NEO6860, a Modality Selective TRPV1 Antagonist: Pharmacodynamics (PD) Analysis following Intra Dermal (ID) Capsaicin injection during a phase I study

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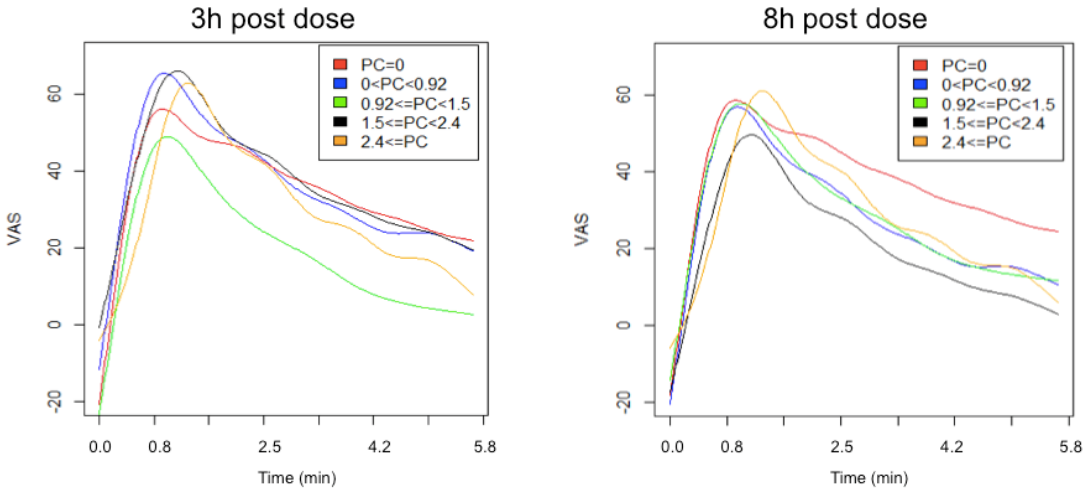
Background. NEO6860, a modality selective antagonist (antagonist effect when activated by capsaicin, but not when activated by heat or pH) at the cloned human transient receptor potential vanilloid subtype 1 (TRPV1) receptor. NEO6860 has a good bioavailability, an increase in exposure with dose increase, and a favorable safety profile up to 800mg, in a Single Ascending Dose (50 mg to 1200 mg single dose, plus 500 mg x2, 12 hours apart) phase I study[1]. Due to the mechanism of action of NEO6860 on TRPV1, the pharmacodynamic effect of the drug was tested in a phase I study following interdermal (ID) capsaicin provocation.

Methods. Following capsaicin ID in the forearm of 56 men, evoked-pain intensity was measured continuously up to 5 minutes on a visual analogue scale (VAS: 0-100 mm, 0 = no pain, 100 = Maximal Pain). Data were analyzed using a linear mixed model and categories of plasma concentration (based on the 25th, 50th, and 75th percentiles). The area of secondary hyperalgesia (ASA) was measured, 5 and 30 min post injection using 60 g weighted von Frey hair (. the pharmacodynamic assessments were performed pre-dose, 3 h, and 8 hours post dose. Linear regression was used to analyse the ASA data.

Results. Treated subjects had a maximum VAS value 8.3 mm lower than non-treated subjects (p = 0.05), at the 3-hour and 8-hour timepoints. The estimated curves for the trajectory of VAS over time show that evoked-pain in treated group decreased faster (p < 0.0001), at 3-h (1.92 mm lower in treated subjects, p < 0.0001) and 8-h (6 mm lower, p< 0.0001) timepoints. Al subjects with concentration >0 declined more quickly than subjects with zero 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). See figure below, showing the VAS over time at 3 hours (left figure) and 8 hours (right figure) timepoints.



PC: plasma concentration in mcg/mL.

Treated subjects had a statistically significant lower mean ASA especially when restricted to subjects with a baseline area at or greater than 12.5 cm^2 (aligned with thresholds recommended by Wang et al[2]. In the table below, treatment effect estimates (in cm2) are stratified by baseline values.

	Baseline Area (cm^2)											
Time post ID capsaicin	**≥ 0**			**>12.5**			**>20**			**>50**		
	N	**Treatment Effect**	**p**	**N**	**Treatment Effect**	**p**	**N**	**Treatment Effect**	**p**	**N**	**Treatment Effect**	**p**
5 minutes	56	-3.53	0.48	49	-9.11	0.12	43	-12.87	0.04	15	-20.52	0.04
30 minutes	56	-8.98	0.07	51	-11.96	0.03	45	-14.56	0.02	18	-24.16	<0.01
Overall[a]	56	-6.59	0.18	51	-10.94	0.03	45	-14.60	0.01	18	-21.38	<0.01

[a] Adjusted for time by including indicator variables for the 8-hour measurement, and another indicator variable to denote if the measurement occurred 5 or 30 minutes post injection.

The categorical effect of plasma concentration on ASA by baseline area is shown below.

	Baseline Area (cm^2)			
Time post ID capsaicin	**≥ 0**		**>12.5**	
		p		**p**
0	Reference	--	Reference	--
¨0<PC < 0.916	-3.08	0.58	-9.24	0.11
0.916≤PC<1.5	-7.64	0.14	-11.87	0.03
1.5≤PC<2.4	-6.40	0.22	-9.46	0.09
2.4 ≥ PC	-8.85	0.10	-12.71	0.03

PC: plasma concentration in mcg/mL.

Results demonstrate that NEO6860 has an effect on ASA when considering the dose level and the plasma concentration. However, the dose effect doesn't appear linear: for instance at 30-minutes post capsaicin injection, the mean (Standard Deviation) change from baseline in the 1200mg group was -11.9 (26.4) cm^2, which is similar to the reduction observed in the placebo (-6.13 (9.61)), 50 mg (-10.3 (19.7)), 100 mg (-6.27 (13.5)) and 200 mg (-7.28 (15.7)). The mean changes were numerically superior in the intermediate dose levels: 400 mg, 500mg 12h apart and 800 mg show -16.2 (10.1), -21.5 (32.8) and -30.2 (25.2) cm^2 reduction respectively. Similarly, the effect of NEO6860 plasma concentration seamed to reach a maximum at 0.916 mcg/L.

Conclusion. In this phase I study, PD assessment was performed following capsaicin ID injection in healthy male subjects, on both evoked-pain and secondary hyperalgesia. Data demonstrate target engagement for NEO6860, and suggest that the association between dose / exposure and PD effect may not be linear. These findings should be taken into consideration for the design of further phase II, dose-finding studies.

(1) Brown W et al. J Pain 2017;18(6):726-738.
(2) Wang et al. J Pain 2008;9(12:1088-1095