THE EFFECTS OF THE FABP5 INHIBITOR ART26.12 IN A RAT MODEL OF DIABETIC PAINFUL NEUROPATHY

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Introduction

Inhibitors of fatty acid binding protein 5 (FABP5) are effective in multiple models of pain, inhibited by antagonists of CB_1, TRPV1 and PPARα. The potent (Ki 0.77 ± 0.08 μM) and selective (>10x) FABP5 inhibitor ART26.12 (Figure 1) is under development with Artelo Biosciences under a license agreement with Stony Brook University, with successful data in oxaliplatin-induced and paclitaxel-induced peripheral neuropathy.

The aim of the present study was to examine the potential of ART26.12 in another peripheral neuropathy; the streptozotocin (STZ)-induced model of painful diabetic neuropathy.

Methods

Male Wistar rats were treated with STZ which selectively ablates insulin-producing β cells in the pancreas (55mg/kg IP) on day 0. By day 9-11 (neuropathic baseline; NeuP), animals had developed painful neuropathy as assessed by measurement of withdrawal threshold using calibrated von-Frey monofilaments applied to the plantar surface of the hindpaw, and diabetes (measured via blood glucose levels, ~30 mmol/L). Animals were treated orally with ART26.12 (25 or 100 mg/kg, BID) from day 15 for seven days, with von Frey measurements on day 15, 17 and 21, 2 hr after dosing (see Figure 2 schedule). Duloxetine was given on test days as an example of standard care. In vivo studies were carried out at Transpharmation, UK with ethical approval.

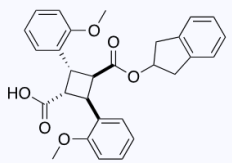

Figure 1. ART26.12

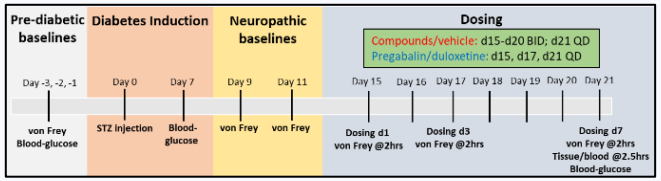

Figure 2. Study design

Update on ART26.12 Toxicology and DMPK

1. ART26.12 showed selectivity against a broad panel of enzymes and receptors with no off-target effects of concern.
2. ART26.12 has no in vitro toxicological effects, and has a NOAEL (No-Observable-Adverse-Effect-Level) of 1000 mg/kg/day after 14 days in rodents and dogs.
3. ART26.12 displayed dose-dependent plasma exposure following oral administration of solution or suspension formulations.
4. In the present STZ study, no adverse effects were observed following administration of ART26.12 at 25 and 100mg/kg twice daily for 7 days.

Results

All animals lost weight as a result of STZ treatment. Animals treated with Duloxetine lost significantly more weight compared to STZ+vehicle (Figure 3A). Terminal blood glucose levels were not different between groups (Figure 3B).

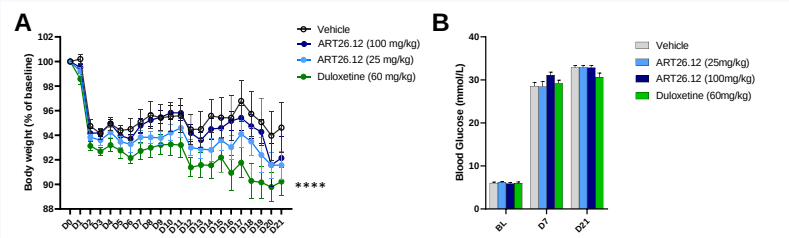

Figure 3. Changes in body weight (****p<0.0001 significant difference comparing duloxetine to STZ/vehicle) (A) and blood glucose responses (B) to ART26.12 in the STZ neuropathic pain model. Data is expressed as mean ± S.E.M. (n=7-10).

On day 15 (D15), after the first dose of ART26.12, withdrawal thresholds were significantly higher than neuropathic baseline (NeuP) levels with the higher dose of 100 mg/kg, suggesting reduced mechanical allodynia (Figure 4). On the third (D17) and seventh days (D21) of dosing, both 25 and 100 mg/kg ART26.12, significantly increased withdrawal thresholds. Duloxetine was only effective on the seventh day (D21).

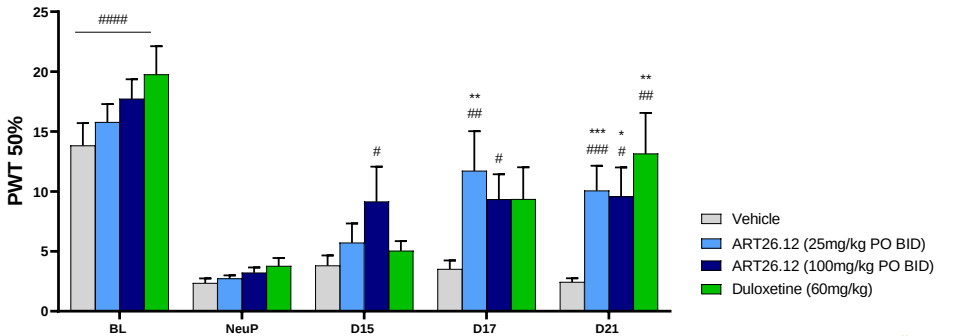

Figure 4. Mechanical allodynia measured using von Frey filaments. Data were analysed with a Mixed-effects model (REML) followed by Holm-Šídák's post hoc analysis. *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001 indicate statistically significant difference when compared to the STZ+vehicle group at the same timepoint (between-group comparison). #p<0.05, ##p<0.01, ###p<0.001, and ####p<0.0001 indicate statistically significant difference when compared to NeuP in the same group (within-group comparison). Data is expressed as mean ± S.E.M (n=7-10).

Quantitative bioanalysis by LC-MS/MS of terminal plasma and spinal cord levels of ART26.12 in STZ-treated animals showed an average plasma concentration of 5 ± 1.2 μM (25 mg/kg) and 39 ± 5.7 μM (100 mg/kg) and spinal cord concentration of 0.20 ± 0.09 μM (25 mg/kg) and 0.22 ± 0.11 μM (100 mg/kg)(Figure 5).

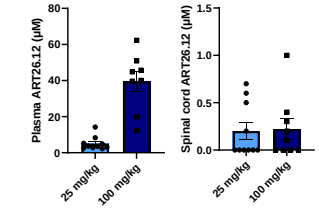

Figure 5. Terminal concentrations of ART26.12.

Conclusion: ART26.12 reduces mechanical hypersensitivity in a rat model of diabetic painful neuropathy. DMPK and toxicological studies continue to show a desirable drug profile for ART26.12. These data support the further development of ART26.12 as a novel therapeutic agent in peripheral neuropathies.

Acknowledgements:
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