A proof-of-concept study with pharmacokinetics demonstrating anti-pruritic activity of oral nalbuphine in hemodialysis patients with uremic pruritus

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Abstract

Uremic pruritus is an itch that develops secondary to the uremia of kidney failure. The condition has been associated with an imbalance between endogenous μ and κ-opioid agonists in human studies

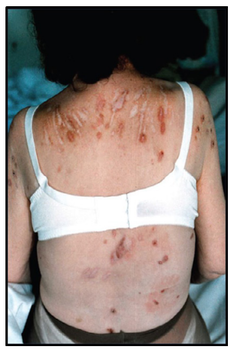
Nalbuphine is a synthetic opioid with both μ-opioid antagonistic and κ-opioid agonistic receptor properties. The impact of Nalbuphine ER on uremic pruritus was explored following oral administration of nalbuphine in end-stage renal disease (ESRD) subjects receiving intermittent hemodialysis (HD) therapy three times a week with mild to persistent pruritus.

The study was a single site, open label, non-randomized, parallel group, escalating dose safety and PK study in HD subjects. Subjects (n=14) were administered oral nalbuphine HCl ER tablets and dose escalated from 30 mg to 240 mg BID every three days over 17 days. Pharmacokinetic parameters (Cmax and AUC/O-12h) were obtained after the first dose and at steady state at each dose level. Subjects self-reported their worst daytime and nighttime itch intensity using a scale of 0 (none) to 10 mm (maximal possible intensity) itch Visual Analogue Scale (VAS) score. Subjects were closely monitored for adverse events throughout the study. Mean pre-dose VAS score (average of daytime and nighttime score) was 4.0 and ranged from 1.2 (mild) to 6.6 (moderate pruritus). A dose-dependent decrease in itch was noted in 13 out of 14 patients with a mean change in VAS score from baseline ranging between –0.9 at 30 mg to –2.8 at 240 mg BID dose. A clear direct relationship between exposure (AUC and Cmax) and change in VAS score was observed and provided the basis for future PK/PD model construction. Though exploratory, these data demonstrate that Nalbuphine ER may be effective in reducing itch at therapeutically safe doses and could offer relief for UP patients from a serious and deleterious condition.

Uremic Pruritus

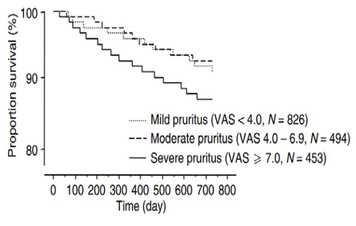
- Uremic pruritus (UP) is a common symptom among dialysis patients that is associated with significant, deleterious impairment of the patient quality of life *(Pisoni 2006, Narita 2006)*
- Mechanistic studies indicate the involvement of opioid receptors. In particular, in animal studies, μ-antagonism and κ-agonism were shown to have anti-pruritic effects *(Umeuchi 2003, Carstens 2004, Kuagai 2004)*
- There are no approved therapies in the EU or US
- Though a wide range of anti-pruritic drugs have been suggested for treatment, UP remains a significant unmet medical need and renal transplantation is the only current effective treatment *(Patel 2007)*

Uremic Pruritus:
Serious and life threatening disease in HD Patients



(Mettang 2002)

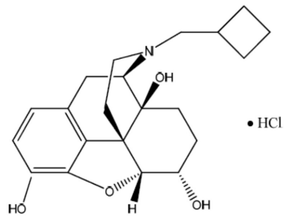
Kaplan-Meier Survival curve as a function of itch intensity
(Narita 2006)



Proposed Mechanism of Itch Suppression

- Mu-kappa opioid circuit interaction thought to be a ubiquitous signaling system in the CNS for a variety of physiological mediated actions *(Pan 1998)*
- Direct antagonism of mu-receptors of the neuronal cell groups facilitating itch signaling since this cell group is activated by endogenous mu-receptor agonists
- Activation of independent neural circuit via opioid kappa agonist that down regulates the cell group facilitating itch response

Nalbuphine Pharmacologic Properties:
μ-antagonist and κ-agonist opioid



Nalbuphine and Itch
Two Independent Pharmacological Mechanisms?

- *Suppression of central mediated itch signal*
  In subjects administered morphine intrathecally, nalbuphine is active against morphine-induced pruritus in human at IV doses equivalent to 60—480 mg oral doses (*Kjellberg 2001*)
- *Suppression of peripheral mediated itch signal*
  Nalbuphine demonstrated activity in Sub-P mouse model following subcutaneous administration at 10 mg/kg/day. *(Hawi 2013)*
- Both mu-antagonist (naltrexone) and kappa-agonist (nalfurafine) opioids have been shown to be effective against types of itch (*Metze 1999, Kumagai 2012*)

Nalbuphine HCl Extended Release Oral Tablets

- Nalbuphine is currently available in injectable form only (Nalbuphine HCl for Injection; Generic Nubain®)
- Oral extended release tablets is being developed in itch conditions by Trevi Therapeutics
- Target drug release profile of 12 hours well suited for BID dosing independent of pH with no dose-dumping in alcohol
- Safety and PK profile of Nalbuphine HCl ER tablets is well characterized in several clinical studies
- Recently completed a Phase 1 PK, safety and tolerability study in UP patients

Clinical Study Design

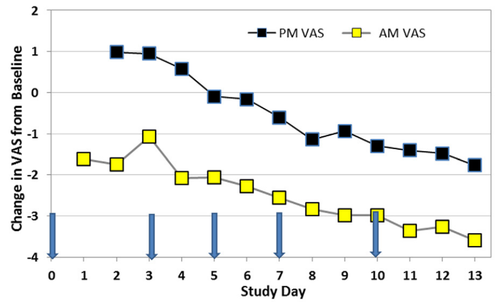
- Single site, open label, non-randomized, parallel group, escalating dose safety and PK study in HD subjects with pruritus on 3-time dialysis a week
- Subjects (n=14) administered oral Nalbuphine ER tablets and doses escalated from 30 mg to 240 mg BID every 2-3 days over 15 days
- Titration mimics intended use in clinical efficacy studies
- PK parameters obtained as a function of dose and dialysis
- Safety and tolerability monitored over duration of study effect on itch explored in study

Monitoring of Itch:
Visual Analogue Score (VAS)

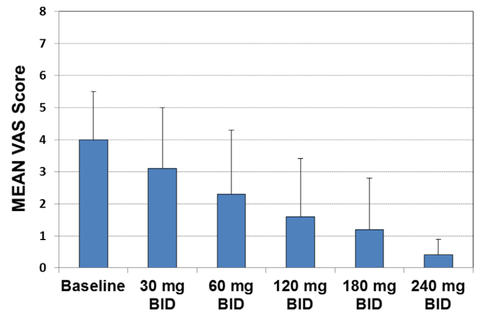
- HD subjects self-reported “their worst itch score”
- Subjects indicated their worst itch on a VAS scale 0 (none) to 10 (worst)
- Subject VAS score obtained twice-a-day AM and PM. Baseline VAS recorded pre-treatment
- Averaged of Worst AM and Worst PM VAS Score
- Change of 20% or 2 points (out of 10) considered clinically significant *(Mathur 2010)*

Results

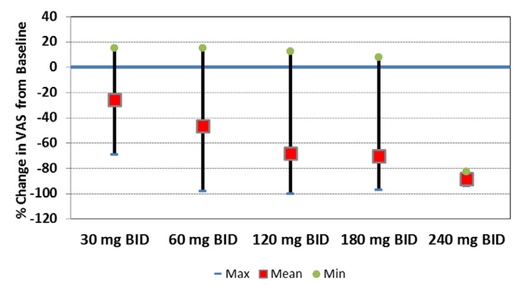
Diurnal Effect: VAS AM < VAS PM
Arrow indicates dialysis



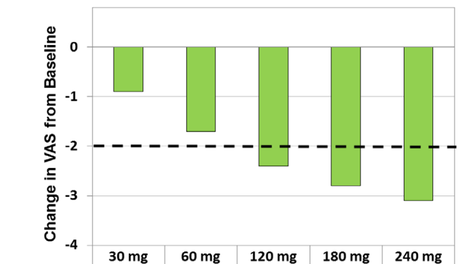
Mean VAS (*Average of AM & PM*) as A Function of Escalating Dose over 15 days



A 20% Change in VAS Considered Significant

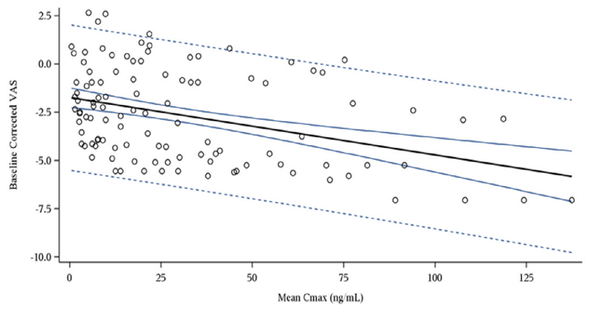


An Average of 2-Points Drop in VAS Within 7-10 Days

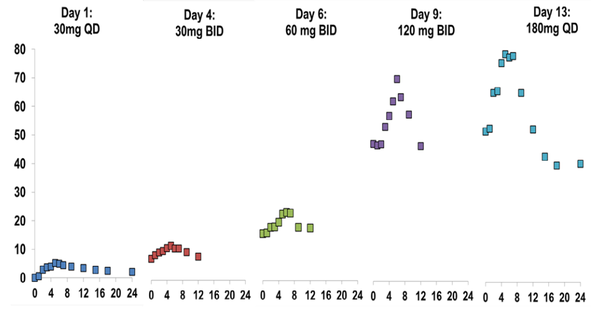


	30 mg	60 mg	120 mg	180 mg	240 mg
VAS Delta	-0.9	-1.7	-2.4	-2.8	-3.1

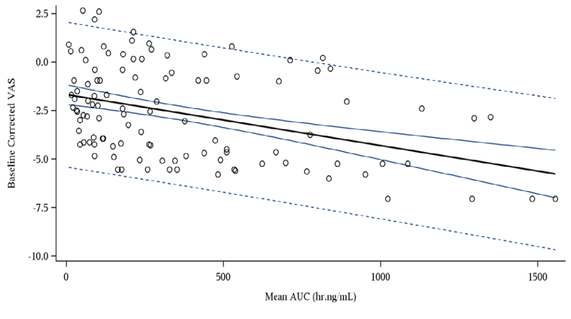
Change in VAS from Baseline as Function of Cmax
P-value for slope < 0.0001



Nalbuphine Plasma Concentration (ng/mL) as a Function of Day, Time and Escalating Doses



Change in VAS from Baseline as Function of AUC
P-value of slope < 0.0001



Summary

- Nalbuphine ER PK in HD subjects nearly dose-proportional with no accumulation upon repeated dosing
- Nalbuphine ER was well tolerated up to 240 mg BID
- HD subjects mean pre-dose VAS score was 4.0 ranging from 1.2 (mild) to 6.6 (severe pruritus)
- Dose-dependent decrease with maximal responses at 60 mg BID or above with decrease exceeding 20%
- A clear direct relationship between exposure (AUC and Cmax) and change in VAS score was observed and provides the basis for future PK/PD model construction
- Exploratory work shows efficacy achievable at therapeutically safe doses and could offer relief for uremic pruritus

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