# Results of a Phase II / Proof-of-concept Trial Assessing NEO6860 in Osteoarthritis Knee Pain and Dosing Considerations.

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**Background.** Current treatments of osteoarthritis (OA) of the knee, such as NSAIDs, have significant limitations in both efficacy and safety. 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, has shown a good bioavailability and a demonstration of a pharmacodynamics (PD) effect as well as a target engagement in a phase I study. Safety profile was very good up to 800 mg single dose, with none of the effects previously observed with first generation TRPV1 inhibitors: no hyperthermia, no change in heat pain perception[1].

**Method.** This proof-of-concept, randomized, double blinded, placebo controlled, 3-period crossover, phase II study compared alternately 1 day (2 doses): NEO6860 (500 mg bid), placebo, and naproxen (500 mg bid) in a random sequence.

**Results.** A total of 54 patients with OA (mean age: 61; mean BMI 29 kg/m2; 35% with hypertension, 14% with dyslipidemia and 10% with diabetes) were included. Pharmacokinetics (PK) data revealed that the exposure was approximately 1.6 times higher when compared with phase I at the same dose ($C_{max}$ = 4337 ng/mL and 2770 ng/mL, respectively). An analgesic effect of NEO6860 was shown using Numerical Rating Scale (NRS) post-exercise, which was the primary outcome measure, at 3 and 24h, using a mixed ANCOVA Model, controlling for period, sequence and treatment as fixed effects and baseline as covariate:

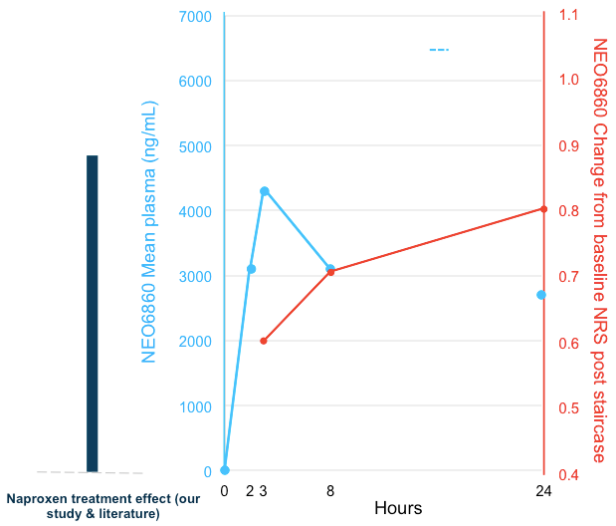
| Least-squares-means (95% CI) Change in NRS from baseline to | NEO6860 (N=52) | Naproxen (N=52) | Placebo (N=50) |
|---|---|---|---|
| 3 hours post-dose, Mean (95%CI) | -0.56 (-0.94 ; -0.19) | -0.7 (-1.09 ; -0.34) | -0.38 (-0.75 ; -0.00) |
| 8 hours post-dose, Mean (95%CI)* | -0.57 (-0.95 ; -0.20) | -0.65 (-1.02 ; -0.27) | -0.83 (-1.20 ; -0.46) |
| 24 hours post-dose, Mean (95%CI) | -0.67 (-1.09 ; -0.26) | -0.97**(-1.39 ; -0.55) | -0.29 (-0.71 ; 0.13) |

*: 8 h post dose was the primary endpoint; **: $p < 0.05$ comparing naproxen to placebo.

The observed effect for NEO6860 was below the hypothesis used for power estimate for this exploratory trial, explaining in part the *p* values ≥ 0.05. Treatment effect (observed NRS post exercise, active - placebo) at 24 hours is 0.5 for NEO6860 and 0.7 for naproxen. This needs to be compared with treatment effect reported in literature[2] (assuming an SD at 1.8): 0.3 for acetaminophen, 0.6 for celecoxib and 0.7 for naproxen. The safety profile was suboptimal, but comparable to that in a prior phase I study, taking into consideration the unexpectedly high level of exposure. Adverse Events (AEs), mostly mild in intensity, reported in this study were mainly headache, nausea, dizziness, fatigue, and hypoaesthesia. Two severe AEs (each in one patient) were reported during NEO6860 period (feeling hot and headache,) and resolved within one day. Importantly, no hyperthermia and no change in heat pain perception were reported.

**Dosing Consideration.** The features of NEO6860, as indicated by this early phase II study need to be optimized to demonstrate a medically viable program. The high level of exposure observed in our population was an unexpected finding. As observed in preclinical studies (unpublished data) and phase I study[1] on NEO6860, it is expected and very likely that the frequency and severity of AEs will decrease with reduced dosing.

NEO6860 associated reduction in NRS post exercise was time-dependent in our study, increasing from 3 hours to 24 hours post dosing, and not explained by exposure to the drug, as shown in the figure below. We hypothesize that treatment effect with NEO6860 will continue to increase over time, after day 1, reaching or even exceeding the effect of naproxen (black bar).




NEO6860 dose could be significantly reduced, likely by up to 10-fold, without negatively impacting its efficacy: (1) the estimated efficacious NEO6860 concentration in human, corrected for protein binding, is 100 ng/mL, which is more than 40 times less than the observed exposure as measured by the $C_{max}$ after a first administration. (2) PD data from the phase I study show a maximum effect at a level of exposure 10 fold below levels observed in our phase II study. In addition, maximum PD effect was not observed at the highest level of exposure, suggesting a non-linear PK/PD relationship. (3) No correlation was found between PK (as measured by AUC) and the NRS post exercise reduction in our phase II / PoC study, suggesting that patients were already at the plateau of efficacy.

We and others[3] have demonstrated in animal models, using isobolographic measurements, that the combination of a TRPV1 antagonist with various NSAIDs results in synergistic increase in the level of induced analgesia. Thus, a combination of NEO6860 with a low dose of NSAIDs may prove to be more effective than a standard high-dose NSAIDs treatment.

**Conclusion.** Altogether, this clinical study confirms the preclinical hypothesis: NEO6860, a modality selective TRPV1 antagonist produces analgesia without inducing hyperthermia or impaired noxious heat perception observed in non-modality selective TRPV1 antagonists. Future investigations should emphasize on: 1- reducing the NEO6860 dose, which may maintain (or even improve) the analgesic effect with multiple dosing (eg 15 days for instance), 2- testing NEO6860 in combination with NSAIDs to improve analgesia and potentially alleviate safety concerns of current treatments of OA, 3- exploring other chronic pain conditions such as neuropathic pain.


(1) Brown W et al. J Pain 2017;18(6):726-738.
(2) Bannuru R et al. Ann Intern Med 2015;162: 46-54.
(3) Rose T et al. Bioorg Med Chem Lett 2014;24(24):5695–5698.