ACD440 – A Novel TRPV1 Antagonist for the Topical Treatment of Pain

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Background and Aim:

TRPV1 is a non-selective cation channel involved in the transmission and modulation of pain. It can be activated by a wide variety of exogenous and endogenous physical and chemical stimuli. Systemic administration of antagonists of the transient receptor potential cation channel subfamily V1 (TRPV1) have been shown to produce adverse effects on thermoregulation like increase in core body temperature or other thermosensory deficits. This triggered the development of a formulation of a potent and selective TRPV1 antagonist for topical use (ACD440). Potential topical use is supported by an in vivo study in the rat carrageenan model, where local administration of ACD440 reversed carrageenan-induced heat hyperalgesia by 53%, while systemic and i.t. administration had no effect. The current proof-of-mechanism study in healthy volunteers explored the effects of topically administered ACD440 on evoked pain stimuli on intact, UVB irradiated and mechanically stripped skin.

Methods:

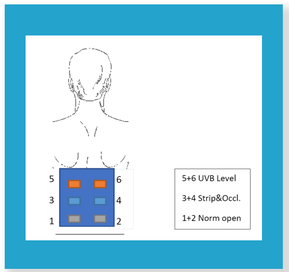
This double-blind, randomized, placebo-controlled study of ACD440 gel used a split body design. The study included 24 healthy male and female volunteers aged 18 - 64 years with a Fitzpatrick skin type of II or III. Exclusion criteria included significant illness, medical/surgical procedure or trauma within 4 weeks, positive COVID 19 PCR test, other pain conditions, history of photosensitivity disease and dermatological diseases in the intended test area.

Table 1. Study design and endpoints

	Optimized Penetration	Normal Skin	UVB irradiated skin
Safety	Tolerability on skin with impaired barrier	Tolerability on normal skin	Tolerability on inflamed skin
Efficacy outcome measures	LEP (PtP) VAS pain (0-100)	LEP (PtP) VAS pain (0-100)	LEP (PtP) VAS pain (0-100) Pin prick hyperalgesia Inflammation

Laser algesimetry[1] endpoints included overall Peak-to-Peak (PtP) amplitudes of the Laser evoked potentials (LEPs) (µV), Pain eVAS 0-100-mm, Weighted Needle Threshold (WNT) determination of mechanical hyperalgesia and evaluation of erythema by Skin Reflection Spectrometry.

Fig 1. Experimental setup



ACD440 or placebo gel was applied to 6 areas, exploring 3 conditions: normal skin, skin optimized for penetration (subjected to stripping) and skin exposed to 2MED (minimal erythema dose) of UVB. ACD440 or placebo gel was applied once daily for 5 days, on Days 1-3, before UVB on Day 4 and at 24 h after UVB (Day 5).

Statistics:

The study was powered to detect a treatment difference at a two-sided 5 % significance level with a statistical power of 80 % to detect a 2.5 µV difference in PtP-Laser amplitude. The statistical analysis was based on the comparisons of the AUC (Area Under the Curve) parameter derived from the efficacy endpoints at all observation time points. The variables were analysed using a linear mixed regression model. The regression included the classification variable treatment (Placebo, ADC440) and the corresponding baseline values (pre-dose measurement on normal skin) as fixed effects and the intercept over the subjects as a random effect.

Results

Fig 2. ACD440 reduced laser evoked PtP and pain intensity over Day 1-5 compared to placebo **on normal and normal-optimized skin**, *** p<0.001.

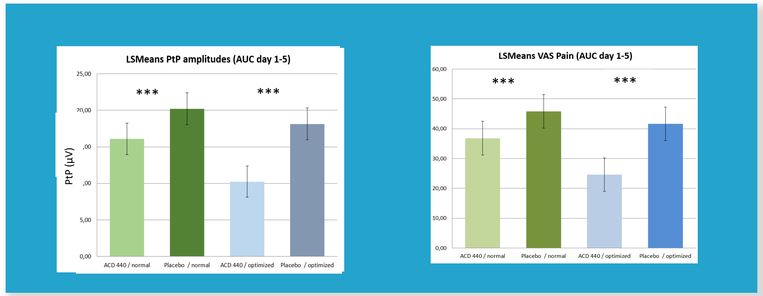


Table 2. ACD440 reduced laser evoked PtP and pain intensity, and pinprick hyperalgesia vs. Placebo after **UVB** irradiation.

	Change vs. placebo	P-value
PtP (µV) (SE)	-4.12 (1.33)	0.005
VAS (0-100) (SE)	-8.48 (2.23)	0.001
WNT (mN)	8.06 (3.88)	<0.05

Conclusions: ACD440 significantly reduced LEP amplitudes and VAS pain intensity in all skin conditions, as well as reducing UVB induced pinprick hyperalgesia. Erythema was not affected. There were no local or systemic adverse events.

[1] Schaffler et al.: Br J Clin Pharmacol. 2017 Jul;83(7):1424-1435. doi: 10.1111/bcp.13247