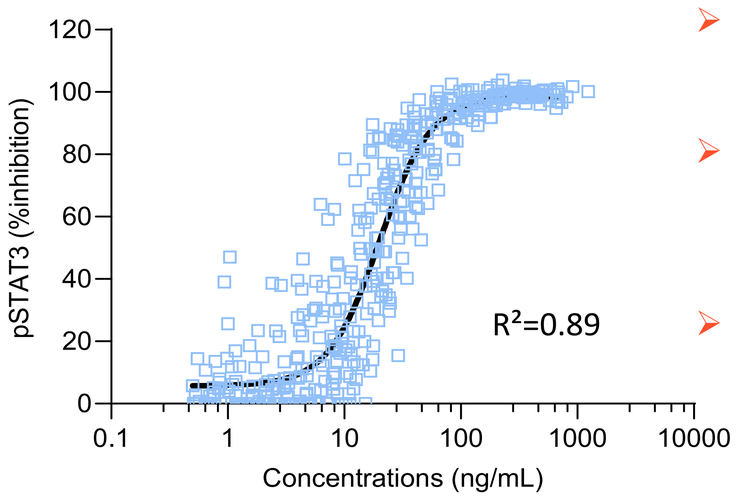
- Normalized RNA-Seq analysis of whole blood showed A-005 dose-dependent inhibition of SIGLEC1 gene expression and Type 1 IFN composite gene expression.





Aggregate Type I IFN score calculated as the median normalized expression of the following genes: HERC5, IFI27, IFIT1, RSAD2.

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



- IFNα-induced pSTAT3 in $CD3^+$ 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.[5]
- 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 **effectively crossed the blood-brain barrier**, with a 1:1 plasma-to-CSF free drug ratio exceeding cellular IC_{50} threshold.
- A-005 achieved maximal target inhibition, evidenced by suppressed pSTAT signaling, SIGLEC1 and Type 1 IFN gene expression.
- A-005 demonstrated a **strong PK/PD correlation** for the TYK2 PD marker (pSTAT3) in both SAD and MAD cohorts.
- This Phase 1 study supports advancement of A-005 into further clinical evaluation of efficacy and safety 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*
[5] *Sharma et al. ACTRIMS Forum 2025, Poster No. P335*

Disclosures

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