NALBUPHINE ER TABLETS IN HEMODIALYSIS PATIENTS WITH SEVERE UREMIC PRURITUS: MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Jayant Kumar[1], Paul Crawford[2], Vandana Mathur[3], Howard Hait [4], Thomas Sciascia[4]

[1]Renal Medicine Associates, NM, [2]Research by Design, IL, [3]MathurConsulting, CA, [4]Trevi Therapeutics, CT USA

BACKGROUND

- A recently conducted study of 73,000 United States dialysis patients reported that 60% have pruritus and that 30% are moderately to extremely bothered by it[1].
- Uremic pruritus is associated with significant decreases in quality of life (QoL), sleep, and greater use of IV antibiotics, ESA, and iron[1].
- The pathogenesis of uremic pruritus may involve endogenous κ/μ opioid ligand ratio imbalance[2,3].
- Nalbuphine ER tablets (NAL) are a κ-opioid agonist/μ-opioid antagonist being developed for chronic pruritic conditions.

METHODS

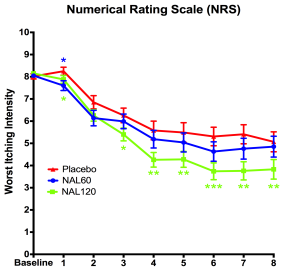
- In this multicenter, randomized, double-blind trial 373 hemodialysis patients were randomized (1:1:1) to NAL 60 mg (n=128) or 120 mg (n=120) or placebo (n=125) BID and treated for 8 weeks. Background antipruritic medications were allowed.
- The primary entry criteria were a mean numerical rating scale score (NRS) ≥ 4.5 (0 [no itch] -10 [worst possible itching]) with at least 2 of 6 scores ≥5 and a Patient-Assessed Disease Severity of B or C (sometimes or often bothered by scratch marks, and problems sleeping because of itching, feeling sad/agitated because of itching).

Table 1: Baseline Characteristics

	NAL ER 120 mg (N = 120)	NAL ER 60 mg (N = 128)	Placebo (N = 125)
Age (years)	55 (12)	55 (12)	56 (12)
Gender (% male)	58	54	60
Race (White/Black) (%)	53 / 47	45 / 52	48 /49
Hemodialysis Duration (years)	4.7 (4.2)	4.8 (4.0)	4.5 (4.4)
Diabetes (%)	50	56	48
PVD/PVD Intervention (%)	14 / 2	16 / 6	12 / 4
MI/Ischemic HD Intervention (%)	8 / 15	12 / 21	17 /7
Access (AVF/AVG/tunnel cath) (%)	73/18/9	75/15/8	70/18/11
Urea Reduction Ratio/Kt/V	74/1.6	74/1.6	75/1.6
iPTH (pg/mL)	452 (455)	382 (318)	464 (390)
Phosphate (mg/dL)	5.6 (1.5)	5.4 (1.8)	5.7(1.8)

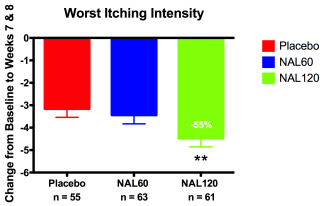
RESULTS (Severe Subgroup)

Figure 1: Itching Reduction over Time



*p<0.05, **p<0.01, ***p<0.001, NAL120 vs. placebo
*p<0.05 NAL60 vs. placebo
Data are means (SEM)

Figure 2: Change in Itching



*p<0.05, **p<0.01 vs. placebo
Data are means (SEM)
Weeks 7 and 8 defined the "Evaluation Period"

Figure 3: Itch MOS Sleep Disruption

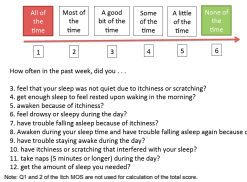
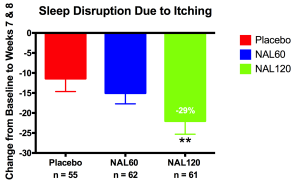


Figure 4: Change in Sleep Disruption



*p<0.05, **p<0.01 vs. placebo
Data are means (SEM)
Weeks 7 and 8 defined the "Evaluation Period"
The ItchMOS range is 0 (least disruption) - 100 (greatest disruption)

RESULTS, continued

- Demographics, dialysis adequacy, phosphorus, PTH, and antihistamine use were balanced (**Table 1**). The mean duration of itching was 3.2 years.
- The study overall met its primary endpoint: The NRS in the NAL 120 mg group declined by 49%, from 6.9 (1.5) to 3.5 (2.1), p = 0.017 vs. placebo. The effects were significant within 1 week following titration and durable over 8 weeks.
- Among a subgroup of 183 patients with severe pruritus (baseline NRS ≥7.0), examined post-hoc, itching intensity in those randomized to NAL 120, decreased by 55% (from severe to mild, mean NRS 8.2 to 4.5) [**Figures 1 and 2**] and sleep disruption (Itch MOS, **Figure 3**) due to itching improved significantly [**Figure 4**].
- Itching-related Quality of Life (Skindex-10) improved, but not significantly (NAL120 vs. placebo, p = 0.114).

CONCLUSIONS

- The trial met its primary endpoint, demonstrating a significant reduction in itch intensity in the NAL120 group vs. placebo in hemodialysis patients with moderate and severe uremic pruritus receiving background antipruritic drugs such as antihistamines and corticosteroids.
- The effect of NAL 120 was evident within 1 week following titration and was durable for the full 8-week treatment period.
- Among the subgroup of patients with severe uremic pruritus (NRS ≥7.0) at baseline receiving NAL 120, itching intensity and sleep disruption decreased significantly.
- This largest-to-date randomized trial in uremic pruritus demonstrated the efficacy of Nalbuphine ER tablets for one of the most distressing complications of end-stage renal disease.

REFERENCES

1. Ramakrishnan International J Nephrol Renovas Dis 2014
2. Kumagai *In* Itch Basic Mechanisms and Therapy 2004
3. Wang and Yosipovitch Int J Dermatology 2010