Background

- NKTR-181 is a new mu-opioid analgesic molecule designed to provide clinically relevant analgesia while reducing CNS mediated side effects.1
- The abuse properties of opioid analgesics are believed to be related to their rapid entry into the CNS.2
  - NKTR-181 exhibited a slower rate and extent of CNS uptake in rats compared to commonly used opioids.3,4
  - NKTR-181 displayed markedly lower abuse liability than commonly used opioids in self-administration studies in rats and non-human primates.3,5
  - NKTR-181 is a new chemical entity (NCE) that does not rely on a formulation approach to prevent its conversion into an abusable form of an opioid.

Objectives

The objective of this Phase 1 clinical study was to determine the safety, tolerability, pharmacokinetics and opioid pharmacodynamics of single oral doses of NKTR-181 in healthy human subjects.

Methods

Study Design

- Healthy subjects in groups of 15 received single 10, 20, 40, 80, 160, 320, or 500 mg oral doses of NKTR-181 solution (n=12) or placebo (n=3) following an overnight fast.
- Methods

Results

NKTR-181 is Well-tolerated Across a 50-fold Range of Doses

NKTR-181 was well tolerated at all doses evaluated; most adverse events (AEs) were mild and no serious adverse events were reported. Most frequent AEs observed at the highest doses tested were consistent with AEs characteristic of an opioid agonist, such as constipation, headache and nausea.

 NKTR-181 Exhibits Linear Pharmacokinetics, T1/2 of 2 to 4 hr and T1/2 of ~12 hr

Figure 1: Pharmacokinetic Modeling Results: Representative subject at each dose level (left) and predicted median (90% CI) from all subjects (right). [Note: Y-axis range changes with dose]

Extent and Duration of Miosis Increases with Dose, with Maximum Miosis at 4 to 6 hr

The extent and duration of analgesic effect based on LHR and TPP also increased with administered dose. Estimates of KEQ were similar across all measures of opioid effect, further indicating slower rate of NKTR-181 CNS entry. EG50 and IC50 values were similar, suggesting that all opioid effects occurred at similar NKTR-181 exposures. (Table below)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Median TPP Area Above Baseline</th>
<th>Median LHR Area Above Baseline</th>
<th>Median TPP vs. LHR</th>
<th>Median TPP vs. EG50</th>
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These results provide evidence of a correlation between measures of pain tolerance and CNS opioid effect indicated by the extent and duration of miosis.

Conclusions

- NKTR-181 produces concentration/dose-dependent central analgesic response in healthy subjects as measured by hand withdrawal latency in the cold pressor model.
- The time course of central opioid response to NKTR-181 significantly lags the time course of drug in plasma, consistent with a reduced rate of CNS uptake.
- NKTR-181 half-life is approximately 12 hours following oral administration of drug in solution, supporting twice daily dosing.
- NKTR-181 is currently in Phase 2 development for the treatment of chronic pain in patients with osteoarthritis of the knee.