

Poster #122

Title: Small-Molecule HGF/MET Positive Modulators Effectively Reduce Pain-Related Behaviors in a Rat Model of Diabetic Neuropathy

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Methods

Validation of HGF/MET Phosphorylation

- HEK293 cells were treated with HGF 1 ng/mL and varying concentrations of ATH-1018 or ATH-1019
 - HGF at 1 ng/mL was empirically determined as a subthreshold dose of HGF, which does not significantly induce MET phosphorylation (pMET)
- Enzyme-linked immunosorbent assay (ELISA) was used to quantify levels of pMET

Study Design

- On day 0, diabetes was induced in 6- to 8-week-old Sprague Dawley rats by a single dose of STZ at a concentration of 55 mg/kg intravenously (IV)
- On day 4, rats were screened for serum blood glucose levels >250 mg/dL to confirm diabetes
- Neuropathic pain-related behaviors were characterized on day 14
- ATH-1018 and ATH-1019 were investigated in 2 separate studies with similar study protocols
 - Each study had 3 control groups:
 - The sham control group received vehicle rather than an STZ injection on day 0 (n = 12)
 - The diabetic control group received vehicle injections rather than drug treatment (n = 12)
 - The positive control group was treated with pregabalin (10 mg/kg) (n = 12-13)
 - ATH-1018 experimental groups received 4 doses (0.156, 0.625, 2.5, and 10 mg/kg by mouth [PO]) once daily (n = 13, each treatment group)
 - ATH-1019 experimental groups received 4 doses (0.00625, 0.025, 0.1, and 1 mg/kg PO) once daily (n = 12, each treatment group)
 - Treatments were administered from days 15-28

In Vivo Pain Assay

- Mechanical allodynia was assessed using von Frey filaments (1.4, 4, 10, 15, 26, 48, and 60 g)
 - Filaments were pushed against the animal's foot, and the paw withdrawal threshold (PWT, in grams) was established as the force that resulted in a pain response
 - In the ATH-1018 study, behaviors were assessed 1 hour after dosing on days 23* and 28 (treatment days 9 and 14)
 - *Study design planned for assessment on day 21 instead of 23, but research organization ran into COVID-related staffing issues
 - In the ATH-1019 study, behaviors were assessed 1 hour after dosing on days 21 and 28 (treatment days 7 and 14)
 - On day 25, there was an additional evaluation before treatment (treatment day 10, after the 9th dose had cleared from the blood plasma [at >7× the half-life (t_{1/2})])

Statistical Analyses

- Statistical analyses were performed using Prism 9 (GraphPad, Inc.)
 - Mean body weight for control and treatment groups was assessed using a two-way analysis of variance (ANOVA) with Dunnett's multiple comparison test versus the diabetic control group
 - Blood glucose level and PWT metrics for mechanical allodynia were assessed using a one-way ANOVA with Dunnett's multiple comparison test versus the diabetic control group