New Oral Opioid Analgesic NKTR-181: Bioequivalence between Tablet and Aqueous Solution and Lack of Food Effect

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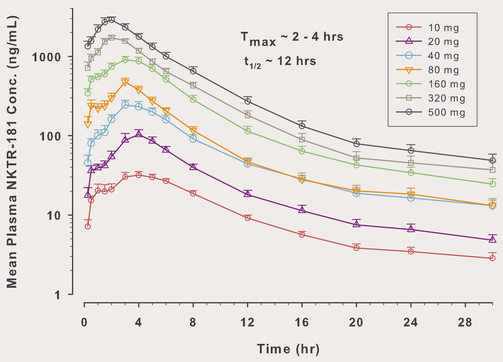
Background

- NKTR-181 is a new mu-opioid agonist designed to provide clinically relevant analgesia while reducing CNS mediated side effects.[1] NKTR-181 has maximal analgesic activity in preclinical models comparable to that of oxycodone and morphine, but demonstrates significantly lower abuse liability.[2] 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.
- NKTR-181 demonstrates predictable, dose-linear pharmacokinetics over a 50-fold range of single oral doses in healthy subjects (Figure 1). NKTR-181 T_{max} is in the range of 2 to 4 hours and half-life of ~12 hours following administration of drug in solution, supporting twice daily dosing.[3]
- NKTR-181 produces a dose-dependent and time-delayed maximal central opioid response, with E_{max} for miosis occurring at 4 to 6 hours, consistent with its reduced rate and extent of uptake into the CNS. NKTR-181 produces a dose-dependent central analgesic response in healthy subjects, as measured by hand withdrawal latency in the cold pressor model.[3]
- Initial trials of NKTR-181 were conducted using a solution administered in fasted conditions; a tablet formulation for future clinical use was developed and compared to the solution in both fasted and fed regimens.

Figure 1: Mean (±SEM) Plasma NKTR-181 Concentration-Time Profiles in Healthy Subjects (n=12 per dose level)



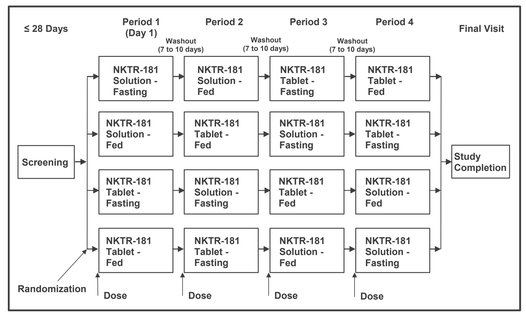
Objective

- To determine the bioavailability of NKTR-181 tablets relative to NKTR-181 oral solution.
- To investigate the effect of administration of NKTR-181 tablets and oral solution with food on NKTR-181 PK.

Methods

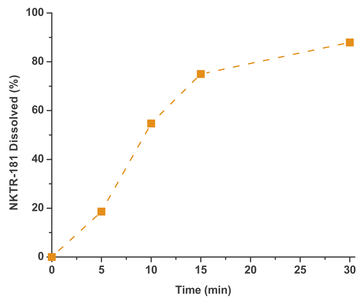
A randomized, single-dose, four-period, four-sequence crossover study was conducted in a panel of 24 healthy subjects consisting of 12 females and 12 males. Subjects randomly received 200 mg NKTR-181 orally as a single tablet or solution while fasted or fed (high fat meal) on 4 occasions separated by one week. Serial blood samples were collected through 48 hr postdose; plasma samples were analyzed using a validated LC-MS/MS method at Intertek Pharmaceutical Services (El Dorado Hills, CA).

Figure 2: Study Schematic Wilson Square Design



NKTR-181 tablets are an immediate release formulation. Dissolution testing showed more than 50% of the drug dissolves *in vitro* in the first 10 minutes with drug release complete in ~30 minutes (Figure 3).

Figure 3: Percent Dissolved vs. Time for 200 mg NKTR-181 Tablets



Results

NKTR-181 Tablets Meet Bioequivalence Criteria Compared to Drug in Solution

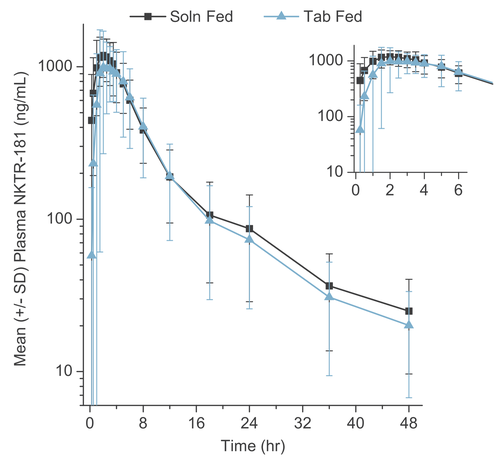
Concentration-time profiles were characterized by rapid initial absorption following administration of NKTR-181 as solution or tablet (Figure 4). NKTR-181 tablets release drug rapidly and consistently both *in vitro* and *in vivo*. PK parameters are summarized by treatment in Table 1.

Table 1: Mean Pharmacokinetic Parameters by Treatment

Mean (SD) PK Parameter Values				
Parameter	Solution fasted	Solution fed	Tablet fasted	Tablet fed
C_{max} (ng/mL)	1815 (789)	1360 (448)	1628 (471)	1525 (593)
T_{max}[a] (hr)	2.3 (0.3, 6.0)	2.0 (0.3, 3.5)	2.5 (1.5, 5.0)	2.7 (1.0, 6.0)
$AUC_{(0\text{-last})}$ (ng·hr/mL)	10012 (4830)	10120 (3669)	8890 (3233)	9075 (3468)
$AUC_{(0\text{-inf})}$ (ng·hr/mL)	10234 (4984)	10569 (3864)	9122 (3420)	9461 (3637)

[a] Median (Min, Max) presented for T_{max}

Figure 4: Mean ±SD (n=24) Plasma NKTR-181 Concentration-Time Profiles after Oral Administration with Food



Tablet/Solution least square mean (LSM) ratios for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ values were 93.8%, 92.7%, and 93.0%, while fasting and 109.0%, 89.3%, and 89.1%, when fed, demonstrating comparable bioavailability of the tablet relative to solution (Table 2). 90% CIs for Tablet/Solution (fasted or fed) LSM ratios for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within the bioequivalence limits of 80% to 125%, indicating that the two formulations are bioequivalent.

Table 2: Comparison of C_{max} and AUC after Administration of NKTR-181 as a Solution or Tablet

Test	C_{max}			$AUC_{(0\text{-last})}$			$AUC_{(0\text{-inf})}$		
	LSM	90% CI Lower	90% CI Upper	LSM	90% CI Lower	90% CI Upper	LSM	90% CI Lower	90% CI Upper
Tablet Fast/Solution Fast	93.8	84.0	104.7	92.7	86.8	99.0	93.0	87.0	99.3
Tablet Fed/Solution Fed	109.0	97.3	122.2	89.3	83.4	95.5	89.1	83.2	95.4

Administration with Food Does Not Affect the Bioavailability of NKTR-181 Tablets

Figure 5: Fed vs. Fasted $AUC_{(0\text{-inf})}$ Values for NKTR-181 Tablets

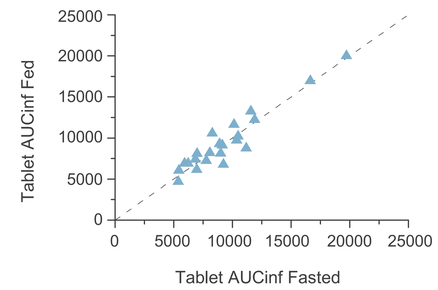


Table 3: Fed/Fasted LSM Ratios and Corresponding 90% CIs for NKTR-181 Tablets

Parameters	LSM	90% CI Lower Limit	90% CI Upper Limit
C_{max}	89.9	80.3	100.7
$AUC_{(0\text{-last})}$	99.6	93.1	106.5
$AUC_{(0\text{-inf})}$	101.2	94.5	108.4

Tablet Fed/Tablet Fasted LSM ratios for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ values were 89.9%, 99.6%, and 101.2%, demonstrating no effect of administration with a high fat meal on NKTR-181 tablet absorption (Table 3). 90% CIs for Tablet Fed/Tablet Fasted LSM ratios for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within the bioequivalence limits of 80% to 125%, indicating the absence of a meaningful food effect.

No Gender Differences in NKTR-181 Pharmacokinetics

Concentration-time profiles in males and females receiving NKTR-181 tablets were very similar (Figure 6) and no gender differences in C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were observed (Table 4).

Figure 6: Mean ±SD (n=12) Plasma NKTR-181 Concentration-Time Profiles in Females and Males after Administration of Tablets with Food

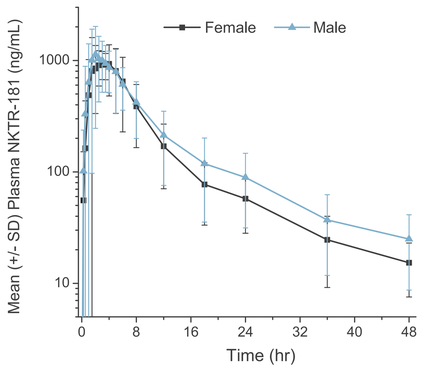


Table 4: Comparison of C_{max} and AUC Between Male and Female Subjects Receiving NKTR-181 Tablets With Food

Gender	PK Parameter (Mean (SD))		
	C_{max} (ng/mL)	$AUC_{(0\text{-last})}$ (ng·hr/mL)	$AUC_{(0\text{-inf})}$ (ng·hr/mL)
Female	1502 (491)	8363 (2289)	8631 (2399)
Male	1547 (705)	9787 (4347)	10291 (4528)

Conclusions

- NKTR-181 tablets are bioequivalent to drug in solution.
- Administration with food does not affect the bioavailability of NKTR-181 tablets.
- There are no gender differences in NKTR-181 pharmacokinetics.
- NKTR-181 is currently in Phase 2 development for the treatment of chronic pain in patients with osteoarthritis of the knee.

References

1. Frontiers in Research Symposium, 2010.
2. Anesthesiology, 2010.
3. American Academy of Pain Management, 2011.

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