**Multiple Dose Pharmacokinetics and Pharmacodynamics of the New Oral Opioid Analgesic NKTR-181**

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**Introduction**

- NKTR-181 is a new mu-opioid agonist molecule designed to provide clinically relevant analgesia while reducing CNS mediated side effects.

- A completed Phase 1 single ascending dose study of NKTR-181 demonstrated that:
  - NKTR-181 has a predictable dose-linear PK over a 30-fold range of doses.
  - NKTR-181 produced a dose-dependent central analgesic response in healthy subjects, with onset in the first 30 minutes and peak in CNS within 2-6 hours.

- The abuse properties of opioid analgesics are believed to relate to their rapid entry into the CNS.1

- NKTR-181 exhibited a slower rate of CNS uptake in rats compared to commonly used opioids.2

- NKTR-181 displayed modest lower abuse liability compared to commonly used opioids in self-administration studies in rats and non-human primates.3

**Objectives**

This is a phase 1, double-blind, randomized, placebo-controlled, ascending multiple dose study of NKTR-181 administered orally in healthy, non-smoking volunteers.

The primary objective was to evaluate the safety and tolerability of ascending dose levels of NKTR-181 administered subcutaneously in a 10-fold range of plasma pharmacokinetic (PK) profile and pharmacodynamic (PD) activity.

**Methods**

- This ascending oral dose study evaluated four dose groups: 100, 200, 300, and 400 mg. Each of four dose levels enrolled 10 subjects, resulting in total of 40 healthy subjects over an eight-day treatment period. Subjects in each cohort received escalating dose of NKTR-181 in a blind manner following an overnight fast. Pharmacokinetics were measured at multiple post-dosing time points and steady state plasma levels were met in approximately 4 days with mean accumulation of 10-fold range of doses.

- A 5-day, placebo-controlled, double-blind, single center, 3-day injury model to assess analgesic effects and propensity as an indicator of the onset of peripheral effect was run based on the NALT (mouse tail immersion) test. NKTR-181 was evaluated in the U.S. at Liettwe Clinical Research (Salt Lake City).

- Phase 2 studies of NKTR-181 in patients with chronic pain are currently being planned.

**Pharmacokinetics**

- NKTR-181 exhibited dose-proportional pharmacokinetics across all dose levels on day 1 and 8. Pharmacokinetic steady state was achieved in approximately 4 days, with mean accumulation of 10-fold range of doses.

- Human data confirms 10-fold slower CNS entry from plasma as compared to oxycodone.

- Plasma levels reach steady state about Day 4.

- Plasma half-life ~12 hours.

- Peak plasma level ~2-3 hours following dosing with an oral liquid formulation at 200 mg twice daily.

**Results**

**NKTR-181 Demonstrates Significant Central Effect Over 12 Hours**

- Figure 2. Peak central effect occurs 3-4 hours following oral dosing on day 1.

**Pharmacokinetics**

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**Conclusion**

- NKTR-181 is an orally available new mu-opioid agonist molecule designed to have a slower rate of brain uptake compared with standard opioid therapies.

- Human data confirms 10-fold slower CNS entry from plasma as compared to oxycodone.

- NKTR-181 produces significant peripheral and central analgesic responses.

- NKTR-181 demonstrates a central analgesic response sustained over 8-day dosing period in the cold-pressor test.

- NKTR-181 also demonstrated analgesic and anti-hyperalgesic peripheral effects in UVB injury model.

- The PK profile of NKTR-181 is well-suited for the treatment of chronic pain.

- NKTR-181 demonstrates analgesia and anti-hyperalgesic peripheral effect following multiple dose administration in a rat model.

- In an experimental model of induced UVB injury, NKTR-181 displays significant anti-hyperalgesic effect following multiple dose administration in a rat model, indicating a potential mechanism of action that NKTR-181 is producing effects on multiple pain modalities through both central and peripheral pathways.

**Conclusions**

- NKTR-181 is a novel and orally available new mu-opioid agonist molecule designed to have a slower rate of brain uptake compared with standard opioid therapies.

- Human data confirms 10-fold slower CNS entry from plasma as compared to oxycodone.

- NKTR-181 produces significant peripheral and central analgesic responses.

- NKTR-181 demonstrates a central analgesic response sustained over 8-day dosing period in the cold-pressor test.

- NKTR-181 also demonstrated analgesic and anti-hyperalgesic peripheral effects in UVB injury model.

- The PK profile of NKTR-181 is well-suited for the treatment of chronic pain.

- NKTR-181 is Safe and Well Tolerated at All Doses Over Entire Dosing Period.

- NKTR-181 was well tolerated over the entire 8-day dosing period in the study at all doses evaluated.

- Most frequent adverse events observed: headache, nausea, and vomiting.

- Results suggest that there are dose proportionate NKTR-181 effects on the CNS and that this CNS-mediated effect persists with multiple dosing.

- The PD and safety profile of NKTR-181 suggest a wide therapeutic window with the drug being generally well tolerated over the entire 8-day dosing period in the study at all doses evaluated.

- Phase 2 studies of NKTR-181 in patients with chronic pain are currently being planned.