ATH-1105, a small-molecule targeting the neurotrophic HGF system, is neuroprotective and prolongs survival in the Prp-TDP43^{A315T} mouse model of ALS

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CONCLUSIONS

1. **Treatment with ATH-1105 significantly protects against body weight loss and prolongs survival in ALS mice**
2. **ATH-1105 treatment can slow disease progression when administered at early or later stages of disease in ALS mice**
3. **The effects of ATH-1105, including protection of sciatic nerve axonal and myelin integrity, are beneficial when administered either alone or in combination with riluzole**

KEY TAKEAWAY

These data highlight the therapeutic potential of ATH-1105 and support its continued development for the treatment of ALS

Acknowledgments

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Disclosures

Andrée-Anne Berthiaume, Kayla N Kleist, Sharay E Setti, Sherif M Reda, Jewel L Johnston, Robert W Taylor, Liana R Stein, and Kevin J Church are employees and stockholders of Athira Pharma, Inc.

Disclaimer

ATH-1105 is an investigational therapy and has not received FDA approval nor been demonstrated to be safe or effective for any use.

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INTRODUCTION

- ALS is a complex and fatal neurodegenerative disease preferentially impacting motor neurons[1]
- ALS is characterized by progressive neuromuscular dysfunction in association with multiple ongoing pathological processes including motor neuron degeneration, axonal demyelination, systemic inflammation, and extranuclear TDP-43 protein accumulation[2,3]
  - Up to 97% of people with ALS exhibit TDP-43 proteinopathy,[4-5]
- The Prp-TDP43^{A315T} transgenic mouse model of ALS recapitulates many of the key features of ALS, rendering it a useful tool for preclinical investigation[6,7]
- Promotion of neurotrophic HGF signaling system activity has been reported to have beneficial effects in preclinical models of ALS through its multimodal neuroprotective and neurotrophic actions[8-11]
- We have developed a series of novel small molecule positive modulators of the neurotrophic HGF system for systemic delivery,[12] including the orally bioavailable and brain penetrant ATH-1105[13]

OBJECTIVE

Evaluate the impact of ATH-1105 treatment on survival, neuromuscular function, and sciatic nerve integrity in the Prp-TDP43^{A315T} mouse model of ALS

METHODS

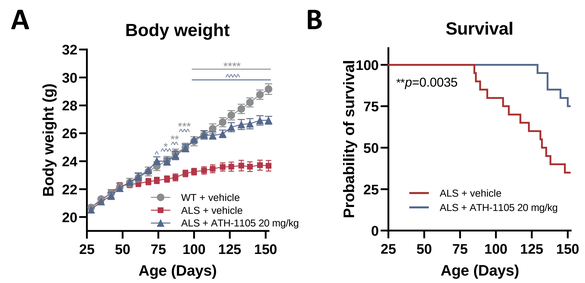
Evaluating efficacy in Prp-TDP43^{A315T} ("ALS") mice

Figure 1. In vivo study designs

- In three independent studies, one-month-old male mice were sorted into **(A)** 3, **(B)** 4, or **(C)** 5 groups and given daily treatment according to group assignments. Sample size for Study 1 was 20 mice per group at experiment start. Sample size for Study 2 and Study 3 was 10 mice per group at experiment start
- All studies contained the following groups:
  - WT + vehicle: WT mice treated with vehicle daily
  - ALS + vehicle: Prp-TDP43^{A315T} ("ALS") mice (JAX #010700) treated with vehicle daily
  - ALS + treatment: Prp-TDP43^{A315T} ("ALS") mice treated as depicted in Figure 1
- Tests of motor and nerve function, and quantification of plasma biomarkers and pTDP-43 in the sciatic nerve were carried out as described in a previous publication from our group[13]

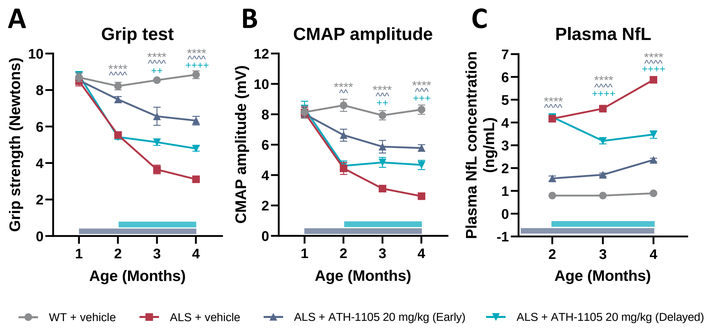
RESULTS

Figure 2. (Study 1) ATH-1105 normalizes body weight and prolongs survival in the Prp-TDP43^{A315T} mouse model of ALS



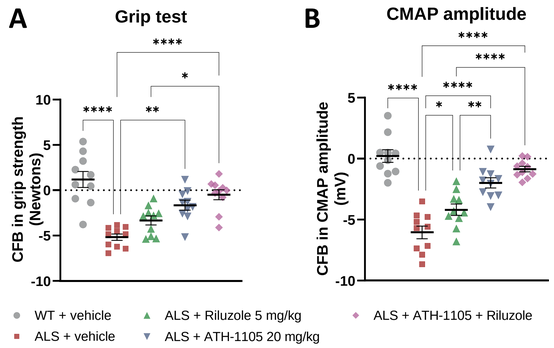
(A) Graphical representation of body weight in grams, collected approximately every 7 days from 1 month of age (28 days old). Data are presented as mean ± SEM. Statistical significance determined by mixed-effects model analysis followed by Dunnett's multiple comparisons. "*" represents WT + vehicle versus ALS + vehicle comparisons. "^" represents ALS + ATH-1105 20 mg/kg versus ALS + vehicle comparisons. The following applies to all symbols: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. **(B)** Graphical representation of probability of survival by age, in days (maximum of 152 days old). Data are presented as Kaplan-Meier survival probability curves. Statistical significance determined by log-rank (Mantel-Cox) test; n = 20 mice per group at experiment start.

Figure 3. (Study 2) Disease progression is attenuated in ALS mice following early or delayed treatment initiation with ATH-1105



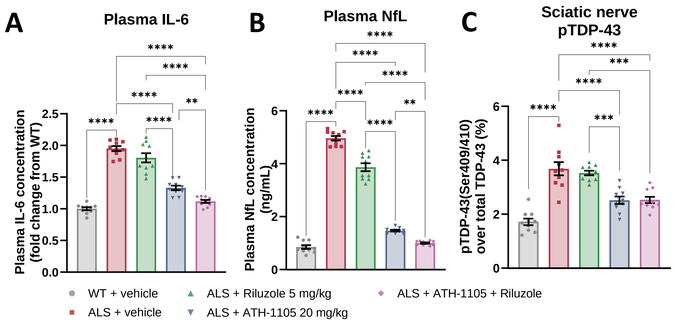
Graphical representation of **(A)** grip strength, in Newtons, and **(B)** CMAP amplitude, in mV, from 1 to 4 months of age. **(C)** Quantification of plasma NfL levels from 2 to 4 months of age. Solid bars along x axis depict treatment duration for the early intervention (bottom; dark blue) and delayed intervention (top; teal) ATH-1105-treated groups. Data are presented as mean ± SEM. Statistical significance determined by mixed effects analysis with Dunnett's multiple comparisons test versus ALS + vehicle group. "*" represents WT + vehicle vs ALS + vehicle. "^" represents ALS + ATH-1105 (Early) vs ALS + vehicle. "+" represents ALS + ATH-1105 (Delayed) vs ALS + vehicle. The following applies to all symbols: * p <0.05; ** p <0.01; *** p <0.001; **** p <0.0001; n=9-10 mice per group.

Figure 4. (Study 3) ATH-1105 treatment alone or in combination with riluzole improves motor and nerve function in ALS mice



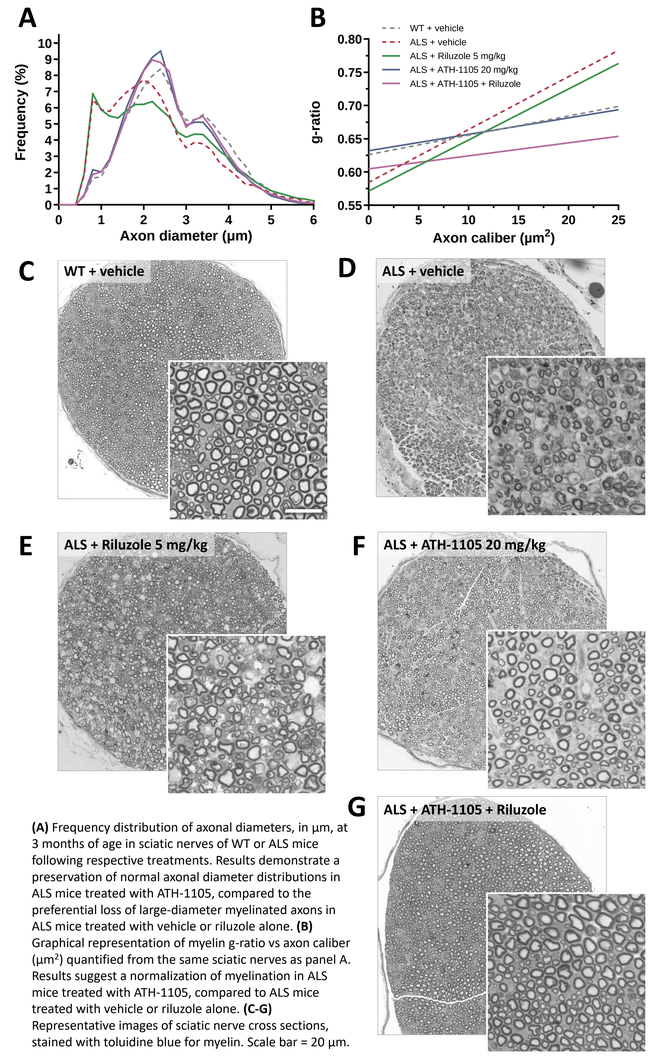
Graphical representation of change from baseline (CFB; 1 month of age) at three months of age in **(A)** grip strength and **(B)** CMAP amplitude, where a value of "0" represents no progression in ALS-related neuromuscular dysfunction over the two-month experimental time course. Data are presented as mean ± SEM; n=10 each. Statistical significance determined by one-way ANOVA with Dunnett's multiple comparisons. Comparisons versus WT + vehicle included in analyses, but not shown. * p <0.05; ** p <0.01; *** p <0.001; **** p <0.0001.

Figure 5. (Study 3) ATH-1105 demonstrates greater anti-inflammatory effects, neuroprotection, and pTDP-43 reduction in ALS mice compared to riluzole at the doses tested



Graphical representation of **(A)** IL-6 and **(B)** NfL levels in plasma and **(C)** the percent of total TDP-43 phosphorylated at Ser409/410 in homogenized sciatic nerve at 3 months of age, following 2 months of respective treatments. Data are presented as mean ± SEM. Statistical significance determined by one-way ANOVA with Dunnett's multiple comparisons. Comparisons versus WT + vehicle included in analyses, but not shown. * p <0.05; ** p <0.01; *** p <0.001; **** p <0.0001; n=10 mice per group.

Figure 6. (Study 3) ATH-1105 treatment alone or in combination with riluzole preserves axonal integrity and myelination in the sciatic nerve



(A) Frequency distribution of axonal diameters, in µm, at 3 months of age in sciatic nerves of WT or ALS mice following respective treatments. Results demonstrate a preservation of normal axonal diameter distributions in ALS mice treated with ATH-1105, compared to the preferential loss of large-diameter myelinated axons in ALS mice treated with vehicle or riluzole alone. **(B)** Graphical representation of myelin g-ratio vs axon caliber (µm^2) quantified from the same sciatic nerves as panel A. Results suggest a normalization of myelination in ALS mice treated with ATH-1105, compared to ALS mice treated with vehicle or riluzole alone. **(C-G)** Representative images of sciatic nerve cross sections, stained with toluidine blue for myelin. Scale bar = 20 µm.

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Abbreviations: **ALS**, amyotrophic lateral sclerosis; **ANOVA**, analysis of variance; **CFB,** change from baseline; **CMAP**, compound muscle action potential; **HGF**, hepatocyte growth factor; **IL-6**, interleukin 6; **mV**, millivolts; **NfL**, neurofilament light chain; **PO**, oral gavage; **pTDP-43**, phosphorylated TDP-43; **QD**, once a day; **SEM**, standard error of the mean; **TDP-43**, TAR DNA-binding protein 43; **WT**, wild type