The study was a single site, open label, non-sis (HD) therapy three times a week with mild to persistent pruritus. 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. Pharmacoki were administered oral nalbuphine HCl ER tablets and dose escalated from 30 mg to 240 mg BID every three days over 17 days. Pharmacoki were obtained as a function of dose and dialysis. Titration mimics intended use in clinical efficacy studies and doses escalated from 30 mg to 240 mg BID every 2-3 days over 15 days. Mettang 2002: 3495–3505: 5. Narita I, Omori K, Gejyo F et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney Int 2001; 59: 533–540. Nalbuphine Pharmacologic Properties: μ-antagonist and κ-agonist opioid. Nalbuphine is a synthetic opioid with both μ-opioid antagonistic and κ-opioid agonistic receptor properties. Nalbuphine is effective in reducing itch at therapeutically safe doses and could offer relief for UP patients from a serious and debilitating condition.

Abstract

Ureemic Pruritus

- Ureemic pruritus (UP) is a common symptom among dialysis patients that is associated with significant, deleterious impairment of the patient quality of life (Pious 2006, Nanda 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, Carpentier 2004, Kogai 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 current effective treatment (Patel 2007).

Uremic Pruritus: Serious and Life threatening disease in HD Patients

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

(Mottling 2002)

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.

Proposed Mechanism of Itch Suppression

- Mu-κ opioid circuit interaction thought to be a ubiquitous signaling system in the CNS for a variety of physiologically mediated activities (Pan 1998).
- Direct antagonism of mu-receptors of the neuronal cell groups facilitating itch signaling since this cell group is activated endogenously by 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 μ-antagonist (naloxone) and κ-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 administration.
- Averaged of Worst AM and Worst PM VAS Score: 5.57 ± 0.57. VAS = Visual Analogue Scale.
- 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 PKPD model construction.
- Exploratory work shows efficacy achievable at therapeutically safe doses and could offer relief for uremic pruritus.

Summary

Nalbuphine 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 PKPD model construction.
Exploratory work shows efficacy achievable at therapeutically safe doses and could offer relief for uremic pruritus.

Change in VAS from Baseline as Function of Dose: 0.9 mg to 240 mg BID

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

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

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

Diurnal Effect: VAS AM < VAS PM 

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

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

A 20% Change in VAS Considered Significant

Results