In Study II, the mean Emax of NKTR-181 was administered at 100 mg, 200 mg, and 400 mg as an oral solution compared with oxycodone 15 mg and 30 mg. The majority of TEAEs (67%) were associated with the critical first and second post-dose hours, were significantly lower for the NKTR-181 therapeutic dose range (≤ 600 mg) compared with both oxycodone doses. The maximum pupil constriction observed with the time of maximum pupil constriction was 3.99 (3.0)***‡ (10.7 mg) for 1200 mg supratherapeutic dose, for at least 2 hours post-drug administration. The mean 0-3h AUE0-3h, mean (SE) was significantly lower than both oxycodone doses (p < 0.0001) but not placebo (p = 0.007). The mean Emax scores for all therapeutic doses of NKTR-181 (≤ 600 mg) were significantly lower than placebo on mean (SD) primarily in the first 2 hours post-dose. The mean Emax scores for therapeutic doses of NKTR-181 (≤ 600 mg) had a significantly lower mean time to peak score compared to mean (SD) oxycodone on mean (SD) time to peak score (p < 0.0001). The peak effect of NKTR-181 (≤ 600 mg) was not different in the critical first and second post-dose hours compared with both oxycodone doses.

### SAFETY

- **22 of 42 subjects (52%)** in the safety population reported at least one TEAE in Study I.
- **21 of 41 subjects (51%)** in the safety population reported at least one TEAE in Study II.
- **The majority of TEAEs (67%)** were associated with the critical first and second post-dose hours.
- **32 of 42 subjects (76%)** in the safety population reported at least one TEAE in both treatment phases.

### REFERENCES


### METHODS

- **Subjects**: Healthy, non-opioid-dependent adults (18 to 50 years of age) who reported recreational opioid use in at least 1 occasion within the past year and at least once within the past 12 months (Study I) or within 12 days (Study II).
- **Study design**: Each study included Screening, Qualification, and Treatment Phases (Figure 1).
- **Sample size**: Each treatment phase was completed by 40 subjects in Study I and 54 subjects in Study II.
- **Randomization**: Subjects were randomized to the treatment phases in a double-blind, randomized, placebo-controlled, crossover human abuse potential (HAP) studies conducted in recreational opioid users to assess abuse potential across a wide range of NKTR-181 doses relative to therapeutic doses of oxycodone in a randomized, blinded, placebo-controlled paradigm.
- **Patient population**: Study I included 65 of 69 subjects (94%) in the safety population reported at least one TEAE; Study II included 32 of 42 subjects (76%) in the safety population reported at least one TEAE.
- **Drug liking**: Drug liking was assessed using a linear mixed effects model in the population who received all planned treatments.
- **Other outcome measures**: Included pupil diameter, pain, and safety.

### RESULTS

- In Study I, the mean Emax of NKTR-181 was administered at 100 mg, 200 mg, and 400 mg as an oral solution compared with oxycodone 15 mg and 30 mg. The majority of TEAEs (67%) were associated with the critical first and second post-dose hours, were significantly lower for the NKTR-181 therapeutic dose range (≤ 600 mg) compared with both oxycodone doses. The mean 0-3h AUE0-3h, mean (SE) was significantly lower than both oxycodone doses (p < 0.0001) but not placebo (p = 0.007). The mean Emax scores for all therapeutic doses of NKTR-181 (≤ 600 mg) were significantly lower than placebo on mean (SD) primarily in the first 2 hours post-dose. The mean Emax scores for therapeutic doses of NKTR-181 (≤ 600 mg) had a significantly lower mean time to peak score compared to mean (SD) oxycodone on mean (SD) time to peak score (p < 0.0001). The peak effect of NKTR-181 (≤ 600 mg) was not different in the critical first and second post-dose hours compared with both oxycodone doses.

### CONCLUSIONS

In a phase 3 clinical trial (SUMMIT-07), NKTR-181 administered at 100 mg to 400 mg twice daily for 12 weeks produced no clinically meaningful changes in patients with moderate to severe chronic low back pain.

- **Subjects**: Healthy, non-opioid-dependent adults (18 to 50 years of age) who reported recreational opioid use in at least 1 occasion within the past year and at least once within the past 12 months (Study I) or within 12 days (Study II).
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