

FIRST CLINICAL TRANSLATION OF THE ANTI-NOCICEPTIVE/ANTI-HYPERALGESIC EFFICACY OF A T-TYPE CALCIUM CHANNEL MODULATOR (Z944) USING **LASER EVOKED POTENTIALS** AND VAS IN **UV-B AND CAPSAICIN** IRRITATED SKIN IN HEALTHY HUMANS

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INTRODUCTION

The primary objective of this study was to investigate the acute antinociceptive/antihyperalgesic efficacy of Z944, a small-molecule, piperidine-based T-type calcium channel blocker efficacious in preclinical pain models, on Peak-to-Peak (PtP) amplitude reduction of Laser (radiant-heat) evoked potentials (LEPs) from Vertex-EEG compared to placebo in UV-B-inflamed and in capsaicin-irritated skin.

METHODS

This study was a single-center, double-blind, randomized, split single-dose, placebo-controlled, 4-way crossover study on efficacy and tolerability of Z944 in a total of 16 healthy male Caucasian volunteers, age 18 to 55 years inclusive. Eligible subjects were randomized to start with 1 out of 4 treatment sequences (“intra-individual” crossover) and received split single doses of Z944 and placebo. Total single doses of 0 (placebo), 20, 40, and 80 mg of Z944 were administered as 4 split doses of 0, 5, 10, or 20 mg, respectively, every 2 hours (at 0, 2, 4, and 6 hours) on main assessment days (MAD). There were 4 separate study visits with a minimum 1-week washout period separating each treatment visit. Subjects underwent LEP sessions on

both UV-B-irradiated and capsaicin-irritated skin and completed VAS-Pain (100mm) assessments for each skin condition at 1 hour after each (split) dose of study drug (at 1, 3, 5, and 7 hours). Subjects underwent UV-B irradiation (narrow band 311 nm invisible range at twice the minimum erythema dose / MED to square skin areas of 5 x 5 cm) and an occlusive, topical (30min) capsaicin application (1% alcoholic solution) beginning at -2:00 hours (pre-dose).

RESULTS

For the primary target variable, the objective-quantitative LEP PtP-amplitude from capsaicin skin conditions, an early (1h), distinct, ongoing (>7h) and highly significant (p <.0001) amplitude-suppressive effect of the PtP-amplitudes (analgesia/anti-hyperalgesia) was demonstrated for the highest split single dose of 80 mg of Z944. This effect was also observed for the secondary target variable LEP PtP-amplitude from UV-B-skin (p <.0001). The 2 lower doses of Z944 were also significantly effective vs. placebo in both skin conditions.

Both skin conditions demonstrated sensitization after repeated laser sessions/stimulations over the assessment day, indicating a remaining and/or existing development of hyperalgesia after application of the skin irritants capsaicin and UV-

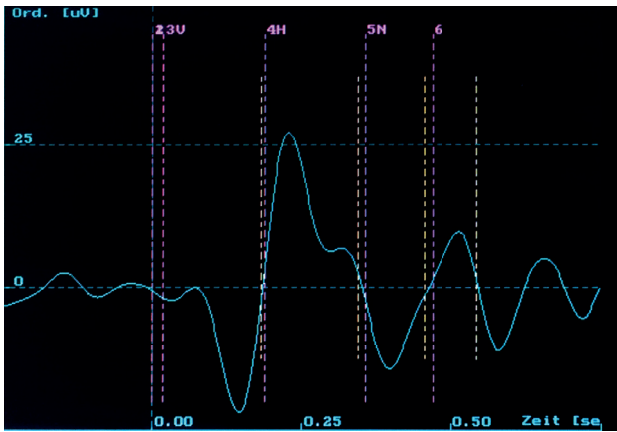
BI,II,III. The maximum effects were different in timing for the two skin conditions, with an earlier maximal effect at 3 to 5h in capsaicin skin and a later maximal effect at 5 to 7h in (inflamed) UV skin. In both skin types the lowest and the medium doses (20 and 40mg) behaved similarly in their effects on the LEP PtP-amplitude paradigm. The effect of the highest split dose of 80 mg in the subjective pain impression score, VAS-P, was quite similar to that seen in the LEP measurements (not shown here). In general there was a development of hyperalgesia seen in both skin types during the treatment visit for placebo in VAS-Post Laser Pain. Dose-dependent Z944 side effects were primarily CNS related.

CONCLUSIONS

T-type calcium channels have been recognized as key targets for therapeutic intervention in a broad range of cell functions and have been implicated in pain signaling. These results represent the first T-type calcium channel modulator to demonstrate clinical translation in pain. Based on these results, a modified release formulation of Z944 is being advanced through further clinical development.

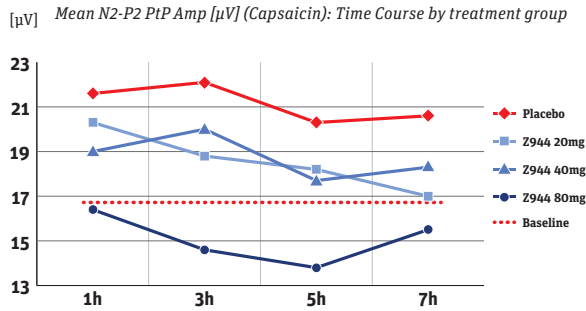
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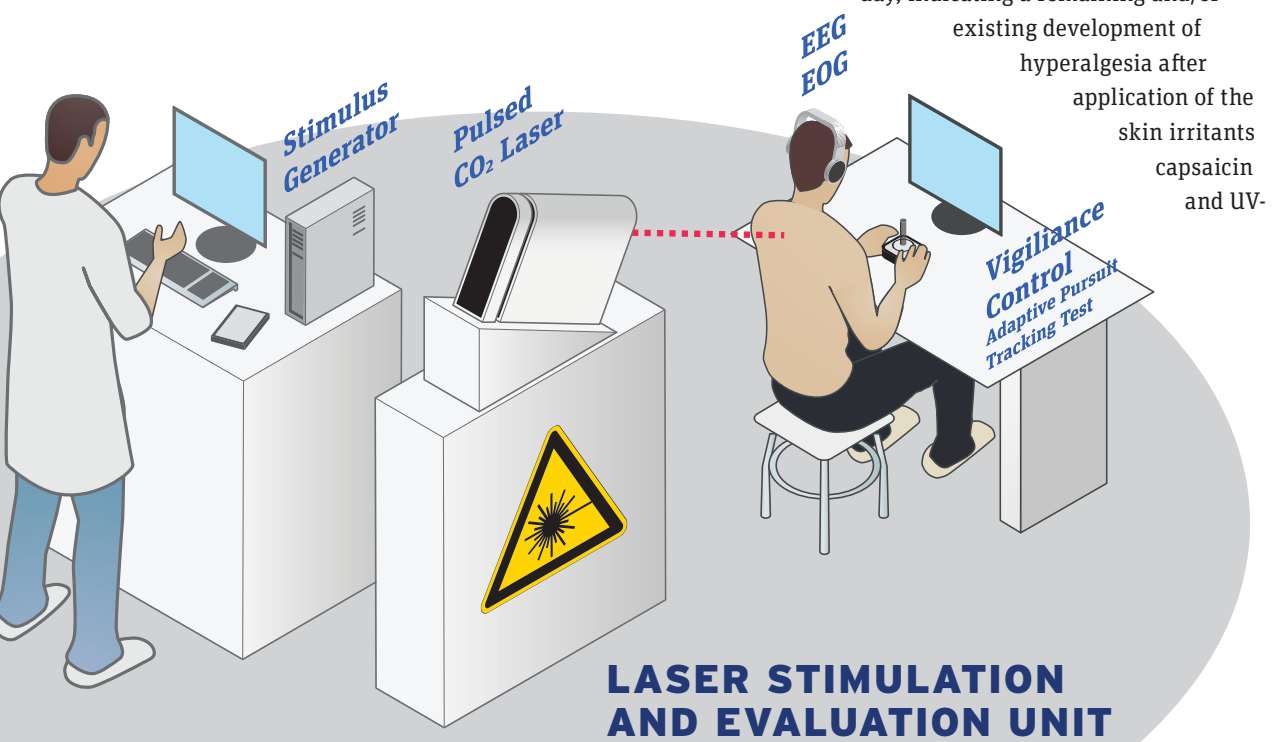
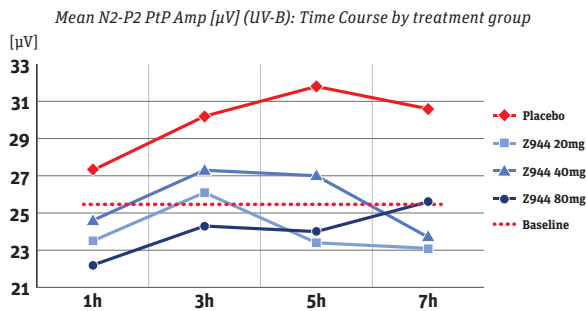


Skin after topical, occlusive capsaicin 1%

TIME COURSE PTP-LEP - CAPSAICIN



TIME COURSE PTP-LEP - UV



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