THE EFFECTS OF THE FABP5 INHIBITOR ART26.12 IN PACLITAXEL-INDUCED 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 at Artelo Biosciences under a license agreement with Stony Brook University for the treatment and prevention of chemotherapy induced peripheral neuropathy (CIPN). We have previously reported positive effects of ART26.12 in oxaliplatin-induced neuropathy in rats.

The aim of the present study was to examine the potential of ART26.12 against a second chemotherapy agent, paclitaxel, in male and female rats.

Methods

ART26.12 (25 or 50 mg/kg BID PO) treatment was initiated for 22 days to adult male and female Sprague Dawley rats (from day -2 to day 20). On Day 0, Day 2, Day 4, and Day 6, paclitaxel (2 mg/kg IP) was administered to induce neuropathy. On Days 15, 16, 19 and 20, mechanical allodynia (Von Frey, left hind paw) and thermal hyperalgesia (cold plate) were assessed 2 hours after ART26.12 dosing. Duloxetine (30 mg/kg PO) was administered as a positive control. In vivo studies were carried out at Transpharmation, UK, under the Home Office project license number PPL-708841.

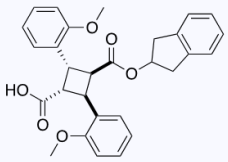

Figure 1. ART26.12

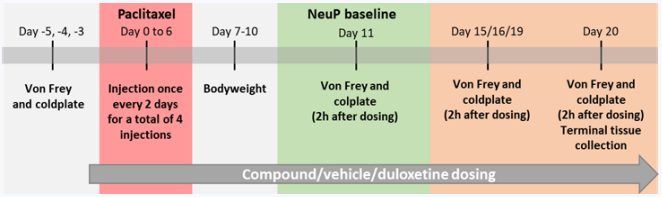

Figure 2. Study design

Results

In paclitaxel-treated male rats, ART26.12 (25 or 50 mg/kg BID PO) prevented the mechanical allodynia on day 15, 16, and 19 in a manner similar to duloxetine (Figure 3). The ART26.12-treated groups did not have a significant reduced withdrawal threshold (allodynia) compared to baselines values over the entire study.

In paclitaxel-treated female rats, ART26.12 (25 or 50 mg/kg BID PO) prevented the mechanical allodynia on day 15, 16, and 19 (Figure 3). In female rats, there was a dose-dependency not observed in male rats. Duloxetine was less effective as an analgesic in female rats than male, with ART26.12 (50 mg/kg BID) showing greater efficacy than duloxetine on Day 15 to Day 20.

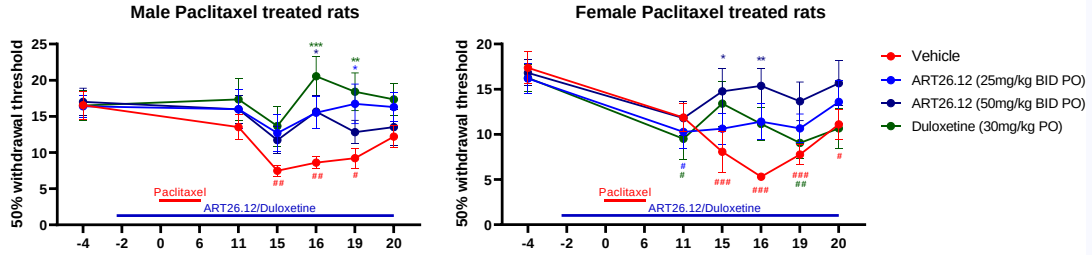

Figure 3. Von Frey thresholds for vehicle and test compound treated groups. *p<0.05, **p<0.01 indicate significant reversal of mechanical allodynia by treatment when compared to the respective group's vehicle values. #p<0.05, ##p<0.01, ###p<0.001 indicate significant decrease in von Frey threshold when compared to the respective group's baseline values. Values are presented as mean ± s.e.m.

In paclitaxel-treated male rats, ART26.12 prevented the cold allodynia on days 15 and 16 at the 25 mg/kg dose. In paclitaxel-treated female rats, ART26.12 prevented the cold allodynia on days 15 and 16 at both doses [data not shown].

In male rats, animals treated with duloxetine gained the least weight over the course of the study (Figure 4), and those treated with ART26.12 (50 mg/kg PO BID) gained the most weight. Female rats were prone to weight loss with each paclitaxel injection (and with duloxetine), but this was not observed in females treated with 50 mg/kg ART26.12.

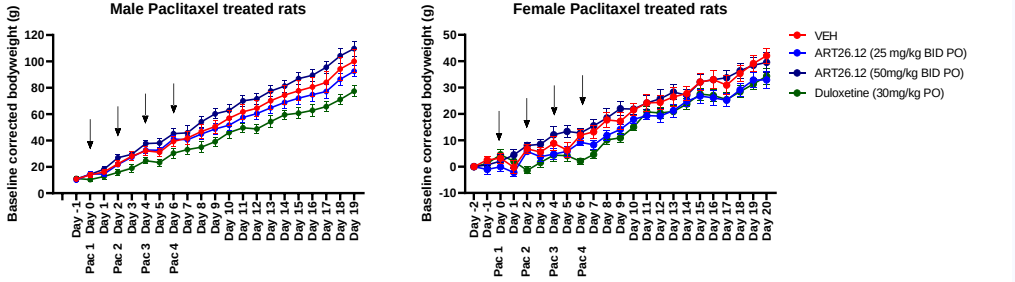

Figure 4. Effect of ART26.12 on the change in body weight in male and female rats treated with 4 doses of Paclitaxel (shown with arrows). Values are presented as mean ± SEM.

Quantitative bioanalysis by LC-MS/MS of terminal plasma samples showed that male and female rats had higher plasma concentrations of ART26.12 with 50 mg/kg compared with 25 mg/kg BID, although this was not associated with a greater analgesic effect.
ART26.12 exposure was ~4x higher in females than males.

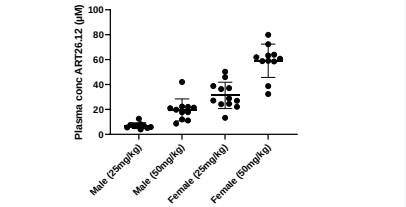

Figure 5. Terminal plasma concentrations of ART26.12 in male and female paclitaxel treated rats.

Conclusion: Prophylactic oral treatment with ART26.12 reduces mechanical and cold allodynia associated with a second chemotherapeutic agent, paclitaxel, in male and female rats. These data suggest a common mechanism of action of ART26.12 capable of preventing allodynia from both taxane and platinum based agents, and support the further development of ART26.12 as a novel therapeutic agent for the prevention and treatment of chemotherapy-induced neuropathic pain.

Acknowledgements:

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