NKTR-181, a novel mu opioid analgesic with inherently low abuse potential and efficacy in multiple preclinical models of pain

INTRODUCTION

• NKTR-181 is a novel mu opioid receptor agonist designed for a reduced rate of entry into the central nervous system (CNS) that is currently in Phase 3 clinical studies for treatment of chronic low back pain. The reduced rate of brain entry of NKTR-181 is an inherent characteristic of the molecule, and has been shown to reduce central side-effects as well as abuse potential (demonstrated in preclinical and Phase 1 human abuse liability studies), while retaining strong analgesic efficacy in preclinical studies of acute visceral pain.

METHODS

Hot Plate Latency: Compound was administered orally and hot plate response (latency to lick hindpaw or jump following placement on a 55°C hot plate) was evaluated at baseline (prior to Cg), and 0.5, 1, 2 and 6 hr post-dose. Male CD-1 mice or Male Sprague Dawley rats were evaluated.

Formalin Paw Test: Compound was administered orally 30 min prior to formalin injection in the hindpaw. Paw flinches were measured using the Automated Nociception Analyzer for 60 min post-formalin. Cumulative number of flinches was measured between 0-9 min defined as Phase 1 and 60 min post-formalin in the hindpaw. Paw flinches were measured using the Automated Nociception Analyzer for 60 min post-formalin. Cumulative number of flinches was measured between 0-9 min defined as Phase 1 and 60 min post-formalin. Cumulative number of flinches was measured between 0-9 min defined as Phase 1 and 60 min post-formalin. Cumulative number of flinches was measured between 0-9 min defined as Phase 1 and 60 min post-formalin.

Thermal Nociception Test: Compound was administered orally 5 min prior to hot plate administration of a single concentration (50% effective dose) in the mouse (A) and rat (B). Time course was evaluated following a single dose and latency tested at 0.5, 1, 2 and 4 min post-dose. Data represent mean ± SEM (n = 10). Two-way ANOVA, Dunnett’s post-test with respect to saline. *p < 0.05.

RESULTS

NKTR-181 Demonstrates Full Analgesic Efficacy in a Centrally-Mediated Pain Model

Table 1. Hot plate latency dose-response of NKTR-181, morphine, oxycodone or saline following oral administration of a single concentration (50% effective dose) in the mouse (A) and rat (B). Time course was evaluated following a single dose and latency tested at 0.5, 1, 2, 4 and 6 hr post-dose. Data represent mean ± SEM (n = 10). Two-way ANOVA, Dunnett’s post-test with respect to saline. *p < 0.05, **p < 0.01.

NKTR-181 Demonstrates Analgesia in Persistent Pain Models

Analgesic efficacy is observed in both Acute and Persistent Phases of the Formalin Paw Model

NKTR-181 Demonstrates Comparable Analgesic Efficacy in Inflammatory Pain Model

Previously demonstrated reduced abuse liability in rats (self-administration and drug discrimination)

CONCLUSIONS

• NKTR-181 exhibits strong analgesic efficacy in multiple preclinical models, comparable to morphine and oxycodone.

• Reducing rate of CNS entry with NKTR-181 does not reduce central mechanisms of analgesic response in preclinical models.

• NKTR-181 previously shown to have reduced abuse liability in preclinical studies.

• Data support NKTR-181 could be the first opioid analgesic that can adequately treat chronic pain without adding to the epidemic of opioid abuse.

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