Effects of ATH434, a Clinical-Phase Small Molecule with Moderate Affinity for Iron, in Hemiparkinsonian Macaques

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INTRODUCTION

ATH434 is a novel brain-penetrant iron-binding small molecule currently in phase 2 clinical trials for Multiple System Atrophy (MSA) based on efficacy in multiple murine parkinsonian models. In Parkinson's disease (PD)[1] and MSA[2] models, ATH434 reduced disease-related excess substantia nigra (SN) iron and aggregated α-synuclein. ATH434 is postulated to redistribute excess labile cellular iron, facilitating its export. Contrary to high-affinity iron chelators previously tested in PD, ATH434's moderate iron affinity precludes it from interfering with endogenous iron trafficking proteins such as transferrin.

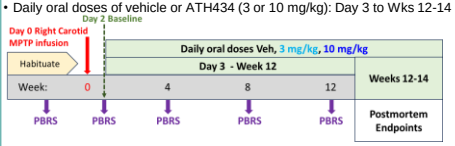
OBJECTIVES

- Determine whether orally-dosed ATH434 improves motor performance in a nonhuman hemiparkinsonian model of PD when administered after symptom onset.
- Relate clinical observations to changes in brain iron, synaptic integrity, and tyrosine hydroxylase positive (TH+) neurons.

METHODS

MPTP Model

- Single right carotid artery injection of MPTP on Day 0
- Parkinson Behavior Rating Scale (PBRS) assessed 5 times: prior to MPTP, Day 2 (pre-dose Baseline), during dosing (Weeks 4, 8, 12)
  - Side Specific Motor, General Motor, General Behavior
  - ↑ scores = worse symptoms
- 12 macaques selected for study based on Baseline PBRS
- Daily oral doses of vehicle or ATH434 (3 or 10 mg/kg): Day 3 to Wks 12-14



Postmortem endpoints

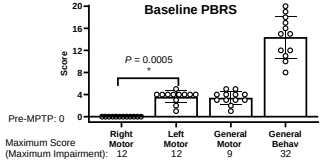
- SN iron (inductively-coupled plasma mass spec.)
- Dopamine transporter (DAT) density (PET)
- TH+ SN neurons (stereology)
- Dorsal striatal synaptophysin (Western Blot)

References

1. ***Finkelstein*** *et al (2017) The novel compound PBT434 prevents iron mediated neurodegeneration and alpha-synuclein toxicity in multiple models of Parkinson's disease. Acta Neuropathol Commun 5.*
2. ***Heras-Garvin*** *et al (2021) ATH434 Reduces α-Synuclein-Related Neurodegeneration in a Murine Model of Multiple System Atrophy. Mov Disord 36:2605-14.* ***Finkelstein*** *et al (2022) The Compound ATH434 Prevents Alpha-Synuclein Toxicity in a Murine Model of Multiple System Atrophy. J Parkinsons Dis 12:105-15.*

RESULTS

Hemiparkinsonian Model at Pre-Dose Baseline

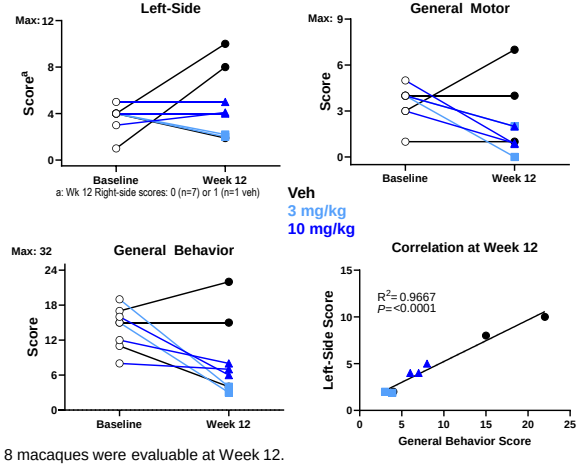


Side Specific: movement, including range

General Motor: fine motor skills, eating, eyeblink

General Behavior: appetite, response to food, activity, appearance, posture, balance, climbing, tremor, freezing, facial expression, defensive reactions

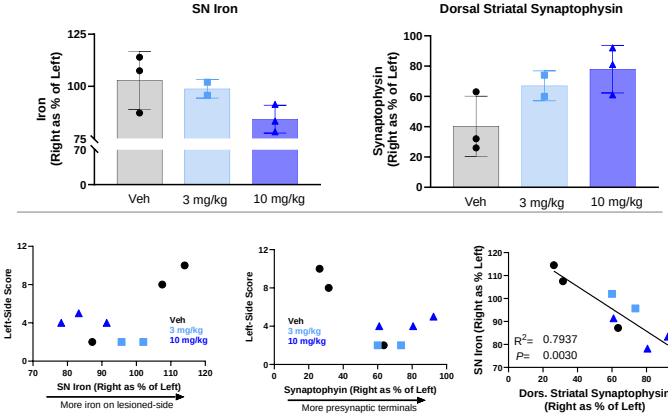
ATH434 Improved Motor and Behavior Outcomes



- 8 macaques were evaluable at Week 12.
- ATH434-treated macaques had stable or improving scores from Baseline to Week 12.
- Two of 3 vehicle-treated macaques did not demonstrate improvement.
- Improved general behavior was well-correlated with reduced motor impairment.

RESULTS

ATH434 Reduced Right SN Iron and Increased Right Dorsal Striatal Synaptophysin



Lesion size by PET and surviving TH+ SN neurons were not impacted by treatment

Right as % Left	Vehicle	3 mg/kg	10 mg/kg
TH+ SN Neurons	52±16%	77±26%	35±16%
DAT Density, Dorsal Striatum ([11C]β-CFT Binding Potential)	55±9%	42±6%	56±8%

CONCLUSION

- ATH434 treatment led to lower right SN iron and improved motor and general behavior scores in this primate model of PD.
- Favorable parkinsonian outcomes were associated with lower SN iron and higher striatal synaptophysin, suggesting functional neurite or synaptic recovery.
- These results support further investigation of ATH434 for the treatment of PD.

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