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

Klaus Schaffler[1], Margaret Lee[2], Mark Versavel[2]
[1]HPR Human Pharmacodynamic Research, Munich Germany, [2]Zalicus Pharmaceuticals Ltd., Cambridge, USA

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.

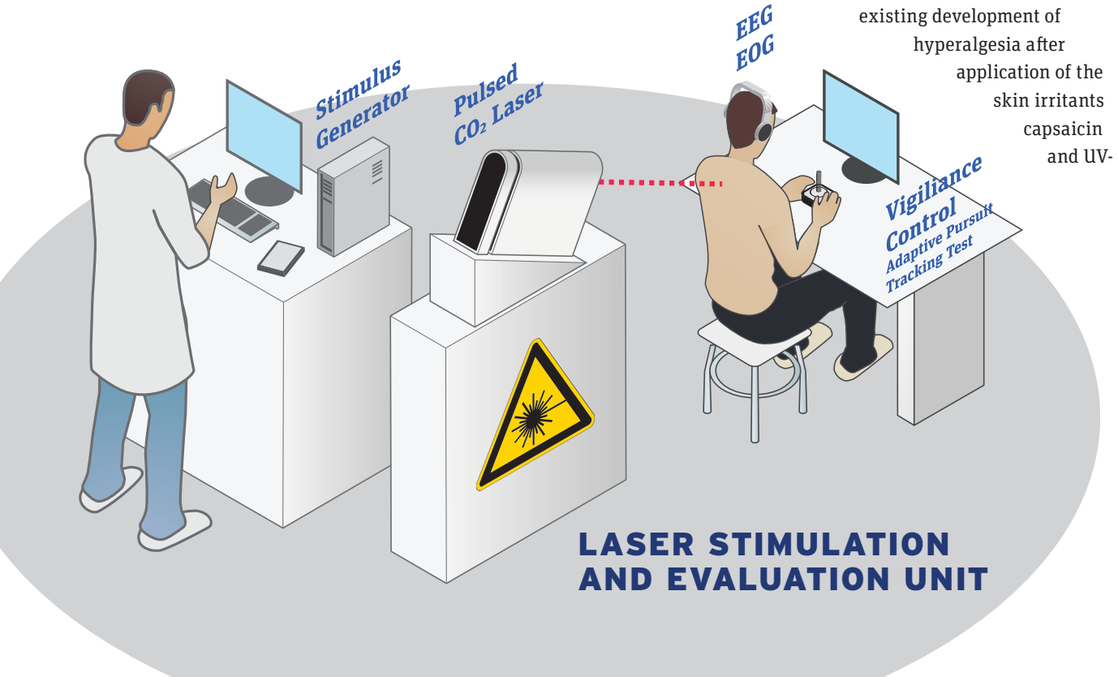
METHODS

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

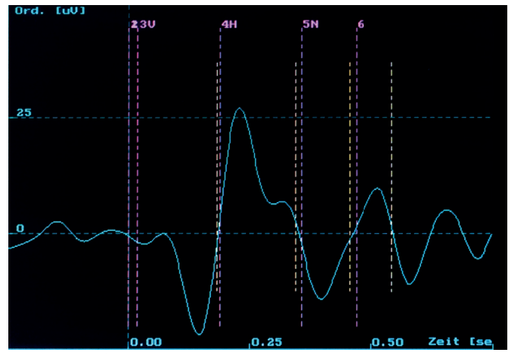
T-type calcium channels have been recognized as key targets for therapeutic intervention in a broad range of cell functions and have been implicated in pain signaling. These results represent the first T-type calcium channel modulator to demonstrate clinical translation in pain. Based on these results,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

REFERENCES

I. E. Hoeben, J. W. Smit, D. Upmalis, S. Rush, K. Schaffler, P. Reitmeir and B. Mangold. Dose-response relationship after single oral dose administrations of morphine and oxycodone IR in a human experimental algesimetric model using laser evoked potentials on UVB-irradiated and capsaicin-irritated skin in PAIN 153 (2012) 1648–1656

II. K. Schaffler, W.R. Duan, A.E. Best, C.R. Faltynek, C. Locke, W. Nothaft. Effects of a novel TRPV-1 antagonist ABT-102 in a human experimental pain study using laser somatosensory evoked potentials obtained from UVB-irritated and normal skin in healthy volunteers, Br. J Clin. Pharm (2012) 75:2, 404-414 (DOI: 10.1111/j.1365-2125.2012.04377.x)

III. K. Schaffler, Proof of efficacy and dose-dependency of NSAID and opiate analgesics in Laser evoked potential paradigm - using capsaicin and UV skin model, Spring Pain Conference, Grand Cayman Island, Apr./May 2008, in Brain Research Reviews, Elsevier, Session: Predicting therapeutic efficacy & experimental pain in human subjects, available online: 31-DEC-2008 DOI information: 10.1016/ j.brainresrev. 2008.12.016

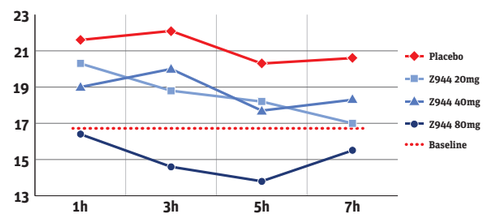


Mean Laser-EP / N2-P2 PtP Amplitude


Skin after topical, occlusive capsaicin 1%

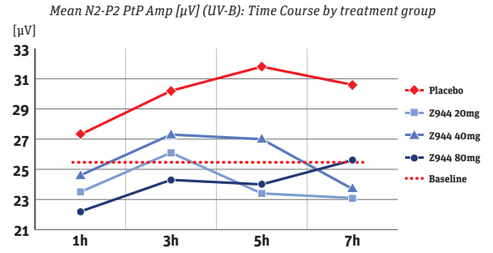
TIME COURSE PTP-LEP - **CAPSAICIN**

Mean N2-P2 PtP Amp [µV] (Capsaicin): Time Course by treatment group



TIME COURSE PTP-LEP - **UV**

Mean N2-P2 PtP Amp [µV] (UV-B): Time Course by treatment group



hpr-cro.com