# NEO6860, a Modality Selective TRPV1 Antagonist: Pharmacodynamics Analysis following Intradermal Capsaicin Injection during a Phase I Study

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## Introduction

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 1200 mg single dose, plus 500 mg x2, 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 single oral doses at various dose levels in healthy volunteers by assessing the level and duration of pain and secondary hyperalgesia using an ID capsaicin model.

## Material & Method

***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.

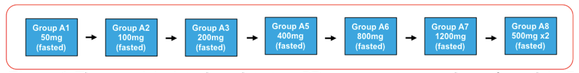


**Figure 1** The capsaicin intradermal test or PD assessment was only performed in 7 groups of fasted males.

Capsaicin test: ID injection of capsaicin, 100 µg in 100 µL of sterile saline, into the skin 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 or 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.

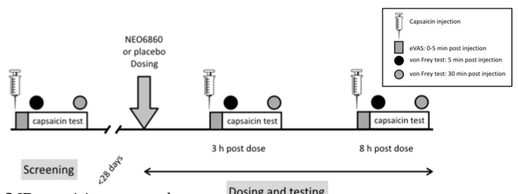


**Figure 2** ID capsaicin test procedures

## Material & Method (con't)

***Statistical Analyses***

Maximum VAS score (maxVAS), time of maxVAS, and area under the VAS curve were considered as outcomes. Separate linear mixed models, that included a random intercept to account for correlation between observations on the same subject, were estimated. Each subject contributed 3 observations to each model: screening, 3, and 8 hours post dose. The effect of time was modeled by including indicator variables for the 3- and 8-hour timepoint. Treatment was considered as a binary variable (yes/no); and using categories of plasma concentration (based on 25$^{th}$, 50$^{th}$, and 75$^{th}$ percentiles among subjects with a nonzero concentration). All subjects were considered as untreated at baseline (before administration of drug). The interaction of treatment and/or dose with time were considered. Only interactions that were statistically significant were retained.

The relationship between time and VAS was smoothed in by using a mixed model representation of penalized thin plate regression splines[33] considering ten knot points. An overall treatment effect was estimated by including a binary treatment indicator. To better understand the association between treatment and evoked pain, separate curves for treated and untreated groups were estimated.

Calculation of the area of secondary hyperalgesia was complicated by zero segment lengths. Multiple imputation via MICE (Multivariate Imputation by Chained Equations) was used to impute these. Linear mixed models were estimated to assess the effect of treatment or dose on secondary hyperalgesia.

## Results

64 subjects randomized, 56 were fasted males and had a PD 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.** MaxVAS values were 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 evidence of a treatment effect on AUC ($P$ = 0.08), 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 (by quartile plasma concentration) and untreated groups, is shown in Figure 3.

Treated subjects had a VAS 6 units lower than untreated subjects ($P$ < 0.0001).

At 3-h time , VAS was 2 units lower for untreated subjects ($P$ < 0.0001).

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

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

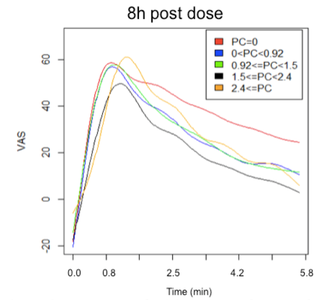


**Figure 3** Trajectory of VAS over time by quartile of plasma concentration (PC, mcg/mL).

***Secondary Hyperalgesia***

Three subpopulations are analyzed based on baseline values of ASA using 3 thresholds (figure 4): 12.5, 20 and 50 cm$^2$ as recommended by Wang et al (5).

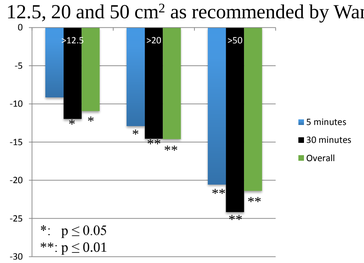


**Figure 4** Change from baseline in area of secondary hyperalgesia (cm$^2$) by baseline ASA categories. P values for pooled NEO6860 subjects vs placebo

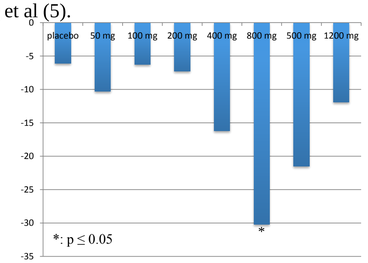


**Figure 5** Change from baseline in area of secondary hyperalgesia (cm$^2$) by dose groups (baseline threshold >12.5). P values for NEO6860 dose group vs placebo

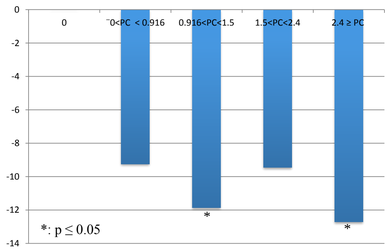


**Figure 6** Reduction of the area of cm2 secondary hyperalgesia (cm$^2$) by plasma concentration (PC) in mcg/mL (baseline threshold >12.5); PC at 0 is used as reference. P values for NEO6860 dose group vs placebo

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 mcg/L.

## Conclusion

In this phase I study, PD assessment was performed in 7 groups (total: 56 subjects, 8 subjects per group) of healthy male subjects, exploring single dose of NEO6860 from 50 mg to 1200 mg. PD assessment was based on the capsaicin ID injection model, measuring both evoked-pain (up to 5 minutes) and secondary hyperalgesia (at 5 and 30 minutes post injection).

Data demonstrate target engagement for NEO6860, and suggest that the association between dose / exposure and PD effect may not be linear in the explored dose range.

These findings should be taken into consideration for the design of further phase II, dose-finding studies.

## References

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