**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 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 doses escalated from 30 mg to 240 mg BID every three days over 17 days. Pharmacokinetic parameters (Cmax and AUC/O) from 30 mg to 240 mg BID every 2 days 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 (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-agonism and κ-agonism were shown to have anti-pruritic effects (Umrich 2003, Carstens 2004, Kuga 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 (Paiati 2007).

### Uremic Pruritus: Serious and life threatening disease in HD 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.
- Titrations mimicked intended use in clinical efficacy studies.
- PK parameters obtained as a function of dose and dialysis.
- Safety and tolerability monitored over duration of 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.

### Results

#### Diurnal Effect: VAS AM < VAS PM

- Arrow indicates dialysis.

#### A 20% Change in VAS Considered Significant

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

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

#### 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

### 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.