ATH-1105, a Small-Molecule Positive Modulator of Hepatocyte Growth Factor (HGF)/MET, is Neuroprotective in a TDP-43 Mouse Model of Amyotrophic Lateral Sclerosis

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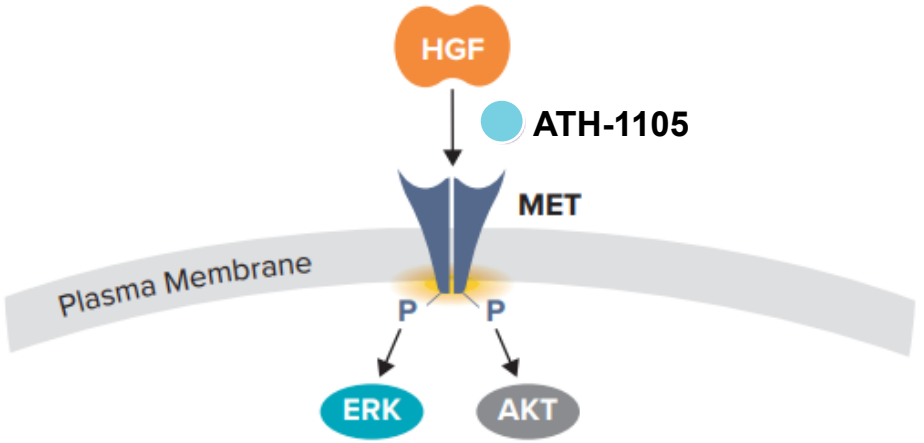
Positive modulation of HGF/MET as a potential treatment for ALS

- ALS is characterized by progressive motor neuron degeneration, demyelination, and systemic inflammation[1]
- The HGF/MET system has the potential to alleviate key components of ALS based on its neurotrophic and neuroprotective properties[2,3]



Neurotrophic

- Neurogenesis
- Neurite outgrowth
- Synaptogenesis
- Regeneration

Neuroprotective

- Maintenance of neuromuscular junction
- Neuron survival
- Anti-inflammation
- Reduced excitotoxicity

Study Objective:

To evaluate the therapeutic potential of ATH-1105, a positive modulator of the HGF/MET system, in a transgenic mouse model of ALS

ALS, amytrophic lateral sclerosis; HGF, hepatocyte growth factor.

References: 1. Hulisz D. Am J Manag Care. 2018;24(15):S320-S326. **2.** Desole C et al. *Front Cell Dev Biol.* 2021 Jun 9;9:683609. **3.** Johnston JL et al. *Neurotherapeutics.* 2022 Dec 20.

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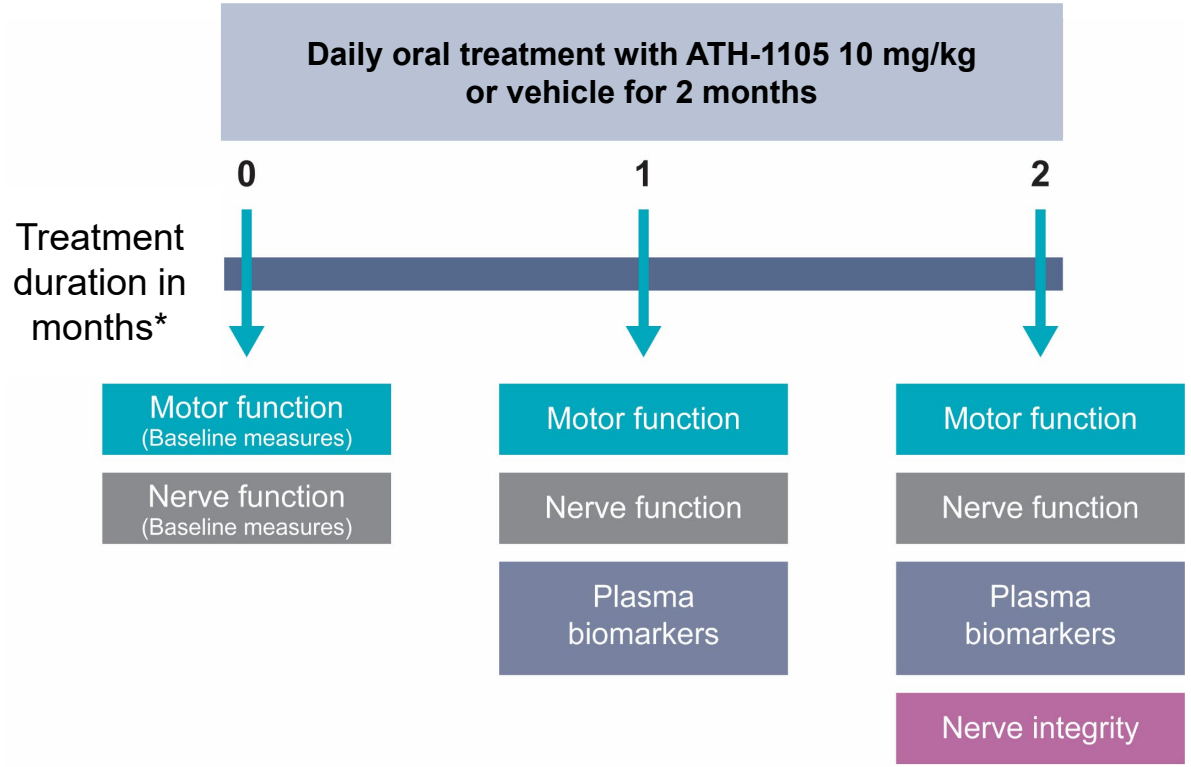
Study design

Animals: Prp-TDP-43^{A315T} transgenic mouse model

- TDP-43 pathology is present in ~97% of people with ALS[1]
- TDP-43^{A315T} mice develop ALS-like deficits in motor and nerve function, motor neuron loss, and systemic inflammation[2]
    - Progressive deficits begin at 2 months of age

Groups: 10 mice per group (male), daily oral treatment from 1 to 3 months of age

1. **WT + vehicle (healthy control)**
   WT mice treated with oral vehicle
2. **ALS + vehicle (disease control)**
   TDP-43^{A315T} mice treated with oral vehicle
3. **ALS + ATH-1105, 10 mg/kg**
   TDP-43^{A315T} mice treated with oral ATH-1105



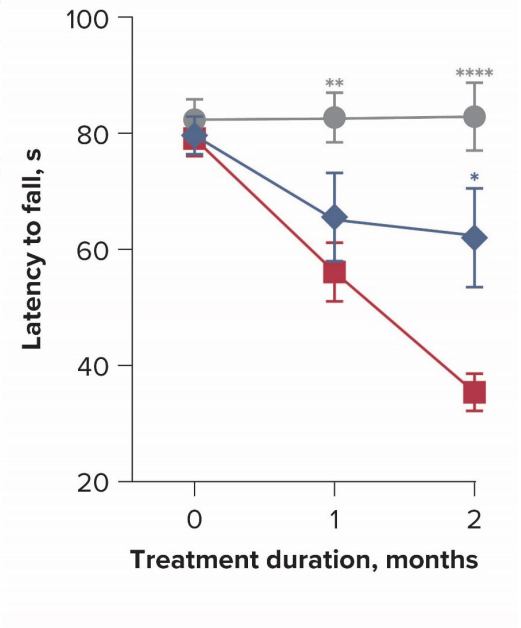
*Treatment started at 1 month of age.
ALS, amyotrophic lateral sclerosis; TDP-43, TAR DNA-binding protein 43; WT, wild type.
References: 1. Scotter et al. *Neurotherapeutics*. 2015;12(2):352-363. **2.** Bargsted et al. *Sci Rep*. 2017;7(1):14266.

ATH-1105 ameliorated motor and nerve function deficits

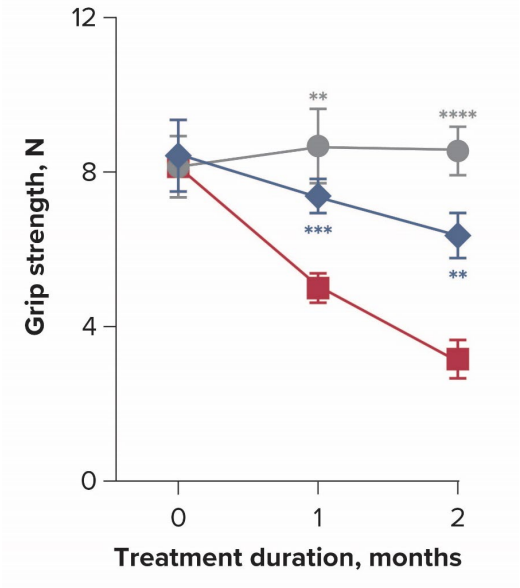
Motor function

- Assessments of balance, coordination, and strength

Rotarod



Grip test

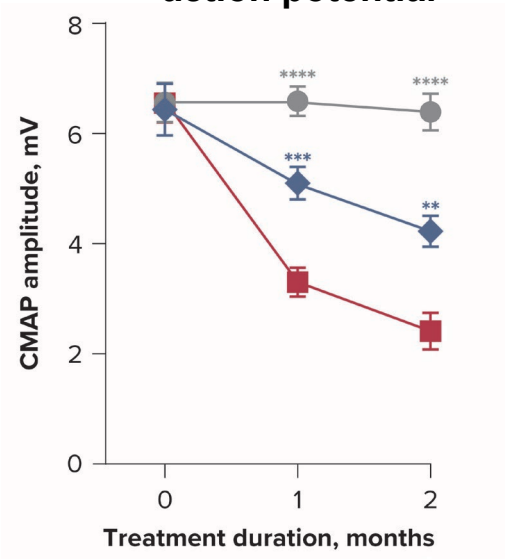


Similar results obtained in Kondziela inverted screen and balance beam tests

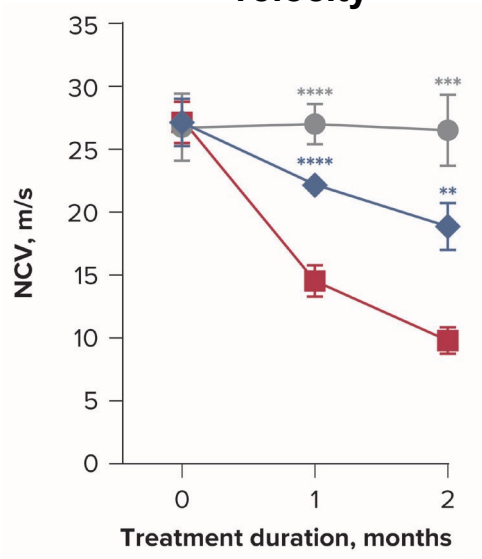
Nerve function

- Sciatic nerve electrophysiology

Compound muscle action potential



Nerve conduction velocity



WT + vehicle ALS + vehicle ALS + ATH-1105 10 mg/kg

ALS, amyotrophic lateral sclerosis; WT, wild type.
Treatment started at 1 month of age. Data presented as mean ± SEM.
Statistical significance was determined by 2-way ANOVA with the Dunnett's test versus ALS + vehicle. * $P < 0.1$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

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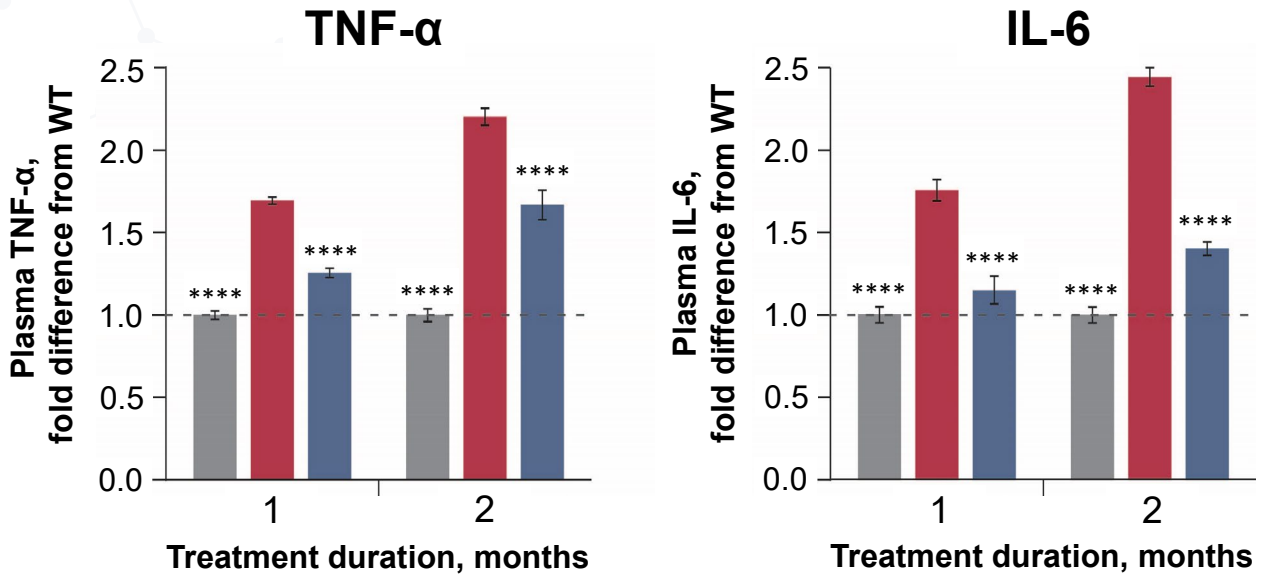
ATH-1105 reduced plasma markers relevant to ALS pathology

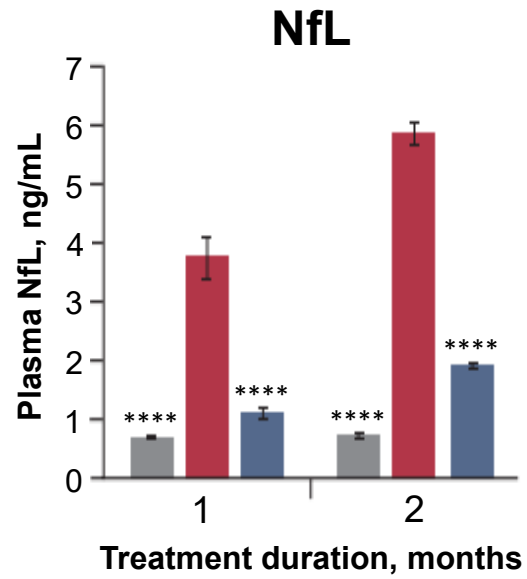
Inflammatory markers

- TNF-α and IL-6 are pro-inflammatory cytokines
- Elevated in the plasma and CSF of people with ALS[1]



Neurodegeneration marker

- Plasma NfL increases proportionally to level of ongoing neurodegeneration[2]
- Elevated in plasma and CSF of people with ALS[2]



ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; IL-6, interleukin 6; NfL, neurofilament light chain; TNF-α, tumor necrosis factor α; WT, wild type.
Data presented as mean ± SEM. Statistical significance was determined by 2-way ANOVA with the Dunnett's test versus ALS + vehicle. ****$P < 0.0001$.

References: 1. Tortelli R et al. *Eur J Neurol.* 2012;19:1561-1567. **2.** Gaetani L et al. *J Neurol Neurosurg Psychiatry.* 2019;90, 870-881.

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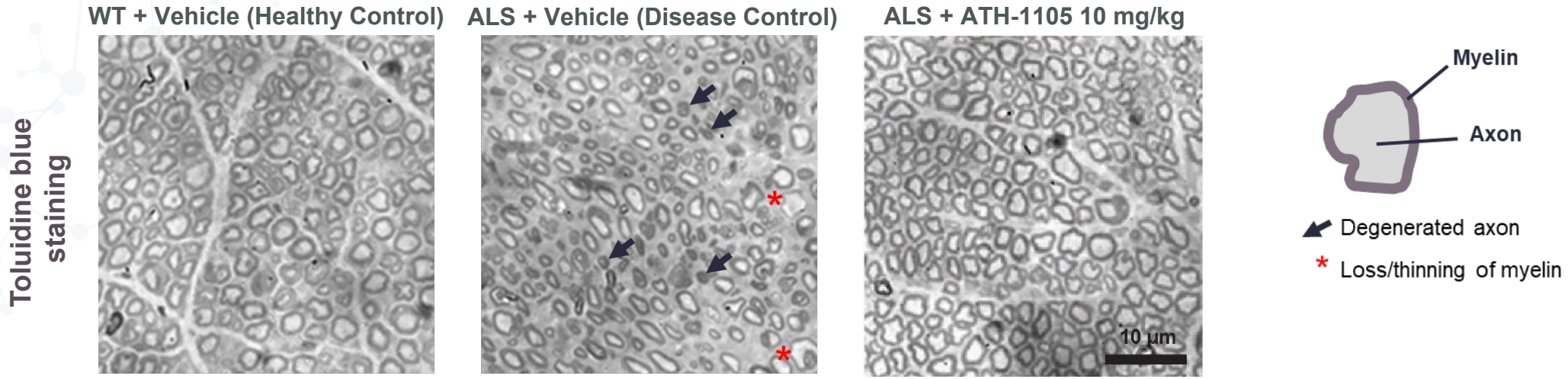
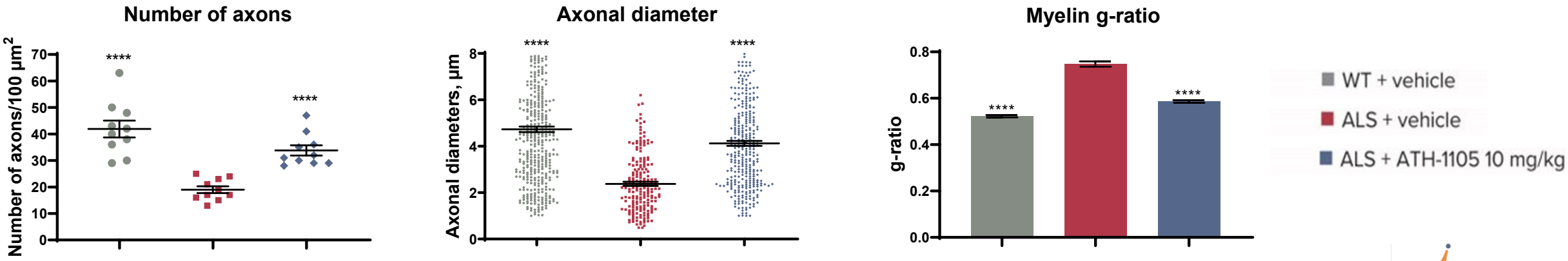
ATH-1105 protected against axon degeneration and demyelination

- Sciatic nerves collected at study termination, following 2 months of treatment





ALS, amyotrophic lateral sclerosis.
Data presented as mean ± SEM. Statistical significance was determined by 1-way ANOVA with the Dunnett test versus ALS + vehicle. ****P < 0.0001.

Summary & Conclusion

- ATH-1105 treatment in a TDP-43 mouse model of ALS resulted in:
  - Improvement in overall motor and nerve function
  - Protection of axonal integrity and myelination
  - Reductions in plasma biomarkers of systemic inflammation and neurodegeneration relevant to clinical ALS

These results highlight the therapeutic potential of ATH-1105, a positive modulator of HGF/MET, in ALS and supports its further investigation

Thank you

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