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

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Introduction

Current treatments of osteoarthritis (OA) pain of the knee, such as NSAIDs, have significant limitations in both efficacy and safety.

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

NEO6860, 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. It has exhibited good bioavailability and a demonstrated a pharmacodynamic (PD) effect as well as target engagement in a phase I study. The safety profile was very good up to 800 mg single dose, with none of the unacceptable effects previously observed with first generation TRPV1 inhibitors (4). The highest well tolerated dose of 500 mg bid, was selected for phase II.

Primary Objective: To evaluate the analgesic efficacy and safety of NEO6860 after 1 day oral dosing (2 doses of 500 mg) in patients with OA of the knee, Kellgren-Lawrence stage I, II or III.

Material & Method

Participants. 54 patients with OA of the knee / 4 sites in Quebec, Canada,

Enrollment criteria:

- Males or females above 40 years of age
- Body mass index (BMI) between 18.0 and 35.0 kg/m2 inclusive
- Patients diagnosed with osteoarthritis of the knee, according to ACR guidelines
- Grade I, II or III using Kellgren-Lawrence score
- NRS post staircase ≥ 4 (out of a maximum of 10)
- WOMAC pain subscale ≥ 6 (out of a maximum of 20) on a 24 hour recall;
- Ability to report pain accurately as determined by the Focused Analgesia Selection Test (FAST): R^2 greater than 0.65

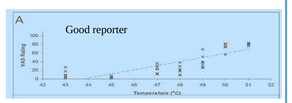


Figure 1: FAST (Analgesic Solutions, Natick, MA). Example of good pain reporter.

Study Design and Procedures. The study was randomized, double blinded, placebo controlled, 3-period crossover: NEO6860 500 mg twice, naproxen 500 mg twice and matching placebos for 1 day.

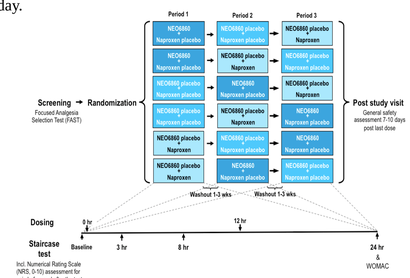


Figure 2: Study design.

Material & Method (con't)

Primary endpoint / Staircase test.

Primary endpoint: mean change in index knee NRS from baseline after the staircase test, to 8 hours post first dose.

Developed by Analgesic Solutions (Natick, MA, USA) . Consists of stepping fully up and down a total of 24 times.

NRS is measured immediately before and after the exercise.

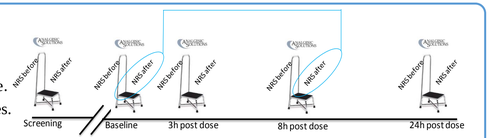


Figure 3: Primary endpoint / staircase test.

Results

Table 1: Patient's Characteristics.

Screened = 153					
Safety Population and mITT	54 (100%)	Mean BMI (SD)	29.1 (4.09) kg/m^2	NRS post staircase screening (SD) [2]	5.7 (1.85)
Treatment completed (3 periods)	50 (93%)	Mean duration of OA (SD)	8.2 (8.77) years	WOMAC pain subscale (SD) [3]	9.9 (2.61)
Mean Age	61.1 ± 9.06 years	Medication (non-OA)[1]	49 (90.7%)	Hypertension	19 (35%)
Female	34 (63%)	Medication OA[1]	45 (83.3%)	Dyslipidemia	8 (14%)
Mean Weight (SD)	79.3 (13.55) kg	NRS screening (SD)[2]	3.5 (2.06)	Type 2 diabetes	6 (10%)

1: Any medication 30 days prior or during the study ; 2: Max value:10; 3: Max value 20.

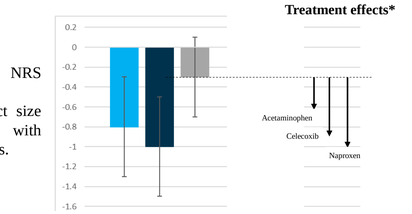
The table 2 below reports the analgesic effect of NEO6860 based on NRS post-staircase, (primary outcome measure) using a mixed ANCOVA Model, controlling for period, sequence and treatment as fixed effects and baseline as covariate:

Table 2: NRS post staircase using a mixed model

	Treatment Group		
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)	-0.72 (-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)

*: p <0.05 comparing naproxen to placebo.

Figure 4: NEO6860 NRS post staircase at 24hrs. Comparison with effect size reported in literature with other analgesic therapies.



Treatment effect estimated further to a meta-analysis of 137 studies in OA pain of the knee (5), assuming a 1.8 SD

Safety profile was suboptimal (see Table 3), mostly due to:

Feel hot, headache, nausea, dizziness, fatigue, and hypoaesthesia.

Two severe AEs: feeling hot and headache, resolved within one day.

No hyperthermia and no change in heat pain perception were reported.

		NEO6860		Naproxen		Placebo	
		N of Events	N of Patients	N of Events	N of Patients	N of Events	N of Patients
TOTAL Adverse Events		207	51	67	34	68	32
Intensity	Mild	179*	49	57	32	58	26
	Moderate	37	22	10	6	10	8
	Severe	2	2	0	0	0	0

*: Most AEs were feel hot / feel warm.

Table 3: Adverse Events by treatment group

Dosing Consideration.

NEO6860 dose could be significantly reduced, up to 10-fold, to improve efficacy / safety ratio:

- Observed exposure in phase II study was 60% above the estimate based on phase I.
- Safety profile observed in phase II is aligned with the high level of exposure and should improve with dose reduction.
- Estimated efficacious NEO6860 concentration in human, corrected for protein binding, is 100 ng/mL: C_{max} ,in phase II is more than 40 times above this threshold.
- 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,
- Maximum PD effect in phase I was not observed at the highest level of exposure, suggesting a non-linear PK/PD relationship,
- No correlation was found between PK (AUC) and the NRS post exercise reduction in our phase II study, suggesting a plateau of efficacy,
- NRS post staircase increases steadily from 3 to 24 hours (Figure), suggesting that NEO6860 efficacy could be time-dependent (and not concentration-dependent) and that analgesia could be improved with multiple dosing,
- We and others (6) have demonstrated in animal models, 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.

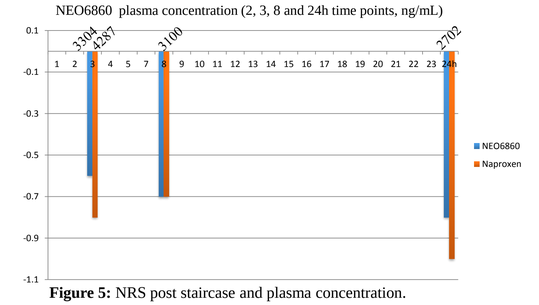


Figure 5: NRS post staircase and plasma concentration.

Conclusion

This phase II / proof-of-concept clinical study confirms the preclinical hypothesis: NEO6860, a modality selective TRPV1 antagonist produces analgesia without inducing hyperthermia or impaired noxious heat perception observed in other non-modality selective TRPV1 antagonists. NEO6860's analgesic effect in this study is in the range of celecoxib's and below that of naproxen.

Safety profile is suboptimal, but aligned with unexpectedly high level of NEO6860 exposure.

Future investigations should focus on:

1- Reducing the NEO6860 dose, which may maintain (or even improve) the analgesic effect with multiple dosing,

2- Testing NEO6860 in combination with NSAIDs to improve analgesia and potentially alleviate safety concerns of current treatments of OA pain,

3- Exploring other chronic pain conditions such as neuropathic pain.

References

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