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

Lynn Weisler, MD, PhD, Aleksandra Ocinic*, PhD, Susan Herzog*, RN, Michael A. Eder*, PhD, Robert Meder*, MD
Lifetree Clinical Research, Salt Lake City, UT; *Nektar Therapeutics, San Francisco, CA

Introduction

• NKTR-181 is a new mu-opioid analgesic molecule designed to provide clinicians relevant analgesic effects while reducing CNS mediated side effects.1
• NKTR-101 produced a dose-dependent central analgesic response in healthy subjects, with onset apparent within one hour of dosing.2
• A completed Phase 1 single ascending dose study of NKTR-101 demonstrated that NKTR-1181 has a predictable dose-linear PK over a 50-fold range of doses.3
• The abuse properties of opioid analgesics are believed to relate to their rapid entry into the CNS.4

The study presented here is a phase 1, double-blind, randomized, placebo-controlled, multiple dose study of NKTR-101 administered orally to healthy male volunteers. The study was conducted in the U.S. at Lifetree Clinical Research (Salt Lake City, UT).

The primary objective was to evaluate the safety and tolerability of ascending oral doses of NKTR-101 administered every 12 hours over 8 days. The secondary objectives were to determine the pharmacokinetic (PK) profile and pharmacodynamic (PD) activity.

Methods

This ascending multiple dose study evaluated four dose levels: 100, 200, 300 and 400 mg. Each of four dose cohorts enrolled 15 subjects, resulting in a total of 60 healthy subjects over an eight day treatment period. Subjects in each cohort received oral doses of NKTR-181 (n=15) in aqueous solution or placebo (n=10) following an overnight fast. Pharmacokinetic was determined from multiple serial blood samples. Serial opioid pharmacodynamic tests included the cold pressor test (CPT) and a UVB injury model to assess analgesic effects and anti-hyperalgesic activity following UVB injury.

Results

Pharmacokinetics

NKTR-101 exhibits dose-linear pharmacokinetics across all dose levels on days 1 and 8. Pharmacokinetic steady state was achieved after 3 days for both Cmax and AUC values. Maximum plasma NKTR-101 concentrations were achieved ~2 hours following dosing on both day 1 and day 8.

PK Parameters After Oral Dosing of NKTR-101

Tmax ~2 hours
Cmax ~5 nmol/L
AUClast ~1.1 nmol/L hr

NKTR-181 Demonstrates Significant Central Effect Over 12 Hours

Figure 1. Mean (+SEM) Plasma NKTR-181 Concentration-Time Profiles in Healthy Subjects on Day 1

Figure 3. Delay in onset of maximum central effect of NKTR-181 reflects slowed rate of entry to the CNS.

Figure 2 presents the pupil diameter vs. time profiles that demonstrate a central effect of NKTR-181 that is maintained over the 12 hour dosing period. The ~2 hour lag in peak central effects reflects the slowed entry of NKTR-181 to the CNS from the plasma. This slowed CNS entry is seen at all doses having central effect and is a property of the NKTR-181 molecule.

Conclusions

• NKTR-101 is an orally-available new mu-opioid agonist molecule designed to have a slower rate of brain uptake compared with standard opioid therapeutics.
• Human data confirms 10-fold slower CNS entry from plasma as compared to oxycodone.
• NKTR-101 produces significant peripheral and central analgesic responses.
• NKTR-101 demonstrates a central analgesic response sustained over the multiple dosing study period. These results indicate that NKTR-101 is producing effects on peripheral pathways through both central and peripheral mechanisms.
• The PK profile of NKTR-101 is well-suited for the treatment of chronic pain.

Separate pharmacokinetic and pharmacodynamic studies in healthy volunteers using NKTR-101 over a 60-day period of twice daily dosing indicate that NKTR-101 may have a more therapeutic window than historical controls. This hypothesis will be confirmed in Phase 2 testing.

References

3. Pharmacol Biochem Behav. 2007; 86:45-54.
6. Pharmacol Biochem Behav. 2007; 86:45-54.
10. Laovic et al., Clinical Pharmacology and Therapeutics, 2006. (Table IV - I to site:equation half-life)