Pharmacokinetics and Pharmacodynamics of Oral NKTR-181, a Novel Opioid Analgesic: Results of a Single Ascending Dose Phase 1 Study

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Conclusions

- NKTR-181 produces a dose-dependent central response in healthy subjects, as measured by hand withdrawal latency in the cold pressor model.
- NKTR-181 produces a dose-dependent and time-delayed maximal central response, with Tmax for miosis occurring at 4-6 hours, consistent with its reduced rate and extent of uptake into the CNS.
- The Tmax of NKTR-181 is 4-6 hours and the compound exhibits an average half-life of approximately 12 hours following oral administration, which could support once or twice daily dosing.
- NKTR-181 demonstrates predictable dose-linear pharmacokinetics over a 5-fold range of single oral doses in healthy subjects.

Background

- The abuse properties of opioid drugs are believed to relate to their pharmacological and pharmacodynamic properties, with NKTR-181 demonstrating significantly lower abuse liability (4).
- The properties of NKTR-181 are inherent in the molecular structure of NKTR-181 and no formulation technology.

Objectives

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

Methods

- A total of 100 subjects were evaluated in this Phase 1 study.
- Seven dose cohorts were evaluated with 15 subjects in each dose cohort (0, 10, 20, 40, 80, 160, and 320 mg).
- Subjects in each dose cohort received single doses of NKTR-181 solution given orally (n=12) or placebo (n=8) following an overnight fast. Dose escalation occurred only in the absence of dose-limiting adverse effects.
- Pharmacokinetics and pharmacodynamics were measured through serial blood samples and pharmacokinetic analysis.

Results

NKTR-181 Shows Dose-linearity, with Cmax at 2-4 hrs. Post-dose

Pharmacokinetics

NKTR-181 Cmax values occurred ~2-4 hours postdose and Cτ and AUC∞ values increased in proportion to dose over the studied range of 10 to 500 mg (Figure 1, Table 1), thus demonstrating dose-linear pharmacokinetics. Plasma half-life was independent of dose and averaged approximately 12 hours.

Pharmacodynamics

The extent and duration of opioid effect, based on the time-course of miosis, increased with administered dose, with the time of maximum miosis between 4 and 6 hours, and duration up to approximately 16 hours (Figure 2).

Reduction in Pupil Diameter is Proportional to Dose

The maximum reduction in pupil diameter decreased in a dose-dependent manner over the dose range of 80 to 500 mg (Figure 3).

Miosis Lags Appearance in Plasma, Consistent with Reduced Rate of CNS Uptake

Although NKTR-181 was rapidly absorbed and detected in plasma within 15 minutes (Figure 1), the time course of miosis lagged the time course of NKTR-181 in plasma, consistent with the reduced rate of NKTR-181 CNS uptake observed in preclinical studies. Figure 4 illustrates the controlled onset and sustained duration of miosis relative to the plasma/NKTR-181 concentration-time profile for the doses resulting in maximal miosis effect.

Pain Tolerance Increases with Dose

The extent and duration of analgesic effect based on CPT parameters of Time to Pain Perception and Pain Tolerance also increased with administered dose. Figure 5 shows plasma NKTR-181 concentration and CPT response vs. time profile for representative individuals who received single 80, 160, 320, or 500 mg doses of NKTR-181.

Safety and Tolerability

NKTR-181 was well-tolerated across a 5-fold range of doses. There were very few reports of AEs with the highest dose tested. Adverse events (AEs) were frequent but most were mild. Mild non-dose limiting AEs at the highest doses tested included AEs characteristic of an active opioid agonist, such as mild dizziness and nausea.

References


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