The Transient Receptor Potential Vanilloid subtype 1 (TRPV1) receptor is a validated peripheral pain target (1). Many pharmaceutical companies have developed TRPV1 for a pain indication up to phase II, but to our knowledge most of these developments have been terminated for two on-target safety concerns: hyperthermia (2) or impaired noxious heat sensation (3).

NEO6860 is a modality selective antagonist (shows full antagonism when activated by capsaicin, but little or no antagonism when activated by heat or low pH) at the cloned human TRPV1 receptor. NEO6860 has good bioavailability, an increase in exposure with dose increase, and a favorable safety profile up to 800 mg, in a Single Ascending Dose (50 mg to 1500 mg single dose, bioavailability >500 mg x 2, 12 hours apart) phase I study (4). Due to the mechanism of action of NEO6860 on TRPV1, the pharmacodynamics effect of the drug was tested in this phase I study following intradermal (ID) capsaicin provocation.

**Objectives**

To evaluate the pharmacodynamics (PD) effect of NEO6860 following oral single doses at various dose levels in healthy volunteers by assessing the level and duration of pain and secondary hyperalgesia using an ID capsaicin modality.

**Materials and Methods**

**Study Design and Procedures.** Ascending dose design, 8 cohorts from 50 to 1200 mg. Randomized controlled trial consisting of 8 subjects in each cohort; 2 subjects to receive placebo, 6 subjects the active treatment.

**Capsaicin test:** ID injection of capsaicin, 100 µg in 100 µl of sterile saline, onto the site of the anterior aspect of the forearm.

**Pharmacodynamics Outcomes.**

*Evoked Pain:* using an electronic Visual Analogic Scale (eVAS) from injection to 5 minutes post injection until the pain intensity returned to zero. Secondary hyperalgesia: using von Frey hair to assess the area of secondary hyperalgesia (ASA), performed twice, 5 and 30 minutes post capsaicin injection.

**Results**

64 subjects randomized, 56 were fasted and had an ADA assessment (PD population): mean age was 32 years old (SD = 11.6 years), with 87.5% being males and almost all patients being Caucasian (90.6%). The mean BMI was 24.7 (SD = 2.55).

**Evoked Pain**

MaxVAS was 8.3 units (out of a maximum of 100) lower in treated vs non-treated subjects. This effect was statistically significant (P < 0.05) at 3-hour and 8-hour timepoints.

**Area under the Vas Curve**

Marginal effect of treatment had a significant effect on AUC (P = 0.021), slightly smaller AUC for treated subjects. Effect was stronger at 8 hour than at 3 hour.

**VAS over Time.** The estimated curves for the trajectory of VAS over time, for treated vs untreated plasma concentrations, and untreated groups, is shown in Figure 3. Treated subjects had a VAS 6 units lower than untreated subjects (P = 0.0001).

At 3-hour time, VAS was 2 units lower for untreated subjects (P < 0.0001). At 8-hour time (Figure 3), VAS was 6 units lower for untreated subjects, (P < 0.0001).

Subjects with concentration <0.1 declined more quickly than subjects with 0 concentration (red curve) at 3h and 8h. Subjects with concentrations between 0.916 and 2.4 mg/mL resulted in the best effects (green and black curves).

**Secondary Hyperalgesia**

Three subpopulations are analyzed based on baseline values of ASA using 3 thresholds (figure 4): 12.5, 20 and 30 cm² are recommended by Wang et al. (5).

**Results demonstrate that NEO6860 has an effect on ASA when considering the dose level and the plasma concentration (figure 5 and 6).**

Mean changes are numerically superior in the intermediate dose levels: 400 mg, 500 mg and 800 mg. Effect of NEO6860 plasma concentration seemed to reach a maximum at 0.916 mg/L.

**Conclusions**

The observed effect of NEO6860 on VAS and ASA is consistent with the known pharmacological profile of capsaicin and the preclinical results with NEO6860.

**References**


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