Analgesic and anti-inflammatory effects of ACD137, a potent and selective negative allosteric modulator of TrkA.

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The NGF/TrkA pathway is a well validated pathway for new analgesics without the side effects and dependency issues observed for opioids. The TrkA-selective negative allosteric modulator ACD137 has analgesic effects in models of neuropathic and OA-like pain. In the CIPN model, ACD137 reverses paclitaxel-induced mechanical sensitivity. In the MIA-model analgesic effects of ACD137 were similar to the anti-NGF antibody Tanezumab, but differentiated by showing a joint protective effect.

Aim
The aim of the present study was to evaluate ACD137, a TrkA-NAM compound, for its pharmacological effects in a neuropathic pain model and in an osteoarthritis (OA)-like pain model.

Background
Selective negative allosteric modulators (NAMs) of TrkA offer a unique approach to selectively attenuate TrkA signaling. It holds potential for treating conditions associated with aberrant NGF or TrkA signaling, such as neuropathic pain including chemotherapy-induced peripheral neuropathy (CIPN), but also in OA pain.

Methods
CIPN was induced by i.p. administration of paclitaxel. On day 15, rats were treated with one single oral dose of ACD137 and mechanical allodynia was tested after 1, 3 and 6h using von Frey filaments.
Mono-iodo acetate (MIA) was used to induce OA in rats and ACD137 was administered twice daily by oral gavage starting from day 3 until day 21. Tanezumab was administered QW on days 3, 10 and 17 by s.q. injections. Mechanical allodynia or non-evoked pain (weight bearing), and inflammation (measured by knee diameter) were assessed at different time points throughout the studies. Knee joint histopathology was examined after hematoxylin and eosin staining. Edema was determined by measuring paw thickness with an electronic micrometer.

Results
ACD137, a potent, selective, and orally bioavailable TrkA-NAM with a Kd of 0.011 nM and a mean IC_{50} value of 0.8 nM on TrkA and >20,000-fold selectivity over TrkB in a cell-based assay, was synthesized in our laboratory during a lead optimization program and selected for further development.

Oral treatment with ACD137 resulted in a significant increase in paw withdrawal threshold when compared to vehicle treated control animals in the CIPN model, with ACD137 showing similar analgesic effect as 100 mg/kg Gabapentin (fig 1).
In the MIA-model of OA, ACD137 reduced non-evoked pain behavior (weight bearing) with similar efficacy as Tanezumab (figure 2). The knee joint diameter was used as a measurement of edema/ inflammation. Both ACD137 and Tanezumab reduced the knee joint diameter (fig 3). At the end of the study, knee joints were collected, fixed and stained. Joint integrity was scored by the Mankin scoring. ACD137 treated animals displayed significantly less joint pathology, suggesting a protective effect of the molecule on knee joint integrity. Tanezumab did not demonstrate any significant differences on joint pathology compared to vehicle treated animals.

Figure 1. Effects of ACD137 on neuropathic pain in CIPN-model

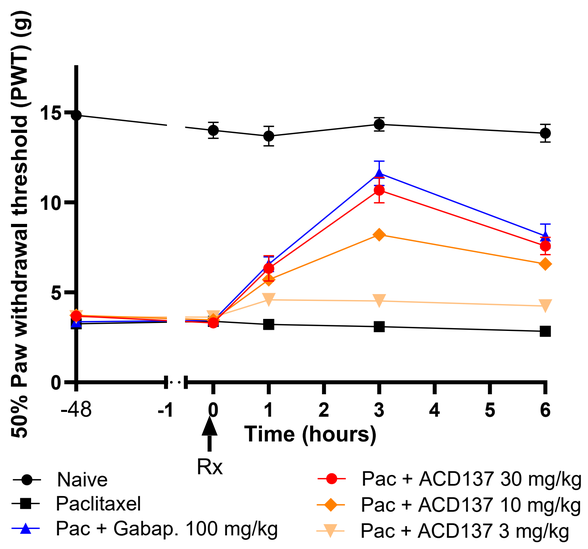


Figure 1.
Paclitaxel was given i.p. on Day 0 (after baseline recording). Paw withdrawal threshold was measured on Day13 after induction (pre-treatment baseline). On Day 15, rats were treated with vehicle (black squares), ACD137 (red, orange and light orange) or gabapentin (blue), and mechanical allodynia was assessed at 0, 60 min, 180 min and 360 min after treatment. Naïve animals are shown as solid black circles. Results are the mean +/- SEM (n=10 animals/ group).

Figure 2. Effects on non-evoked pain in MIA-model

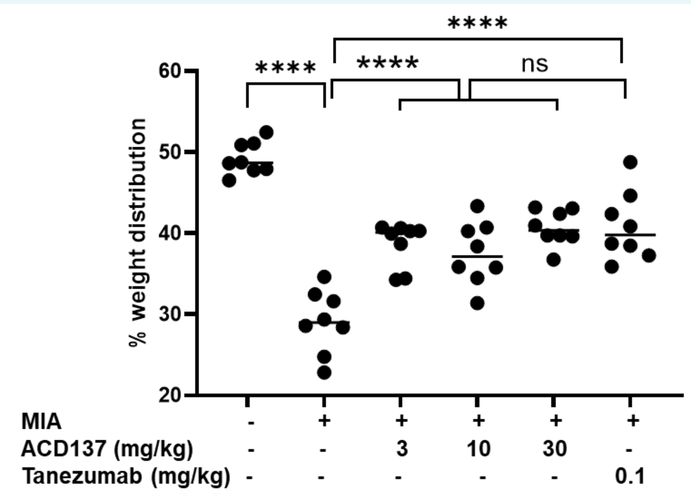


Figure 3. Effects on knee joint inflammation

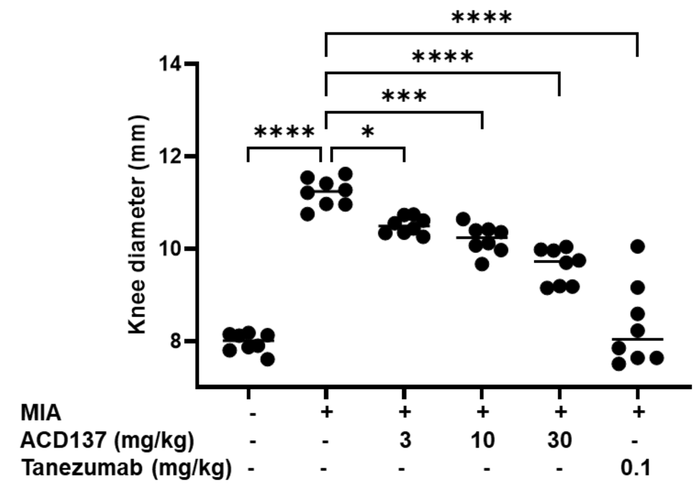
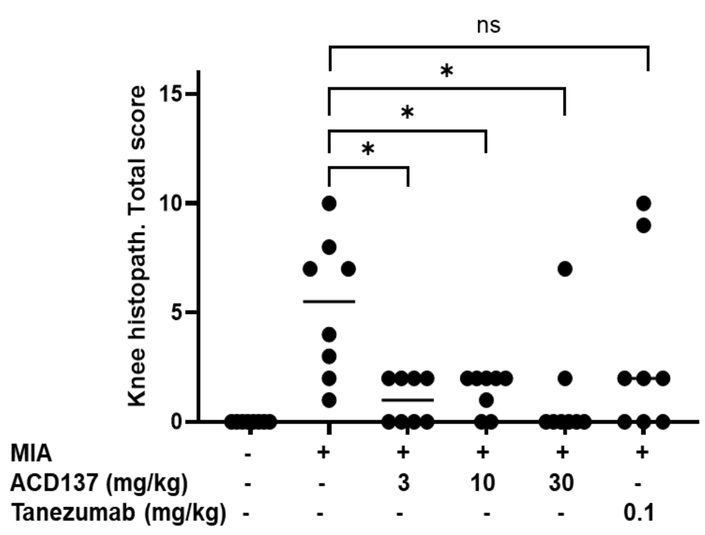


Figure 4. Effects on knee joint pathology in MIA-model



Figures 2-4.
On day 0, osteoarthritis was induced by intraarticular injection of 2 mg/mL MIA at a dose volume of 50 µL in the left hind limb. On day 3, mechanical allodynia was measured and the animals showing 50% reduction in the basal paw withdrawal threshold were randomized into groups. From day 3 to day 21, animals were administered ACD137 twice daily by oral administration or Tanezumab once weekly by intraperitoneal injections. **Figure 2**, weight distribution was assessed on day 20 as a measure of non-evoked pain. **Figure 3,** knee joint diameter was used as a measurement of inflammation. **Figure 4,** after fixation and staining with eosin/hematoxylin, knee joint histopathology was scored using Mankin scoring and used as a measurement of knee joint integrity
Results are the mean with individual animals represented, (n=8 animals in each group).

Discussion
TrkA-NAM's have shown analgesic effects in both neuropathic and nociceptive models, potentially without the side effects and dependency issues observed for opioids. Enhanced pain relief is attributed to the inhibition of NGF/TrkA signaling, attenuating peripheral sensitization and neuroinflammation. Identification of selective and potent TrkA-NAM's could potentially avoid some of the side effects observed for anti-NGF antibodies due to a more selective mechanism of action, while retaining the analgesic efficacy. Selectively inhibiting TrkA will avoid the side effects related to inhibition of proNGF- or NGF-mediated p75NTR-signaling that anti-NGF antibodies potentially could suffer from. The present study supports the analgesic effect of ACD137 in relevant preclinical models for both neuropathic and nociceptive pain. Looking beyond the pain-relieving effects, we have also observed an anti-inflammatory and joint protective effect in the MIA-model, suggesting a broad effect on different pathologies associated with OA. Overall, TrkA-NAMs and specifically ACD137 demonstrate potential as a novel therapeutic approach for alleviating different types of pain, including neuropathic and OA-like pain. The broad pharmacological effect of ACD137 on pain perception inflammation and joint histopathology, highlights its role in advancing pain management.

Conclusion
The NGF/TrkA pathway is a well validated pathway for new analgesics without the side effects and dependency issues observed for opioids. Identification of selective TrkA-NAMs could potentially avoid some of the side effects observed for anti-NGF antibodies or non-selective Trk-inhibitors, while retaining the analgesic efficacy. We describe here that ACD137 have analgesic effects in neuropathic and OA-like pain. The analgesic effect of ACD137 was similar to the effects of the anti-NGF antibody Tanezumab, but interestingly ACD137 differentiated from Tanezumab by showing a joint protective effect as judged by Mankin scoring.

Ethical Permissions
The in vivo studies were performed at Aragen Life Science or at SAI Life Sciences, India. The protocols were approved by the Institutional Animal Ethics Committee (IAEC) (B106-56-23-IPH, B048-75-23-IPH, FB-24-02)

Conflict of interest
All authors are employees of AlzeCure Pharma AB and the studies were fully funded by AlzeCure Pharma AB.

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