The TRPV1 antagonist ACD440 Gel as a tool in pain precision medicine, results of a post hoc analysis

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Oral TRPV1 antagonists have been challenged by systemic target effects, reducing overall heat sensitivity. Using the topical route, local treatment with the TRPV1 antagonist ACD440 Gel has demonstrated high efficacy in reducing evoked heat hyperalgesia in healthy subjects as well as in patients with peripheral neuropathic pain with hypersensitivity to heat, without any systemic side effects. This opens up the possibility for precision medicine in the subpopulations of pain patients with heat hyperalgesia, where current treatments are known to be ineffective.

Aim

To investigate if the topical TRPV1 antagonist gel could exert a clinically meaningful reduction in heat hyperalgesia in patients with peripheral neuropathic pain with sensory hypersensitivity (irritable nociceptors).

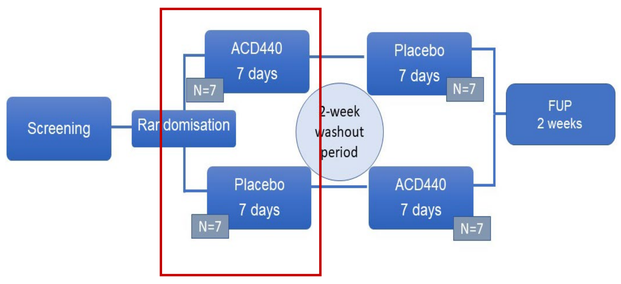
Background

Current treatments for neuropathic pain leave many patients without adequate pain relief. The development of new pain treatments has resulted in numerous failures, to a great extent likely due to too high expectations on the generalizability of the effect across the wide array of pain indications. Many efforts have been made to develop antagonists of the TRPV1 receptor as a treatment for chronic pain, including neuropathic pain. These efforts have failed due to systemic target related effects, increasing the risk for burn and scalding. We have developed a topical gel formulation for local treatment, aiming to circumvent these problems. A Phase 2a study was conducted in patients with peripheral neuropathic pain with an irritable nociceptor (sensory hypersensitivity) phenotype. We here describe the post hoc analysis of this Phase 2 clinical trial in peripheral neuropathic pain, in relation to study design, patient selection and selection of trial endpoints.

Methods

This is a post hoc analysis of a Phase 2a randomized, double-blind, placebo-controlled crossover trial in peripheral neuropathic pain patients with sensory hypersensitivity (Fig.1). Patients received ACD440 Gel 14mg/g or placebo gel for 1 week, with a 2-week washout period between treatments. At screening, patients were characterized by their sensory hypersensitivity pattern, assessing their hyperalgesia to touch (brush stroke), cold (6℃), heat (40℃) and pinprick (8 or 16mN) using a bedside test (Reimer, 2020) (Fig 2). At each baseline and on treatment day 7 in each period, evoked pain to suprathreshold stimulation, as well as spontaneous pain (NRS 0-10) and the Neuropathic Pain Symptom Inventory (NPSI) were assessed.

Fig. 1. Overall study design



The red box depicts the period 1 parallel group post hoc analyses population

Results

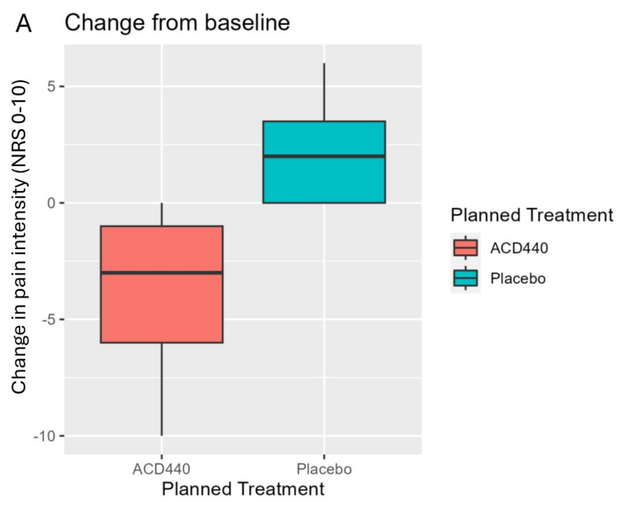
Fourteen male and female patients with probable peripheral neuropathic pain, age 50-85, were randomized and completed the study. Pain etiologies were varied, with an average spontaneous pain of 5.6 (SD 1.4), an overall evoked pain of 6.7 (SD 2.5) and an NPSI total score of 40.5 (SD 16.8). During the primary analyses, there was no difference between groups in spontaneous pain or NPSI scores. However, a statistically significant period effect was seen, prompting a predefined secondary analysis including only data from Period 1, i.e. 7+7 patients. It was clear that only thermally induced pain was reduced. Further post hoc analyses specifically compared the effects of ACD440 Gel vs placebo of treatment period 1 in patients with thermal hyperalgesia and patients with heat hyperalgesia (in red in Fig1). Analyses (Mann-Whitney U-tests) demonstrated a significant reduction in heat evoked pain between ACD440 Gel and placebo gel by -5 (95% -11, 1.2) from baseline in patients with thermal hyperalgesia (p=0.005) (Fig 3a) and by -4 (95%CI -9, 1.0) in patients with heat hyperalgesia only, p=0.029 (Fig. 3b).

Fig. 2. Bedside test kit

Hyperalgesia to touch was tested with a soft Somedic brush, to cold (6℃) and to heat (40℃) by metal Thermorollers, and to pinprick (8 or 16 mN, dependent on gender and body location), at baseline and on Day 7.

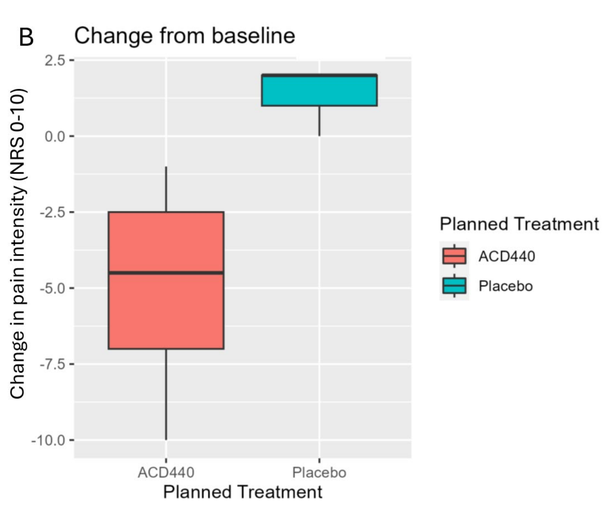
Brush and thermorollers from Somedic SenseLab AB, Sösdala, Sweden). Pinprick stimulators from MRC Systems GmbH, Heidelberg, Germany

Fig. 3a. Response in patients with thermal hyperalgesia



In patients with thermal (cold or heat) hyperalgesia (ACD440:placebo 5:7), heat evoked pain (40°C) was significantly reduced after 7 days of treatment, p=0.005.

Fig. 3b. Response in patients with heat hyperalgesia



In patients with heat hyperalgesia (ACD440:placebo 4:3), heat evoked pain (40°C) was significantly reduced after 7 days of treatment, p=0.028

References

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Discussion

In this post hoc analysis, the overall treatment effect suggests that ACD440 Gel may be effective in reducing pain where TRPV1 receptor mechanisms are important in the initiation or maintenance of pain, e.g. to heat-evoked pain. Thus, these results demonstrate a Proof of mechanism in the treatment of heat hyperalgesia. Going forward, this type of precision medicine for burning pain may be a complementary treatment option for patients where burning pain is a major component of their overall pain experience.

Considering the significant period effect seen in this study, this may be seen as a limitation of the study. In this study we could not detect any change in overall spontaneous pain nor NPSI or its sub-scores, likely due to the short study treatment duration and small sample size. The findings of the present trial are also aligned with analyses of Gillving and coauthors, demonstrating that placebo responses in a crossover trial do not seem to be associated with age, sex, duration of pain, sensory profile or treatment sequence (Gillving, 2020).

Ethical Permissions

The study was conducted at Uppsala University Hopsital, and in accordance with Good Clinical Practice, after regulatory approval by the Swedish MPA (EudraCT 2022-000902-82) and ethics approval by the Swedish SERA (no. 2022-01922-01). The study was preregistered on www.clinicaltrials.gov (NCT05416931).

Conflict of interest

IL is an employee of Cytel Sweden AB, MMH and MS are employees of AlzeCure Pharma AB. The studies was fully funded by AlzeCure Pharma AB.

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