ATH-1105, a small molecule positive modulator of the neurotrophic hepatocyte growth factor system, is neuroprotective when administered prophylactically, therapeutically, or in combination with riluzole in the Prp-TDP43^{A315T} mouse model of ALS

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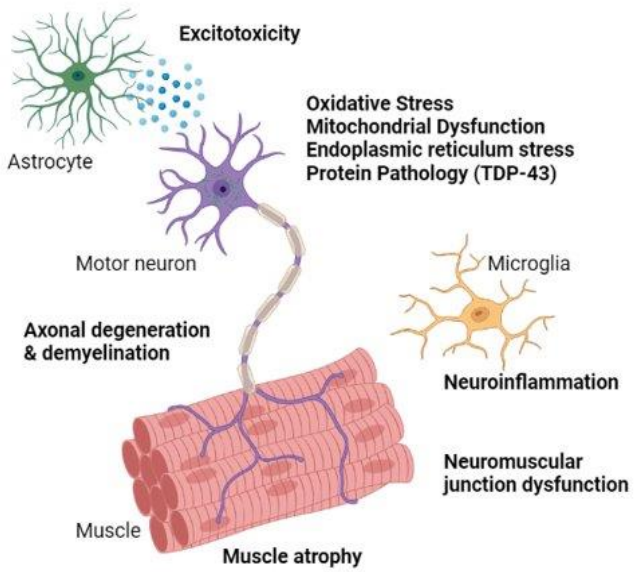
Athira Pharma, Inc.

Disclosures

- All authors are employees of Athira Pharma and hold stock or stock options
- Funding for all studies was provided by Athira Pharma
- ATH-1105 is an investigational therapy and has not received FDA or other regulatory agency approval nor been demonstrated as safe or effective for any use

ATH-1105 has the potential to target key aspects of ALS

ALS is a complex, multi-faceted neurodegenerative disease

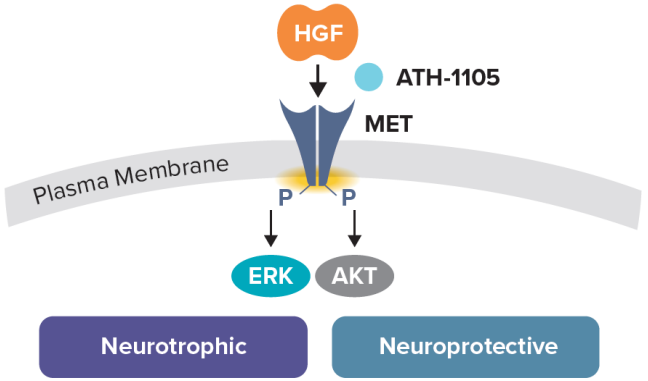


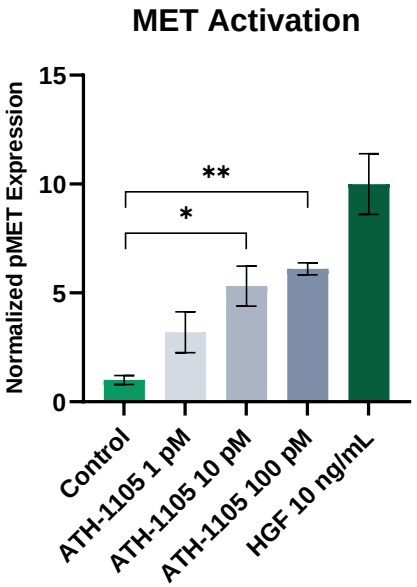
Neurotrophic factors, such as NGF, BDNF, GDNF, and hepatocyte growth factor (**HGF**) stimulate pleiotropic effects that may protect against key pathological insults seen in ALS

- Promotion of HGF has shown benefit in preclinical models of ALS
  - Intrathecal introduction of HGF mitigates ALS symptoms[1]
  - Pharmacological HGF signaling promotion delays ALS model progression[2]
- Challenges with delivery and distribution have impeded the development of neurotrophic factor therapies, but small molecule approaches may offer a promising potential solution

ATH-1105 is designed to enhance the activity of the neurotrophic HGF system

- Small molecule
- Orally bioavailable
- Distributes to the CNS

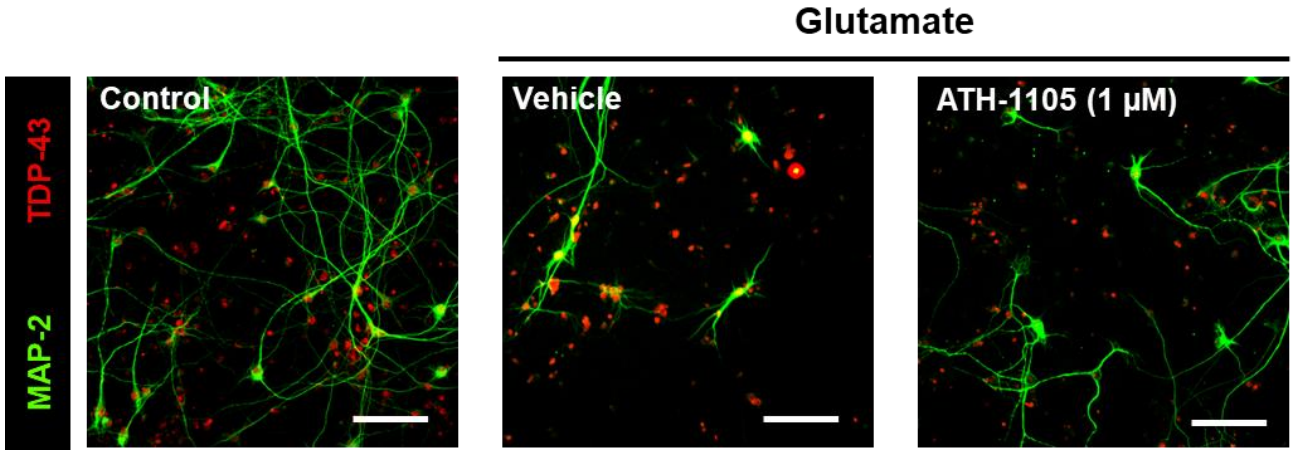




ATH-1105 increases activation of the HGF system, and stimulates downstream signaling through neurotrophic and neuroprotective pathways

1. Genç, B, et al.. 2023. Gene Ther 30, 560–574 (2023)
2. Vallarola, A. et al., 2020. International Journal of Molecular Sciences 21, 8542

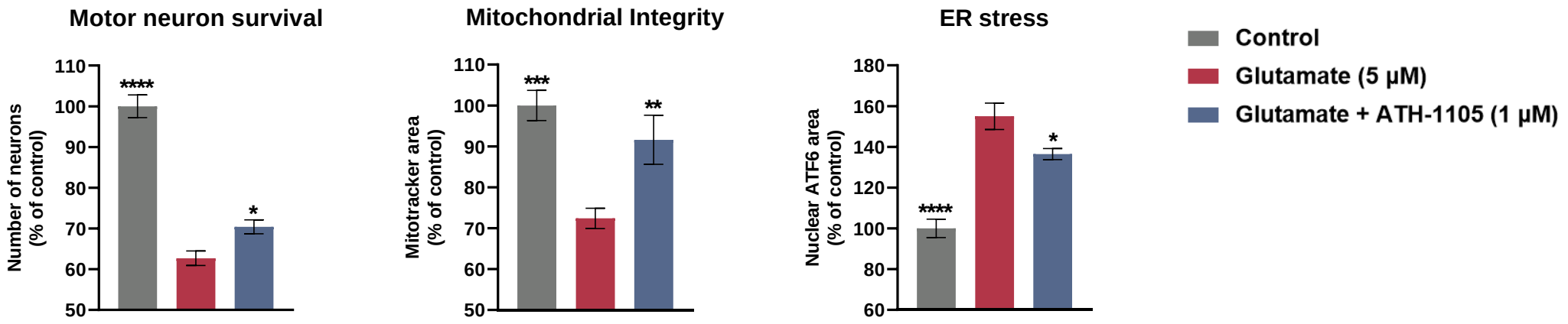
ATH-1105 exerts neuroprotective effects in a SOD1^{G93A} genetic background



Primary motor neuron cultures collected from animals with a SOD1 mutation are sensitive to glutamate-mediated excitotoxicity

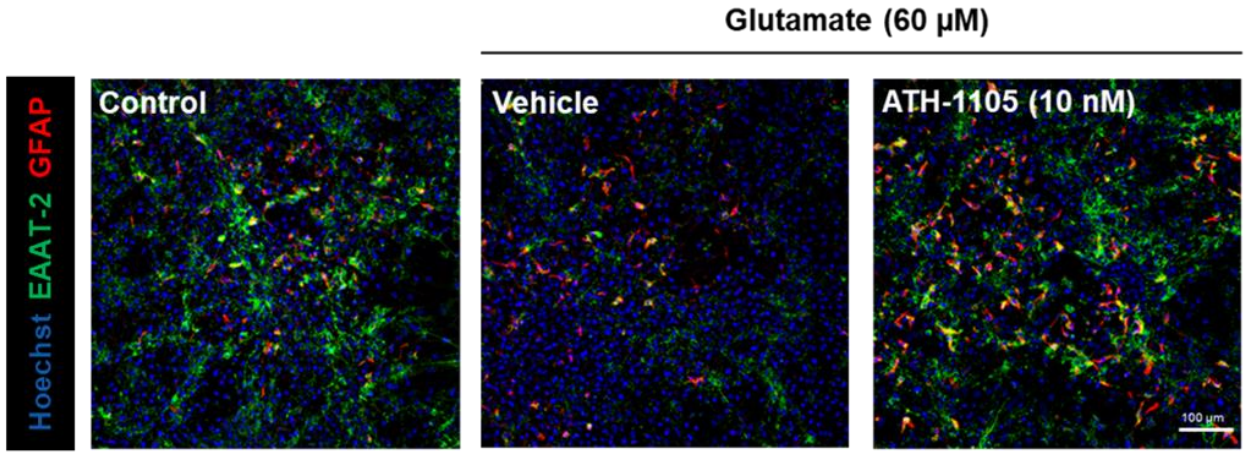
ATH-1105 treatment of glutamate challenged SOD1^{G93A} motor neuron cultures resulted in:

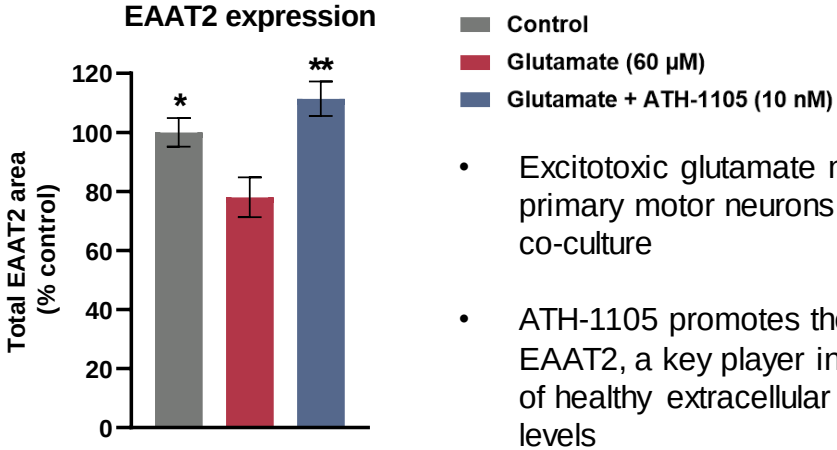
- Increased neuron survival
- Increased mitochondrial integrity
- Reduced ER stress



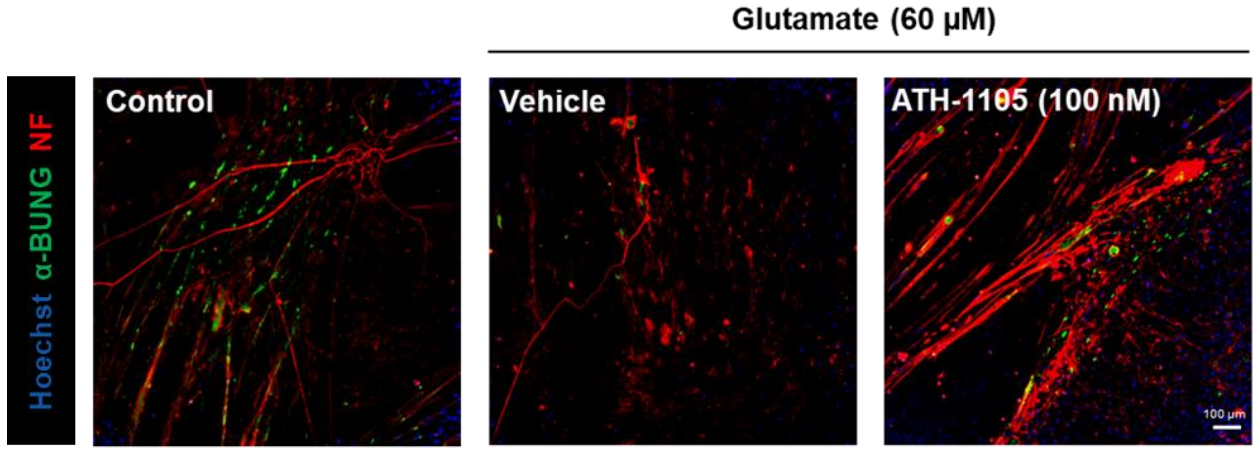
Abbreviations: **ER,** endoplasmic reticulum; **MAP2**, microtubule associated protein 2; **SOD1**, superoxide dismutase type 1 G93A;
Statistics applied: One-way ANOVA with Fisher's LSD; p<0.05, **p<0.01, ***p<0.001, ****<p0.0001 vs. Glutamate alone. n = 5-6. Scale bar = 100 µm. Select doses are shown

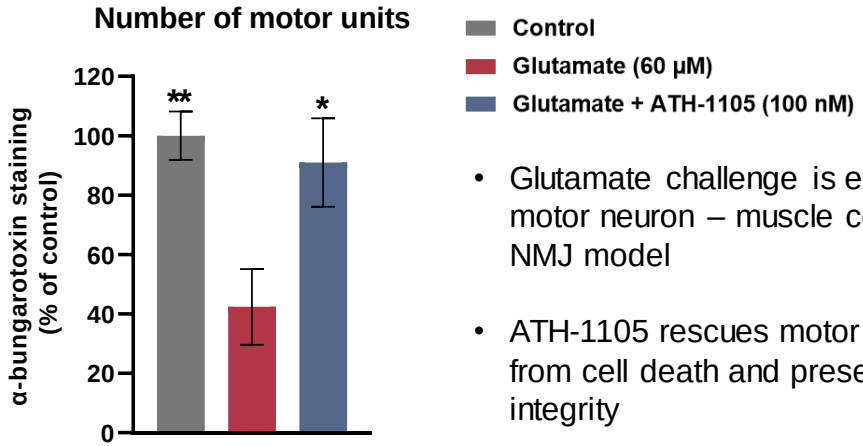
ATH-1105 protects against glutamate-induced toxicity in primary motor neuron-astrocyte and motor neuron-muscle co-cultures





- Excitotoxic glutamate negatively impacts primary motor neurons and astrocytes in co-culture
- ATH-1105 promotes the expression of EAAT2, a key player in the maintenance of healthy extracellular neurotransmitter levels



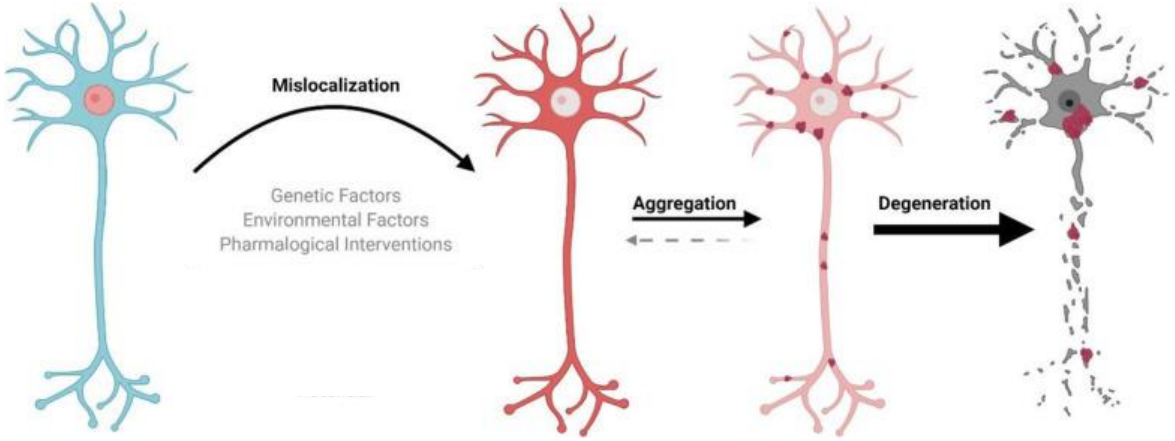


- Glutamate challenge is excitotoxic to motor neuron – muscle co-culture, an NMJ model
- ATH-1105 rescues motor neurons from cell death and preserves NMJ integrity

Abbreviations: **GFAP,** Glial fibrillary acidic protein; **EAAT2,** Excitatory amino acid transporter-2, **α–bung,** alpha-bungarotoxin; **NF**, neurofilament-200
Statistics applied: One-way ANOVA with LSD; *p<0.05, **p<0.01 vs. Glutamate alone. n = 5-6. Scale bar = 100 µm. Select doses are shown

TDP-43 pathology is a hallmark of ALS

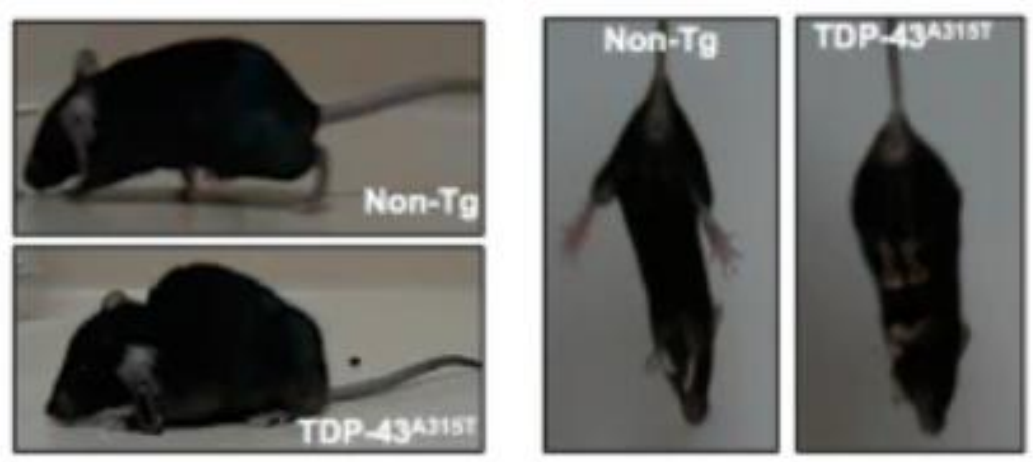
- TAR DNA Binding Protein 43 (TDP-43) is a normal protein with roles in transcription, translation, and mRNA transport and stabilization.
  - Under certain conditions, this protein becomes dysfunctional and accumulates in the cytoplasm[1]
- 95-97% of all ALS patients have cytosolic aggregates of TDP-43; several mutations in TDP-43 have been identified in ALS patients[1,2]



Adapted from Suk and Rousseaux, 2020

TDP-43 mouse model of ALS

- Prp-TDP43^{A315T} transgenic mice ("ALS mice") express mutant TDP-43, resulting in a phenotype resembling ALS—including TDP-43 protein pathology, motor dysfunction, neurodegeneration, and neuroinflammation[3]



Adapted from Bargsted et al., 2017

1. Suk et al., 2020. Mol Neurodegener 15(1):45
2. Wegorzewska et al., 2009. PNAS 106(44):18809-14
3. JAX, Strain #010700, https://www.jax.org/strain/010700
4. Bargsted et al., 2017. Sci Rep 7,14266

Evaluation of ATH-1105 in the TPD-43 mouse model

Previously ATH-1105 has demonstrated :

- Dose-dependent improvement in motor and nerve function compared to vehicle in the ALS mouse model
- Preservation of sciatic nerve morphology
- Reduction in plasma markers of inflammation and neurodegeneration

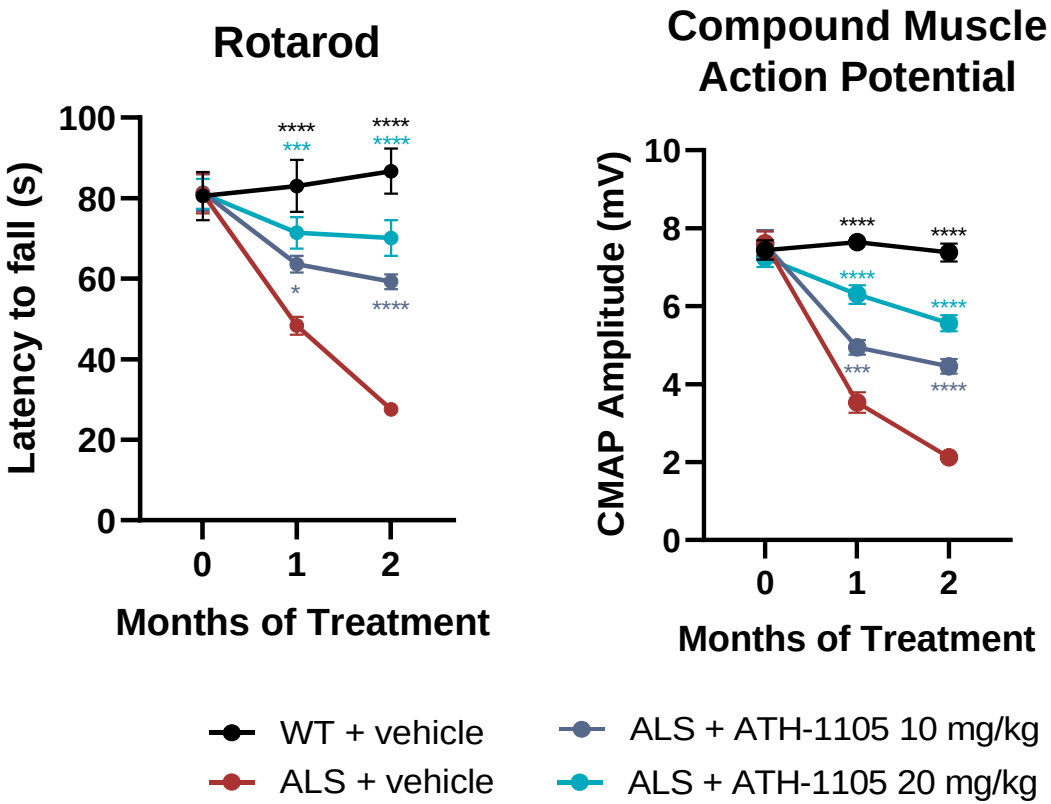
Initial findings presented at MNDA 2022 and AAN 2023

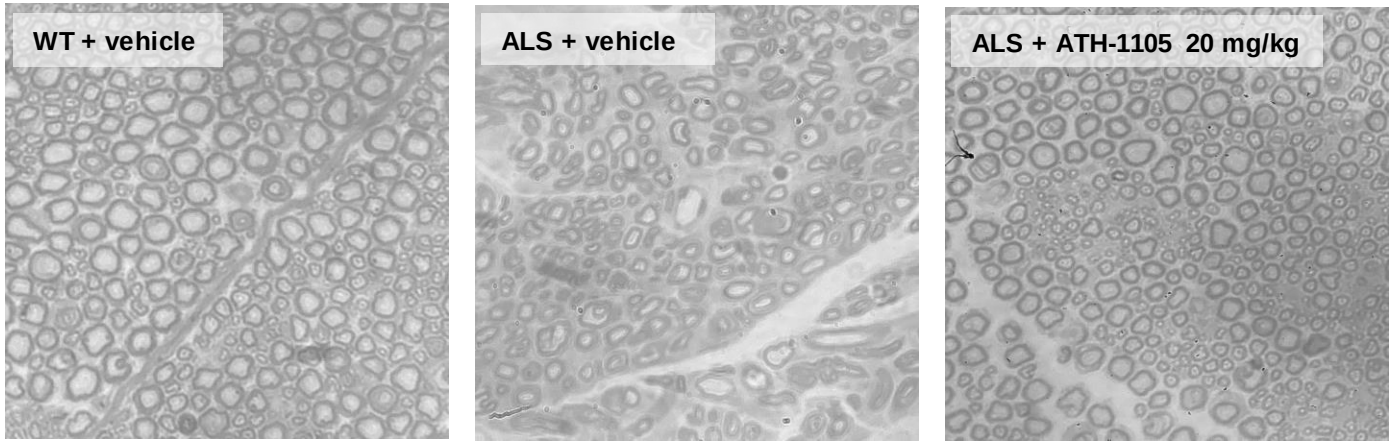
Recent studies for presentation:

- Evaluation of ATH-1105 on survival
- Assessment of effects of ATH-1105 with early (prophylactic) or delayed (therapeutic) intervention
- Evaluation of the effects of ATH-1105 and riluzole, alone and in combination

ATH-1105 exhibits dose-dependent improvement in motor and nerve function in the Prp-TDP43^{A315T} mouse model

- Review of initial findings





Sciatic nerve cross-section

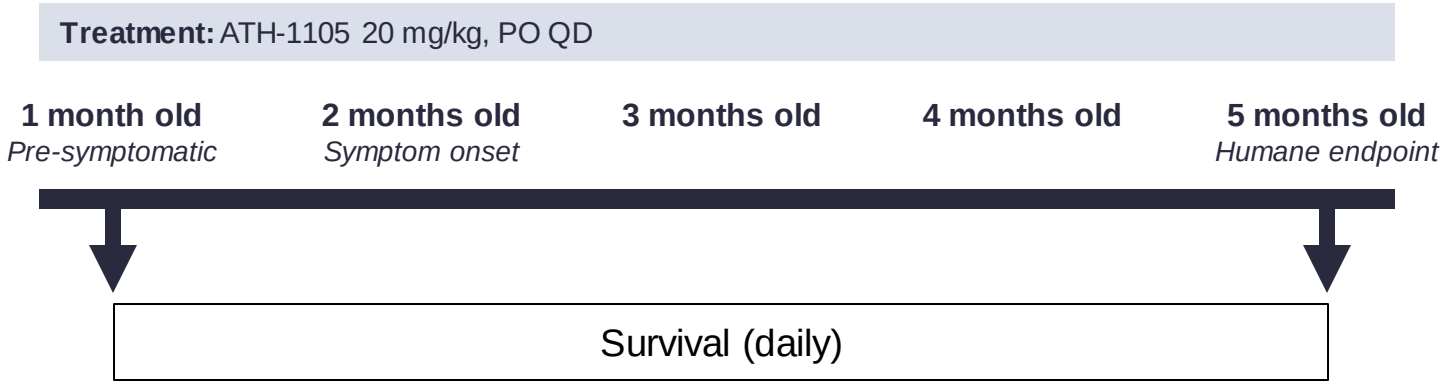
Data presented as mean ± SEM
Statistics applied: 2-way ANOVA with the Dunnett test versus ALS + vehicle. *p < 0.05 ,**p < 0.01; ***p < 0.001; ****p < 0.0001.n = 10 mice per group

Evaluation of the impact of ATH-1105 on survival in the Prp-TDP43^{A315T} mouse model of ALS

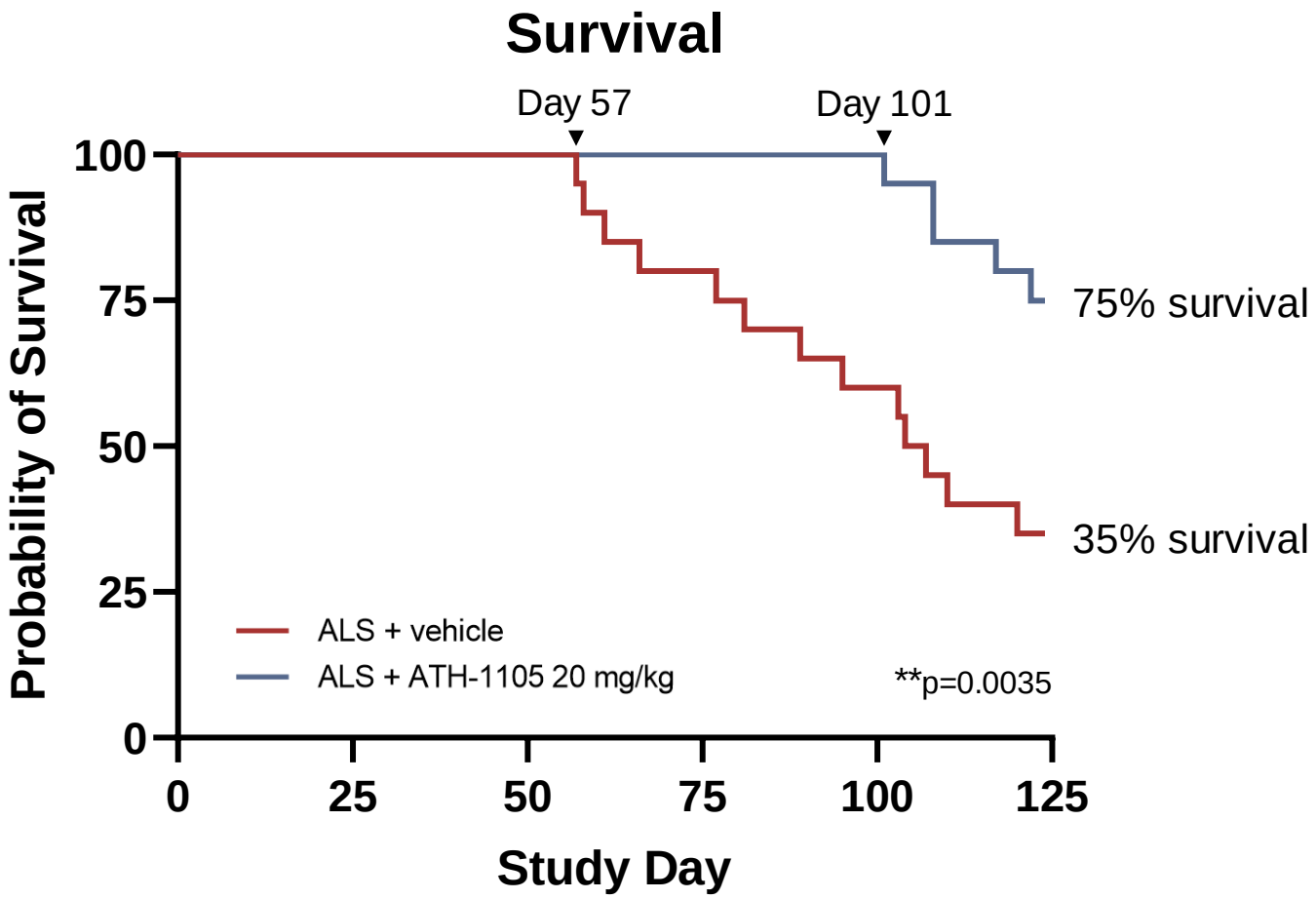
Study design

Groups: 20 mice per group

1. **ALS + vehicle**
   TDP-43^{A315T} mice treated with oral vehicle
2. **ALS + ATH-1105, 20 mg/kg**
   TDP-43^{A315T} mice treated with oral ATH-1105



ATH-1105 significantly improves survival in a mouse model of ALS



Rightward shift = extended survival

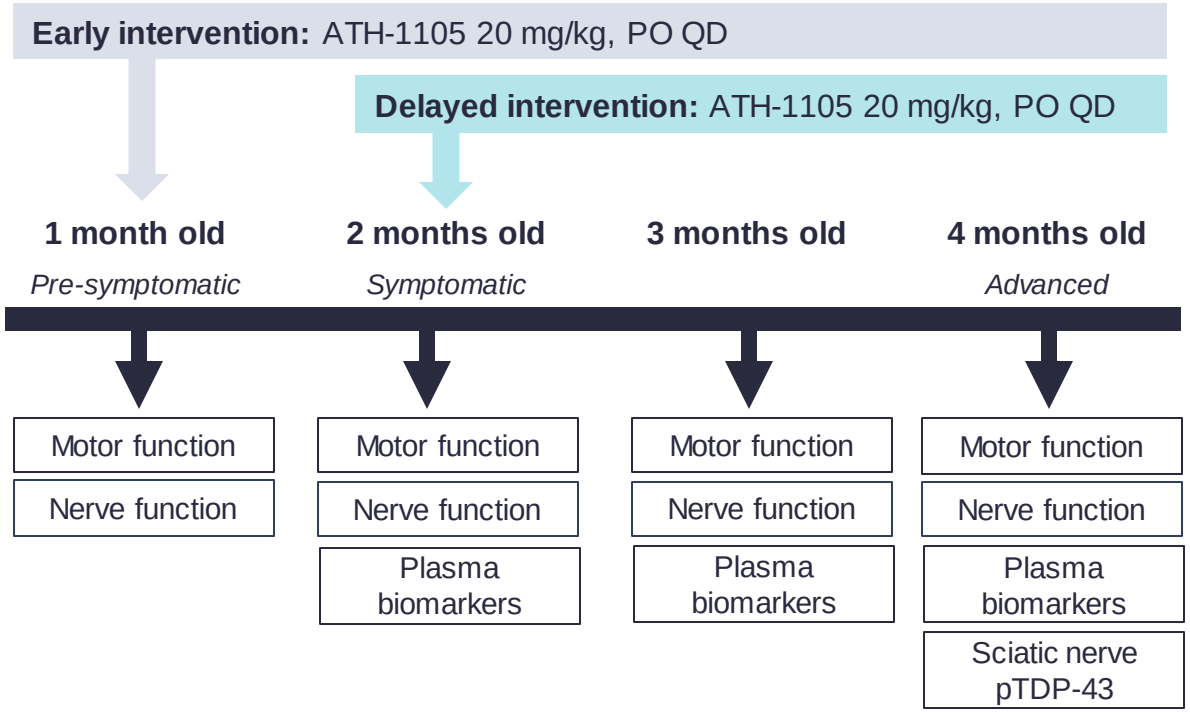
Data presented as Kaplan-Meier curve
Statistics applied: Log-rank (Mantel-Cox) test for survival curve comparison, **p<0.01. n=20 mice per group at start

Assessment of effects of ATH-1105 with early or delayed intervention in the Prp-TDP43^{A315T} mouse model of ALS

Study design

Groups: 10 mice per group

1. **WT + vehicle**
   WT mice treated with oral vehicle
2. **ALS + vehicle**
   TDP-43^{A315T} mice treated with oral vehicle
3. **ALS + Early intervention ATH-1105, 20 mg/kg**
   TDP-43^{A315T} mice treated with oral ATH-1105
4. **ALS + Delayed intervention ATH-1105, 20 mg/kg**
   TDP-43^{A315T} mice treated with oral ATH-1105



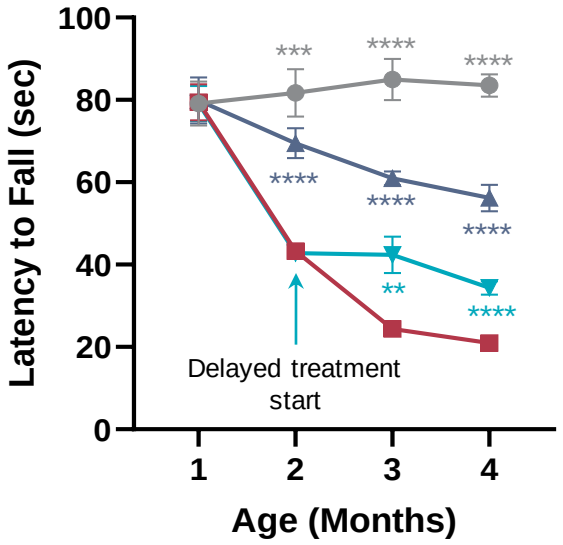
ATH-1105 treatment shows beneficial effects with either early or delayed administration

WT + Vehicle
ALS + Vehicle
ALS + ATH-1105 20 mg/kg (Early)
ALS + ATH-1105 20 mg/kg (Delayed)

Motor function

Similar results observed in grip test, kondziela, and balance beam

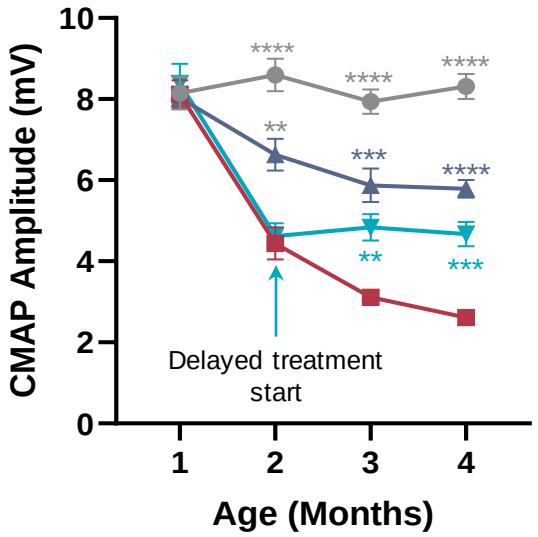
Rotarod



Nerve function

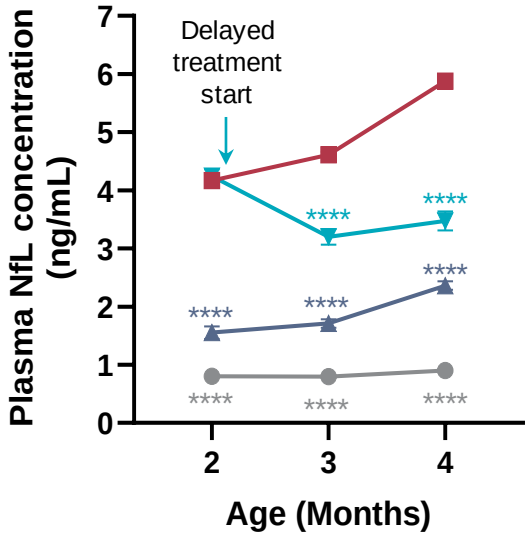
Similar results observed in nerve conduction velocity

Compound muscle action potential amplitude



Neurodegeneration

Plasma NfL



Delayed intervention with ATH-1105 results in a slowing of further disease progression from time of treatment onset

A reduction in plasma NfL levels observed once delayed ATH-1105 treatment begins

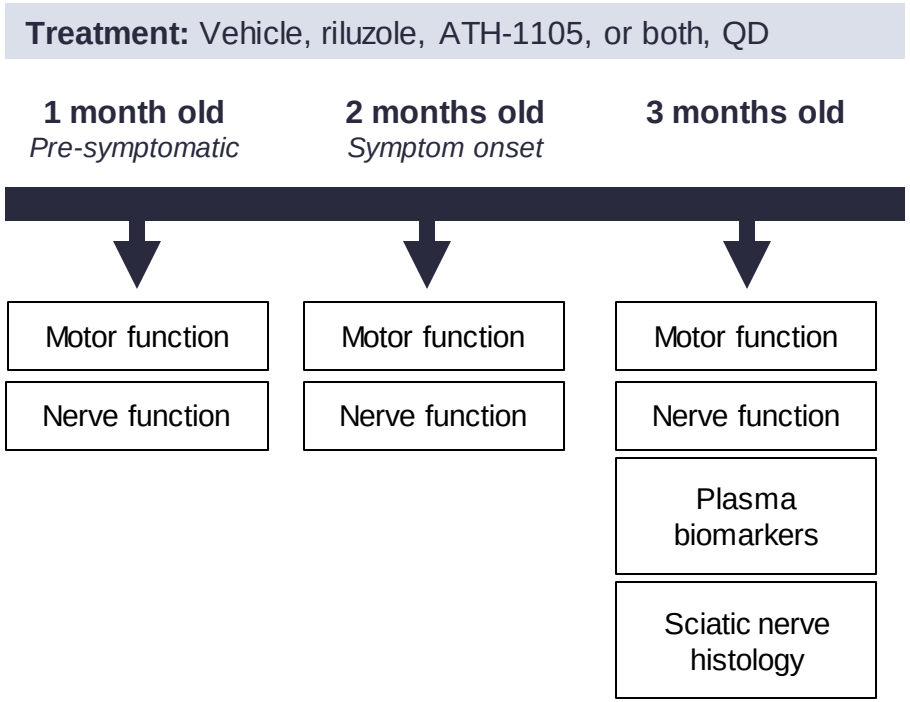
Data presented as mean ± SEM.
Statistics applied: 2-way ANOVA with the Dunnett's test versus ALS + vehicle. **p < 0.01; ***p < 0.001; ****p < 0.0001. n=10 mice per group

Evaluation of the effects of ATH-1105 and riluzole, alone or in combination in the Prp-TDP43^{A315T} mouse model of ALS

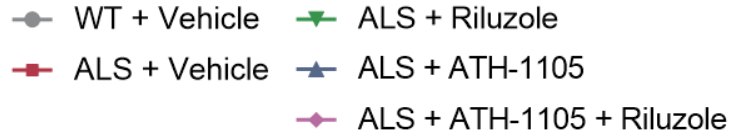
Study design

Groups: 10 mice per group

1. **WT + vehicle**
   WT mice treated with oral vehicle
2. **ALS + vehicle**
   TDP-43^{A315T} mice treated with oral vehicle
3. **ALS + Riluzole, 5 mg/kg**
   TDP-43^{A315T} mice treated with i.p. riluzole once daily
4. **ALS + ATH-1105, 20 mg/kg**
   TDP-43^{A315T} mice treated with oral ATH-1105 once daily
5. **ALS + ATH-1105 + Riluzole**
   TDP-43^{A315T} mice treated with oral ATH-1105 and i.p. riluzole once daily

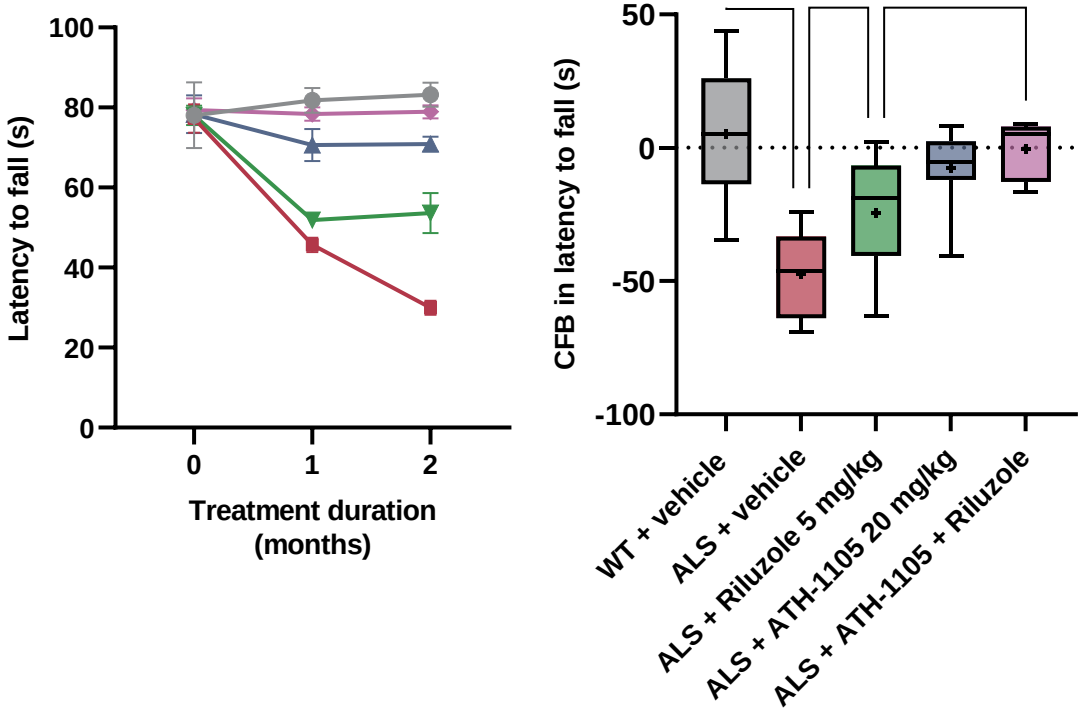


ATH-1105 exhibited superior preservation of motor and nerve function over riluzole in a mouse model of ALS



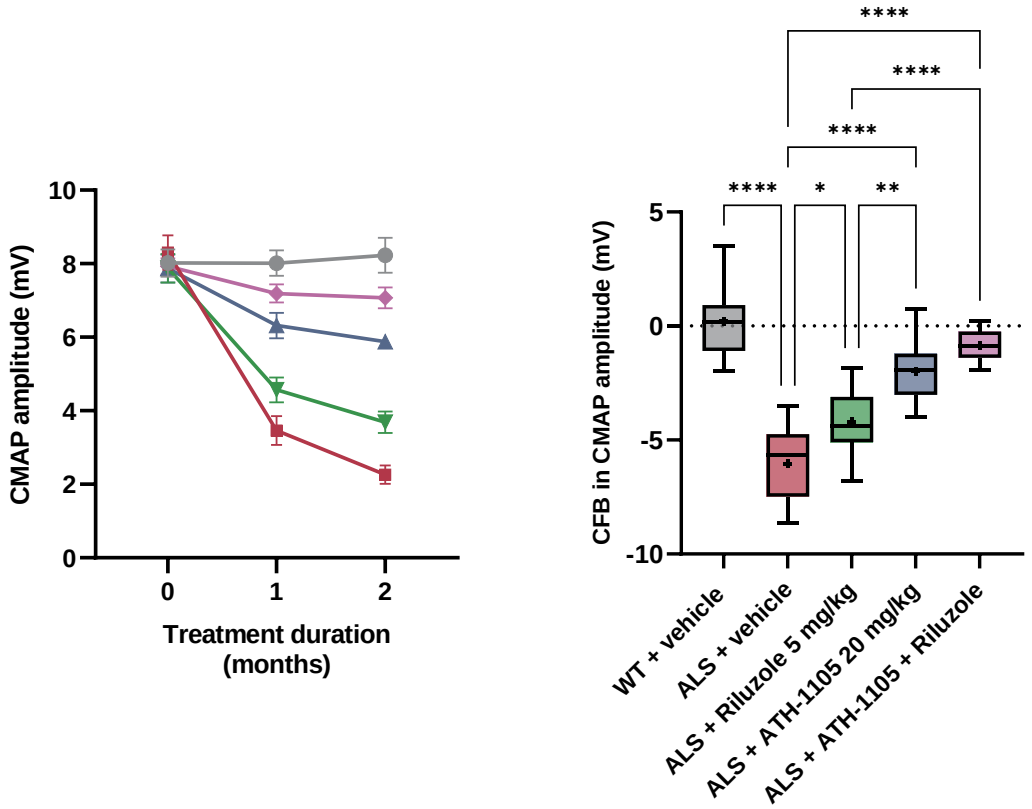
Rotarod

Similar results observed in grip test, kondziela, and balance beam



CMAP amplitude

Similar results observed in nerve conduction velocity



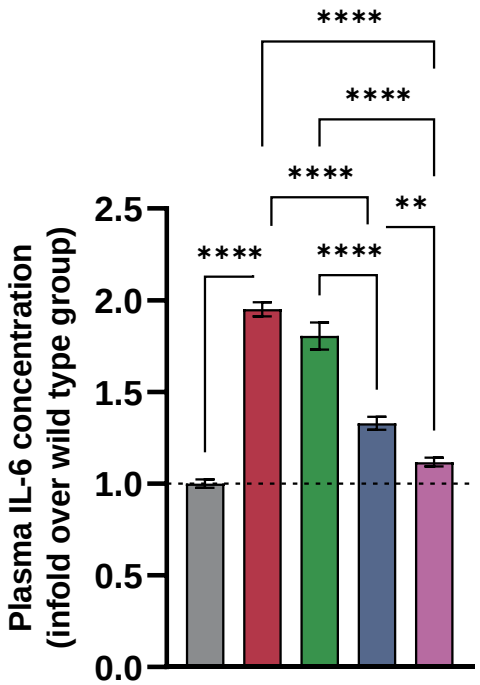
Abbreviations: **CFB**, change from baseline
Data presented as mean ± SEM, and box-and-whisker plot
Statistics applied to CFB: One-way ANOVA with Tukey's multiple comparisons. *p<0.05; **p<0.01; *** p<0.001; **** p<0.0001. n=10 mice per group

ATH-1105 exhibited superior reduction of plasma biomarkers and sciatic nerve pTDP-43 over riluzole in a mouse model of ALS

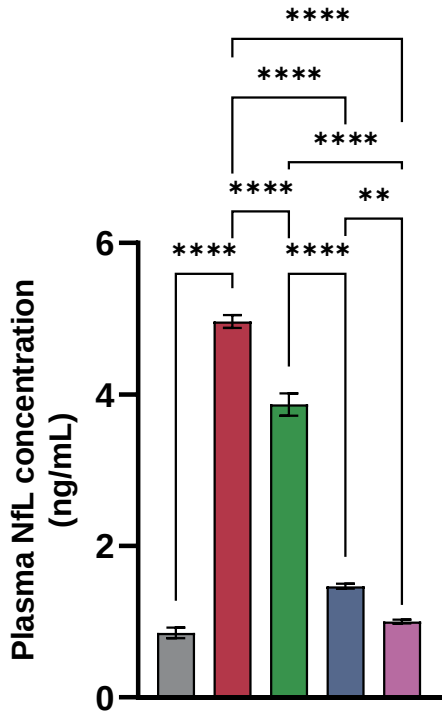
WT + Vehicle
ALS + Vehicle
ALS + Riluzole
ALS + ATH-1105
ALS + ATH-1105 + Riluzole

Plasma IL-6

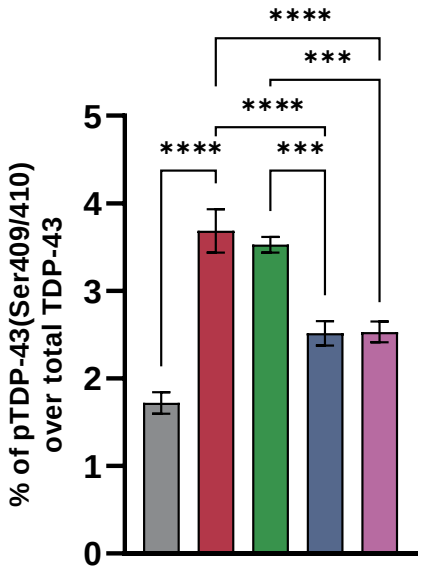
Similar results observed with plasma TNF-α



Plasma NfL



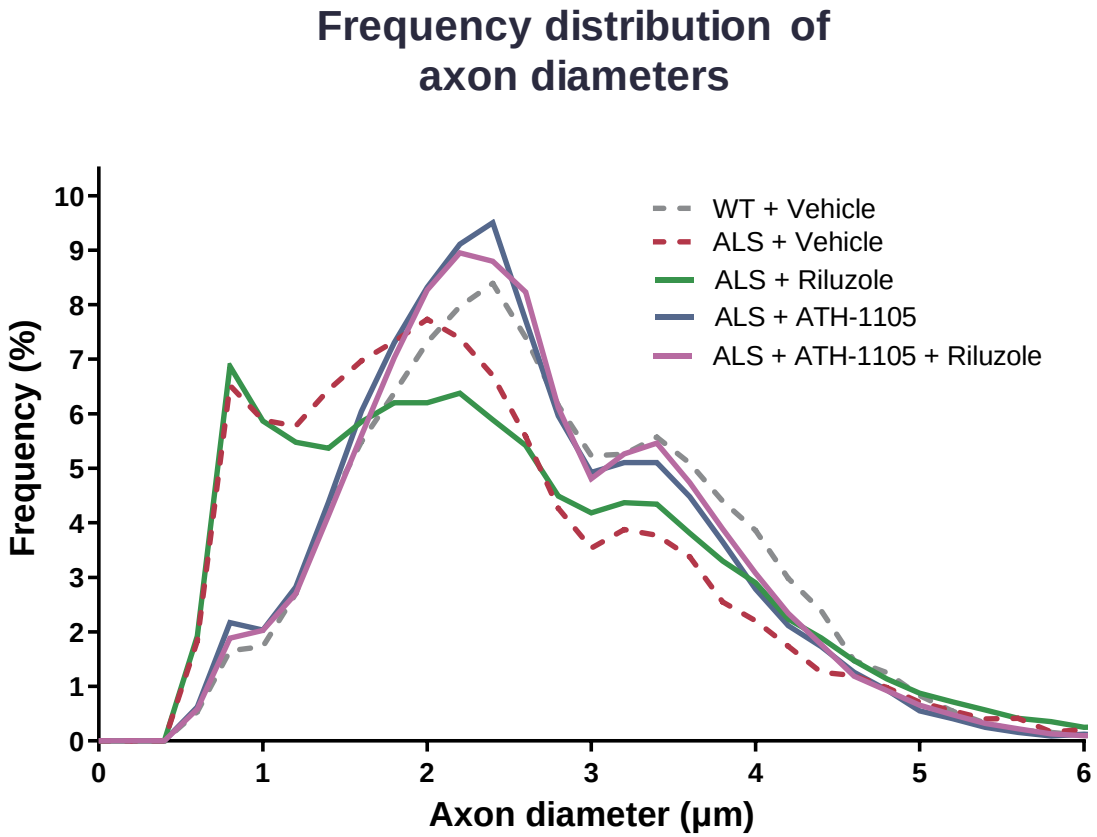
Sciatic nerve pTDP-43



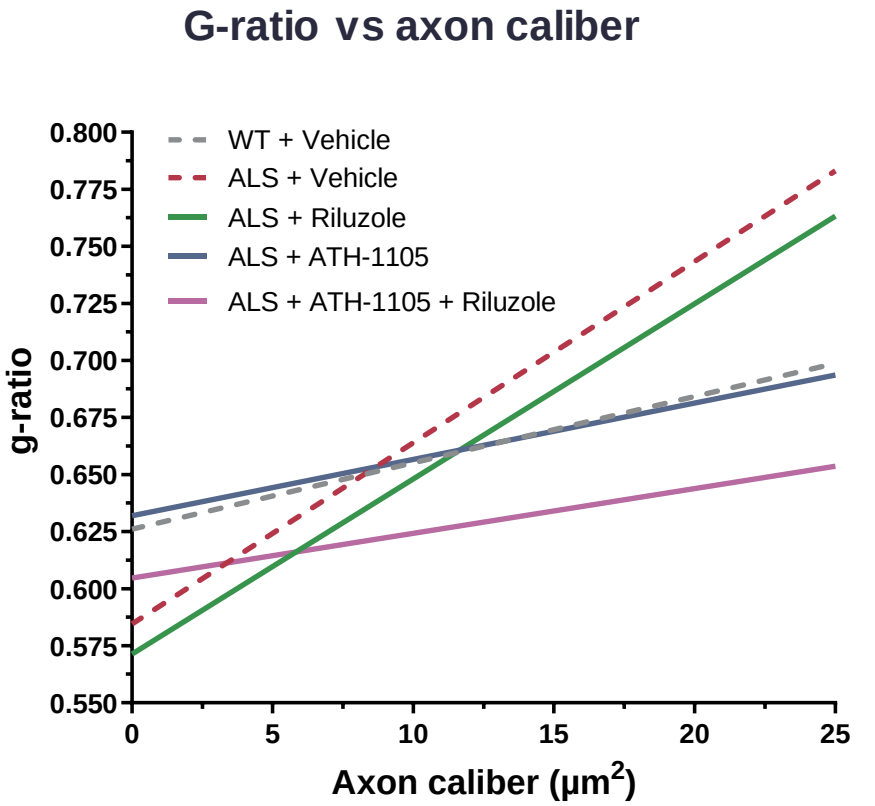
ATH-1105 reduced levels of sciatic nerve pTDP-43, whereas riluzole had no effect under these conditions

Data presented as mean ± SEM. Statistics applied: One-way ANOVA with Dunnett's multiple comparisons vs all groups. *p<0.05, **p<0.01, **p<0.001, ****p<0.0001. Comparisons vs WT + Vehicle included in analysis, but not shown. n=10 mice/group

ATH-1105 exhibited superior preservation of normal sciatic nerve axon diameters and myelination over riluzole in a mouse model of ALS



ATH-1105 protected against selective loss of large-diameter axons



ATH-1105 protected against the thinning of myelin on large-diameter axons

Data supports the continued development of ATH-1105 as a potential therapeutic for ALS

In vitro data reveals multiple mechanisms by which ATH-1105 can protect motor neurons:

- In primary motor neurons, ATH-1105 reduces excitotoxicity, apoptotic signaling, and astrocyte activation while promoting glutamate transporter expression, preserving neuromuscular junction integrity, and improving mitochondrial health

ATH-1105 demonstrated broad effects in the Prp-TDP43^{A315T} mouse model of ALS

- Prevented motor and nerve function decline
- Reduced plasma markers of pro-inflammatory cytokines and neurodegeneration (NfL)
- Extended survival
- Provided benefit when administered both early (pre-symptomatic) and delayed (post-symptomatic)
- Decreased pTDP-43 pathology in the sciatic nerve
- Preserved nerve morphology
- Provided greater benefit than riluzole under the conditions tested, with potential additive effects of ATH-1105 + riluzole observed in several measures

Thank you!