
Print this Page for Your Records Close Window

Control/Tracking Number: 14-A-2543-IASP
Activity: Poster Abstract Submission
Current Date/Time: 3/6/2014 9:22:59 AM

**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**

Author Block: K. D. Schaffler[1], M. S. Lee[2], M. Versavel[3], *[1]Head, HPR-Human Pharmacodynamic Res., Munich, Germany, [2]Res. & Translational Med., Zalicus Pharmaceuticals Ltd., Cambridge, MA, USA, [3]Zalicus Pharmaceuticals Ltd., Cambridge, MA, USA*

*Abstract:*
Aim of Investigation: The primary objective 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. In addition subjective impressions of nociception were recorded using an electronic (100mm) VAS pain score (VAS-P). Methods: This study was a single-center, double-blind, randomized, split single-dose, placebo-controlled, 4-way crossover study of the 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 1 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- and capsaicin-irritated skin and completed VAS-P 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 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 increasing sensitization after repeated laser sessions/stimulations over the

assessment day, indicating the development of hyperalgesia after application of the skin irritants capsaicin and UV-B. The maximum effects were different in timing for the two skin conditions, with an earlier effect at 3 to 5h in capsaicin skin and a later 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. In general there was a development of hyperalgesia seen in both skin types during the treatment visit for placebo (VAS-P). 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.
*:*

Sponsor (Complete):
Are you an IASP member?
: Yes
If yes: Enter your IASP Membership Number (5 digits)
: 48621

Additional Information (Complete):
ACKNOWLEDGEMENTS / DISCLOSURES : This study was sponsored by Zalicus Pharmaceuticals Ltd., Cambridge, USA, the employer of M. Lee and M. Versavel and K. Schaffler was the Principal (study) Investigator.

Topic (Complete):
: +Novel Therapeutic Agents

Keyword (Complete): T-type calcium channel blocker ; Laser EPs ; UV skin ; capsaicin skin ; VAS
Status: Complete