ART26.12, A NOVEL FABP5 INHIBITOR, SHOWS EFFICACY IN BREAST CANCER-INDUCED BONE PAIN

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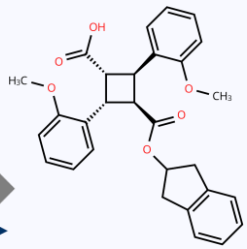
Introduction

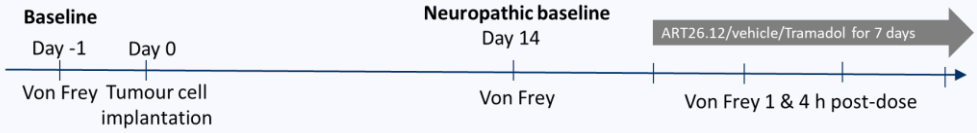
Fatty acid binding proteins (FABPs) are cytosolic proteins that chaperone lipophilic molecules around the intracellular environment. FABP5 is extensively distributed in the dorsal root ganglion, spinal cord and TRPV1+ nociceptors, and genetic deletion of FABP5 reduces pain via CB_1 and PPARα activation, blunting TRPV1 sensitization. Inhibitors of FABP5 are effective in multiple models of pain. The potent (Ki 0.77 ± 0.08 µM) and selective FABP5 inhibitor ART26.12 is under development at Artelo Biosciences under a licence agreement with Stony Brook University (Warren et al., 2024).

The aim of the present study was to establish a potential role for ART26.12 in an as yet untested neuropathy; cancer-induced bone pain (CIBP).

Methods

On Day 0, murine breast cancer cells were injected into the tibial bone cavity of female Sprague Dawley Rats. On Day 15, rats were randomly assigned to groups (n=10/group) using a computer-generated randomization procedure based on body weight and baseline Von Frey (VF) measurements (pain behaviour assay, Fig 1). Animals were treated orally with ART26.12 (25 and 100 mg/kg BID) or tramadol (30 mg/kg IP QD) for seven days. VF measurements were taken 1 and 4 h post-dosing on Days 1, 3, 5 and 7 (i.e. study Days 15, 17, 19, and 21) of drug treatment.





Results

There was no impact of ART26.12 on body weight or bone density. All CIBP rats had swelling below the knee and above the ankle but no other clinical observations throughout the study. Terminal plasma samples taken 2 h post-dosing showed a mean ART26.12 plasma level of 13.5 ± 1.5 µM and 46.3 ± 8.1 µM in the 25 and 100 mg/kg groups.

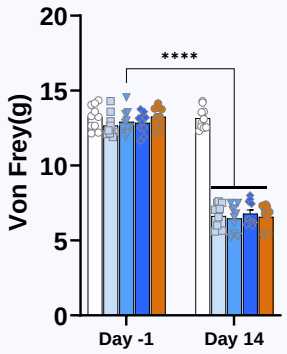


Figure 1. The model induced mechanical sensitivity (decreased paw withdrawal threshold by ~50%) by Day 14 (pre-randomization).

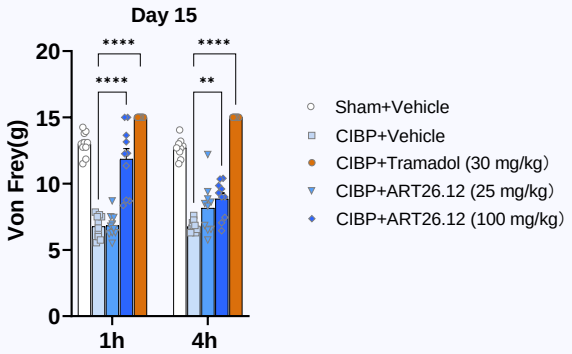


Figure 2. On the first day of drug treatment (Day 15) pain behaviour was improved by oral treatment with ART26.12 at 100 mg/kg at 1 and 4 h post-dosing Tramadol reversed mechanical sensitivity to above baseline values.

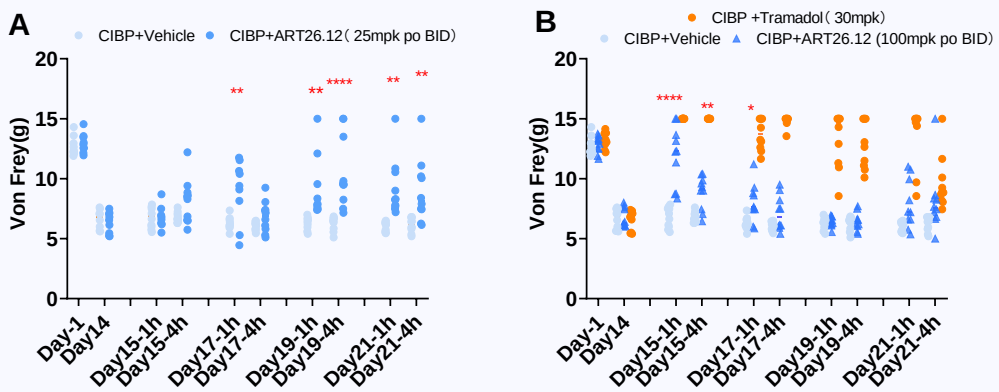


Figure 3. On Day 17 (third day of dosing), pain behaviour was significantly improved by ART26.12 (25 (A) and 100 mg/kg (B)) at 1 h post-dosing. On Day 19 and 21, pain behaviour was significantly improved by 25 mg/kg at 1 and 4 h post-dosing (A); however, the 100 mg/kg dose was no longer effective (B). Tramadol reversed paw withdrawal thresholds to baseline after the first dose, but efficacy deteriorated and became more variable with repeated dosing (B).

Conclusions

- Oral treatment with ART26.12 (25 mg/kg BID) reverses pain behaviour induced by breast cancer cells implanted in rat tibia. This oral dose has been shown to be effective in chemotherapy-induced neuropathy and diabetic neuropathy
- Increasing dose (and plasma exposure) of ART26.12 to 100 mg/kg BID does not increase efficacy
- FABP5 inhibition is a novel non-opioid, non-steroidal analgesic effective in multiple models of peripheral neuropathy