A STUDY OF ACD440 GEL FOR THE TREATMENT OF PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN WITH SENSORY HYPERSENSITIVITY

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Background and Aims

Current treatments for neuropathic pain still leave many patients without sufficient pain relief. Earlier development programs of TRPV1-antagonists for pain treatment during the early 2000's have used an oral administration. There is no published data on investigations of a TRPV1 antagonist for the treatment of peripheral neuropathic pain.

These drugs were all effective in blocking TRPV1-receptors, with effects on heat sensitivity and temperature control, with further development stopped. ACD440 Gel is using a topical approach, targeting the painful areas, intended as precision medicine for reduction of peripheral neuropathic pain with sensory hypersensitivity.

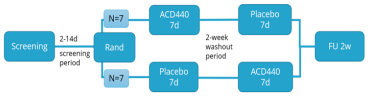
The current study was preceded by a study in healthy volunteers, where it was demonstrated that the ACD440 Gel 14mg/g was able to reach the epidermal TRPV1 receptors and significantly reduce experimental pain induced by a CO2 laser signal. Endpoints in the previous study were Laser evoked potentials and simultaneous pain intensity assessments (Poster at IASP 2021).

The objective of the present study was to confirm that ACD440 gel was able to reach the TRPV1 receptors also in the skin of patients with peripheral neuropathic pain with sensory hypersensitivity, and that the mechanism of action is valid also under these existing pathophysiological conditions.

Methods

Male and female patients, age 18-85, with peripheral neuropathic pain with hypersensitivity (irritable nociceptors) on bedside sensory testing were eligible to be included in this exploratory randomized placebo-controlled double-blind crossover trial (Fig.1). Inclusion criteria also included a pain duration of 0.5-8 years, spontaneous and evoked pain intensity of NRS 4-9, covering a body surface area of 50-600 cm².

Figure 1. Study design



After a 2-14 days screening period, confirming sensory hypersensitivity profile , patients were randomized (Rand) to treatment sequence. Patients received 7 days of twice daily application of ACD440. After a 14-day washout period, patients entered their second treatment period, with a follow-up at 14 days after completed study treatment.

Figure 2. Bedside sensory assessments

Metal rods, 6°C and 37°C respectively, a Pin Prick with a force of 8 or 16 mN and a soft brush were used for assessing suprathreshold evoked pain.

Patients remained on an optimized stable dose of ongoing concomitant medication.

Key endpoint was reduction of evoked pain intensity in the most sensitive quality at baseline bedside QST assessment.

The evoked pain intensity assessments were done using a bedside sensory test, addressing the hyperalgesia evoked by suprathreshold stimulation (Fig.2) (Reimer et al, 2020). For thermal hyperalgesia the test kit included two metal rods, one cold (6°C) and one warm (37 °C). Allodynia to touch was assessed using a soft brush (Somedic Sales AB, Sösdala, Sweden) and mechanical hyperalgesia was assessed using a Pinprick device of forces of 0.8 or 16mN (MRC Systems). The applied stimulus intensities were clearly outside the +2 SD for the respective sex, age and body location (Baron et al, 2017). Other variables included spontaneous pain (NRS 0-10), the Neuropathic Pain Symptom Inventory (NPSI), and the Patient Global Impression of Change (PGIC).

ACD440 Gel 14mg/g and placebo gel were identical in color, smell and texture. Patients received study treatment for 7 days in each study period, with a washout period of 2 weeks (Fig. 1). Patients applied study medication twice daily for 7 days, with a minimum two-week washout between treatment periods.

The sample size was estimated based on the previously conducted study in healthy volunteers, based on an expected reduction in evoked pain by 30%, a power of 0.8, and a 2-sided 95% significance level. For the statistical analysis, the baseline for each period was used for deriving the endpoint of change from baseline.

Exploratory endpoints included change in sensory profile. Evoked pain intensity 4-10 was considered clinically relevant hyperalgesia. This would be a blunt overall estimate of the clinical significance of any hyperalgesia.

Results

After approvals from the Swedish Medical Products Agency and the Swedish Ethics Research Authority, 14 patients were enrolled in the study. All patients had a pre-study verified diagnosis of probable neuropathic pain, with a spontaneous pain rating of NRS 4-9. Etiologies were varied, including PHN (8), post amputation pain (2), peripheral nerve injury (3), chemotherapy induced neuropathic pain (1). (Table 1).

All patients completed the study and all study assessments. There were no treatment related adverse events reported.

No carryover effect was detected, but a significant period effect was obvious. Therefore, an analysis of Period 1 data was conducted, as prespecified (Table 2).

As expected after only 7 days of treatment and a very limited number of study participants, there was no significant change in spontaneous overall pain reports or PGIC (data not shown).

As hypothesized, ACD440 Gel 14mg/g, significantly reduced thermally induced hyperalgesia, by approximately 50% ($p<0.0166$) (Table 3).

Table 1.

Patient characteristics	
Sex	5 male, 9 female
Age, yrs (median[range])	70 (50-85)
Pain duration, yrs (median[range])	4.75 (0.7–7.5)
Etiologies	
Postherpetic Neuralgia	8
Post amputation	2
Peripheral nerve injury	3
Chemotherapy Induced neuropathic pain	1
Ongoing analgesics	9
Gabapentinoid	3
Amitriptylin	1
Opioids	2
Paracetamol	6
Size of body surface area with sensory hypersensitivity, cm², (mean [SD], range)	261 (147), 80-600

Table 2. Differences in baseline scores for the respective treatment periods

Baseline pain scores	Period 1 D1 Mean (SD)	Period 2 D1 Mean (SD)
Spontaneous pain	5.6 (1.4)	5.7 (2.0)
Thermal hyperalgesia	4.1 (3.5)	4.4 (3.7)
Mechanical hyperalgesia	5.2 (3.6)	4.6 (3.1)
Evoked bedside QST pain, worst of all 4 qualities	6.7 (2.5)	6.0 (3.0)
NPSI evoked pain subscore (CPT+MPT+DMA/3) average 24-h recall	5.2 (2.7)	4.6 (1.9)
NPSI total score	40.5 (16.8)	35.6 (17.7)

Table 3. Effects on thermal hyperalgesia.

Endpoint	Sample size	ACD440	Placebo	Difference	P-value
Suprathreshold **temperature** evoked pain (crossover analysis)*, mean (SD)	14	-1.29 (2.11)	0.25 (1.53)	-1.54 (2.13)	**0.0166**
Suprathreshold **temperature** evoked pain, period 1 only (parallel groups)#, mean (SD)	14 (7+7)	-2.07 (2.67)	0.79 (1.50)	-2.86	**0.0064**
Suprathreshold **heat** evoked pain (crossover analysis)*, mean (SD)	14	-1.8 (3.1)	0.4 (3.0)	-2.2 (2.9)	**0.0117**
Suprathreshold **heat** evoked pain, period 1 only (parallel groups)#, mean (SD)	14 (7+7)	-2.9 (3.8)	2.1 (2.5)	-4.0	**0.0058**
Average of all 4 sensory qualities suprathreshold evoked pain, period 1 only (parallel groups)#, mean (SD)	14 (7+7)	-2.07 (2.28)	-0.46 (1.40)	1.61	**0.0670**

*Wilxocon signed rank test, #Wilcoxon Mann-Whitney test. One-sided testing.

Discussion

Eligibility criteria required patients to report evoked hyperalgesia on suprathreshold stimulation of 4 or above. At baseline, all 14 patients demonstrated sensory hyperalgesia to any sensory quality, 12 out of the 14 had thermally evoked hyperalgesia, and 13 of them had mechanically evoked hyperalgesia. This indicates a greater overlap between phenotypes when comparing hyperalgesia patterns vs threshold patterns than as described with full QST (Baron et al, 2017).

Further, the bedside test was feasible for use in a clinical trial. Results also demonstrate the risk of a considerable placebo effect, having a considerable impact on the results. The factors involved could be several. These may include frequent visits at study sites, patient-investigator interaction, the crossover design, and the patient population to a great extent being treatment resistant. The impact of the treatment being a topical treatment route vs oral is unknown.

The magnitude of a placebo effect in trials of topically applied treatments may need additional considerations going forward.

References

Baron R, et al, *PAIN 2017;158(2):p 261-272. February 2017. DOI:* 10.1097/j.pain.0000000000000753.
Reimer,M et al, Pain Reports PR9 5 (2020) e820
http://dx.doi.org/10.1097/PR9.0000000000000820

Conclusion

ACD440 Gel reduced thermally evoked pain in patients with peripheral neuropathic pain with sensory hypersensitivity by a statistically significant and clinically relevant degree. The simplified bedside test was easily applied in a clinical trial setting. The study could demonstrate target engagement and proof of mechanism in peripheral neuropathic pain patients, as the first clinical trial exploring the effect of a TRPV1 antagonist in a peripheral neuropathic pain population.

ACD440 Gel was safe and well tolerable as a topical treatment for patients with neuropathic pain with hypersensitivity (irritable nociceptors). Results support further clinical development. A subsequent clinical trial would be of a larger sample size and a longer treatment duration to enable the evaluation of an effect on spontaneous pain.

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