

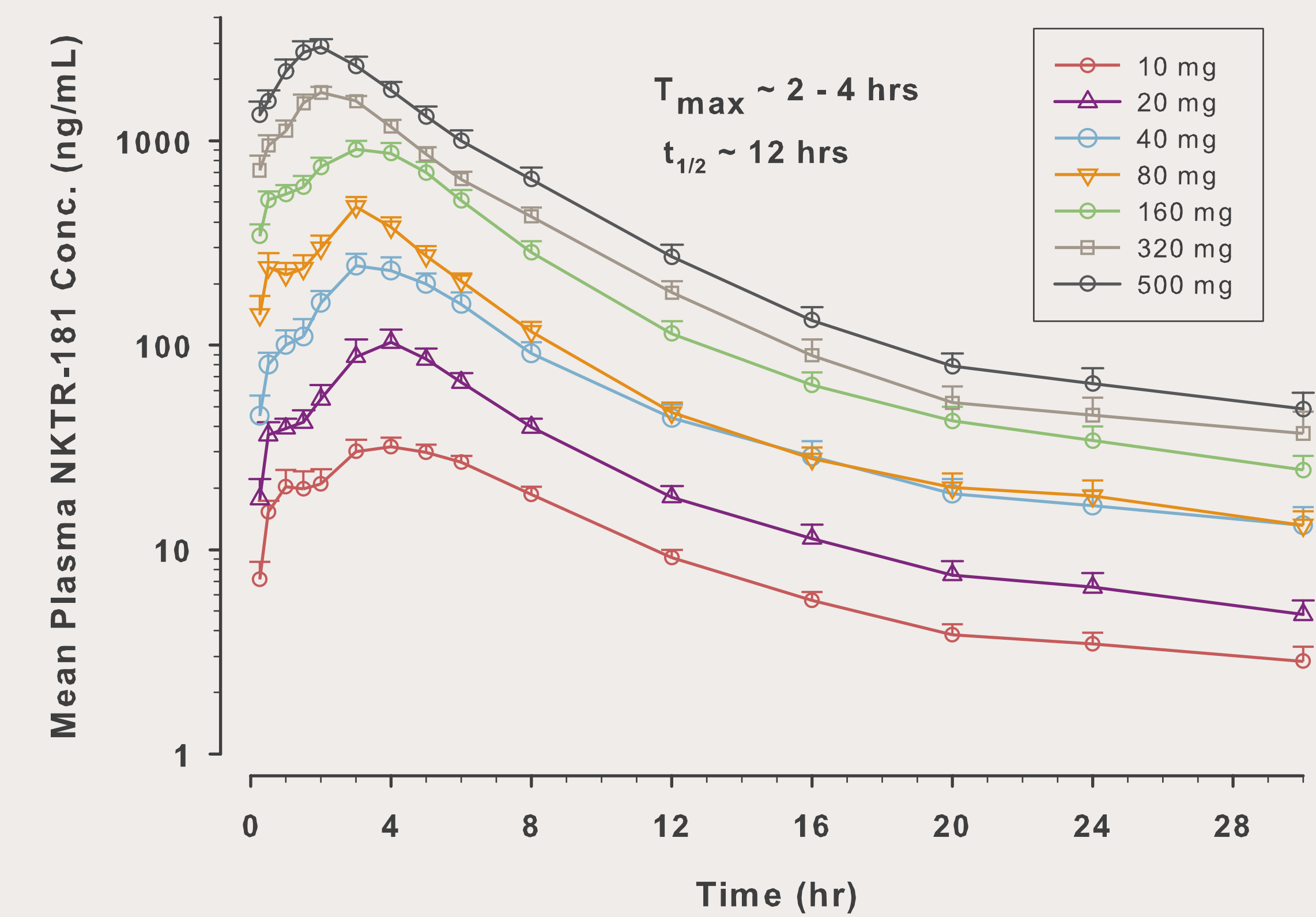
New Oral Opioid Analgesic NKTR-181: Bioequivalence between Tablet and Aqueous Solution and Lack of Food Effect

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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 (\pm SEM) Plasma NKTR-181 Concentration-Time Profiles in Healthy Subjects (n=12 per dose level)



References

- Frontiers in Research Symposium, 2010.
- Anesthesiology, 2010.
- American Academy of Pain Management, 2011.

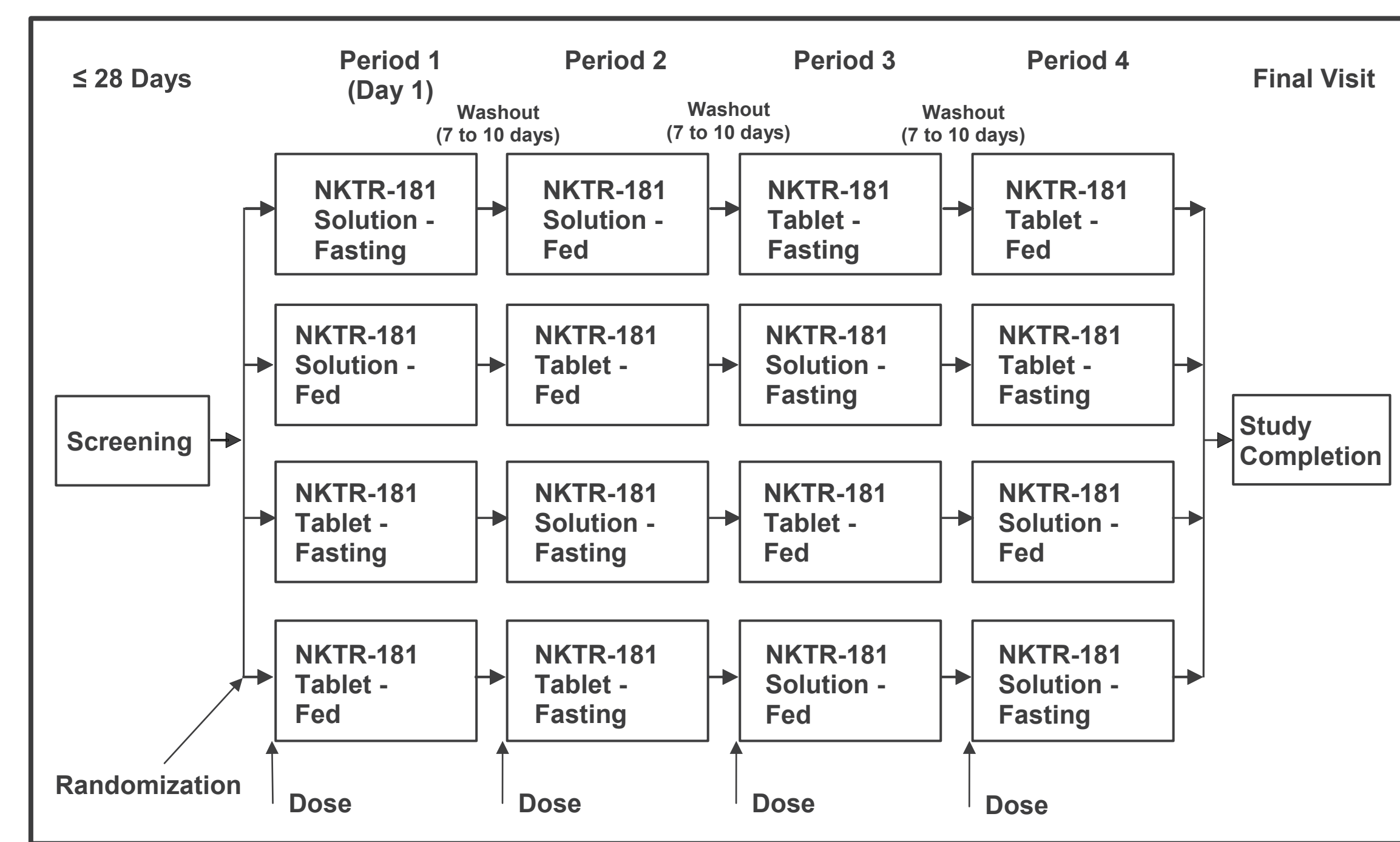
Objective

- 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

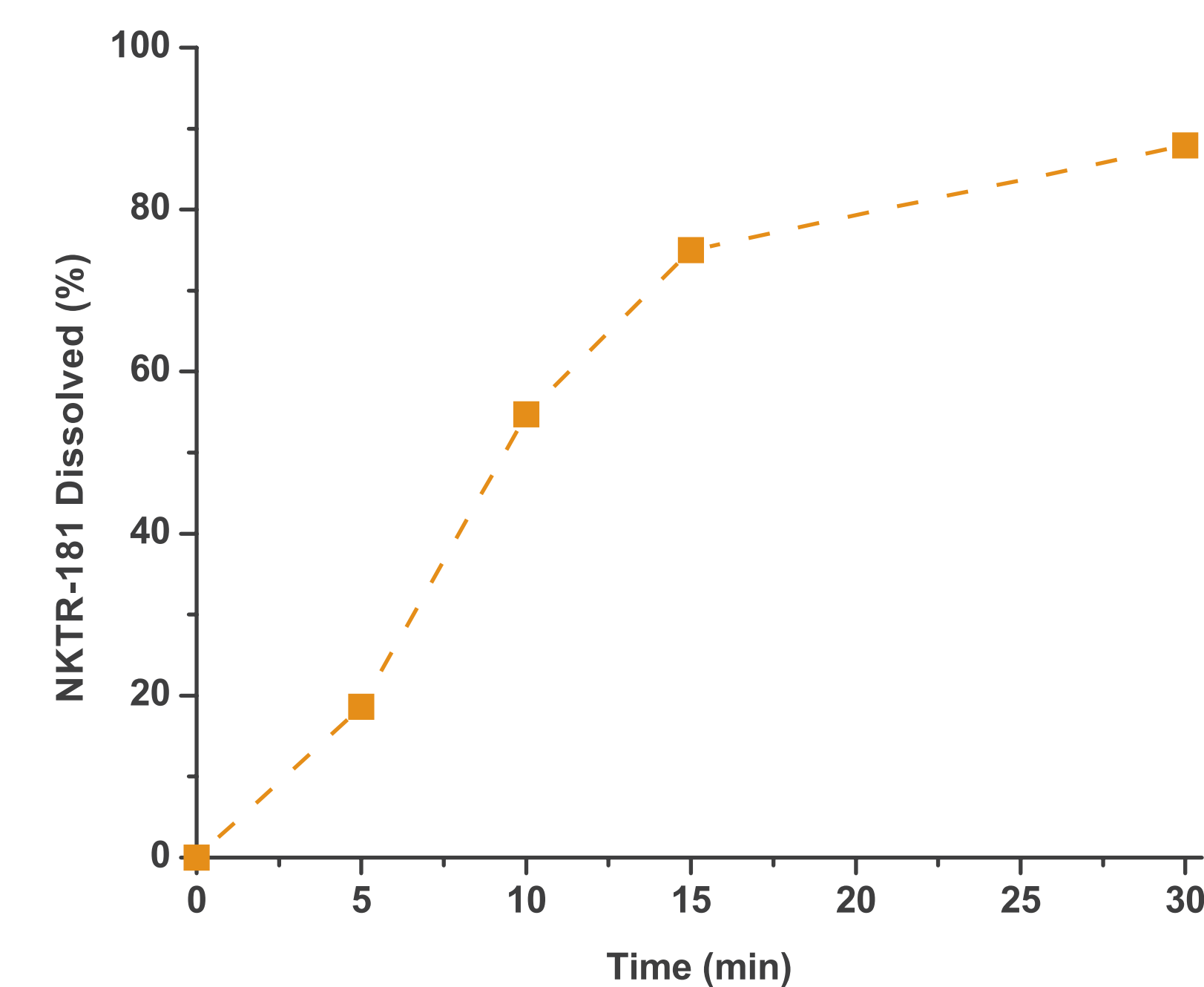
A randomized, single-dose, four-period, four-sequence crossover study was conducted in a panel of 24 healthy subjects consisting of 12 females and 12 males. Subjects randomly received 200 mg NKTR-181 orally as a single tablet or solution while fasted or fed (high fat meal) on 4 occasions separated by 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

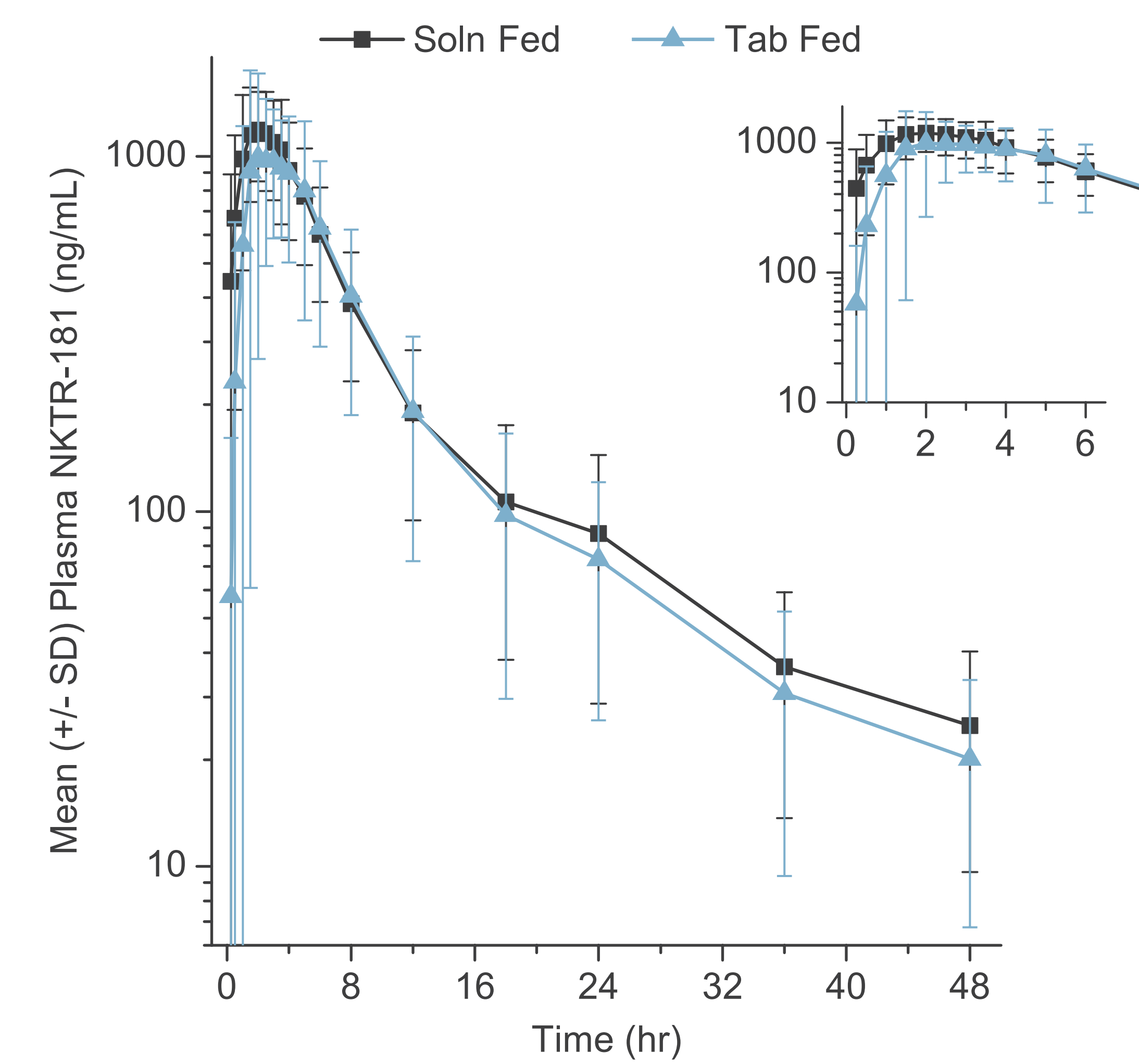
Concentration-time profiles were characterized by rapid initial absorption following administration of NKTR-181 as solution or tablet (Figure 4). NKTR-181 tablets release drug rapidly and consistently both *in vitro* and *in vivo*. PK parameters are summarized by treatment in Table 1.

Table 1: Mean Pharmacokinetic Parameters by Treatment

Parameter	Mean (SD) PK Parameter Values			
	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)
$AUC_{(0-last)}$ (ng·hr/mL)	10012 (4830)	10120 (3669)	8890 (3233)	9075 (3468)
$AUC_{(0-inf)}$ (ng·hr/mL)	10234 (4984)	10569 (3864)	9122 (3420)	9461 (3637)

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

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



Tablet/Solution least square mean (LSM) ratios for C_{max} , $AUC_{(0-last)}$ and $AUC_{(0-inf)}$ 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} , $AUC_{(0-last)}$ and $AUC_{(0-inf)}$ 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	LSM	C_{max}		$AUC_{(0-last)}$			$AUC_{(0-inf)}$		
		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 $AUC_{(0-inf)}$ Values for NKTR-181 Tablets

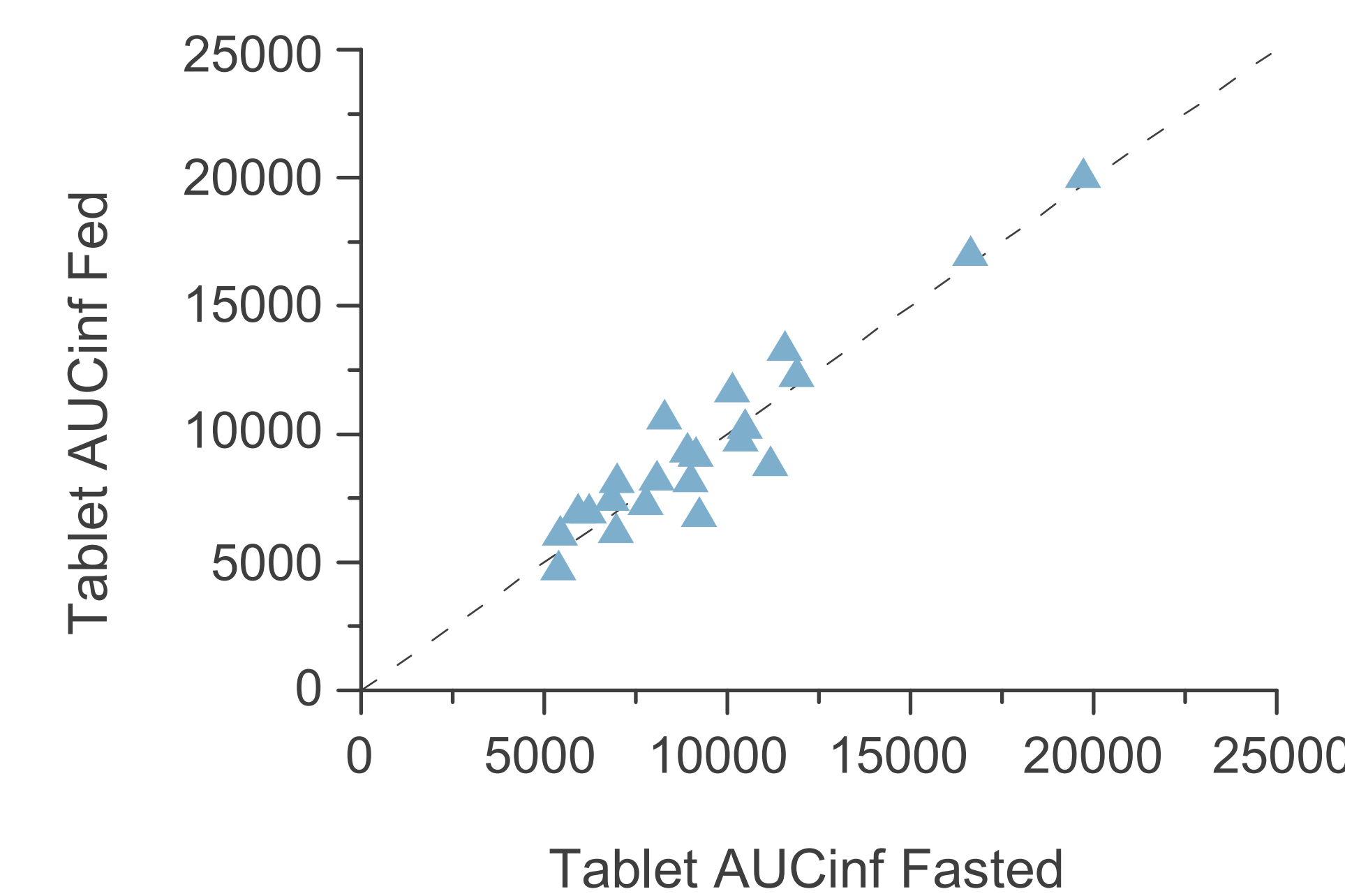


Table 3: Fed/Fasted LSM Ratios and Corresponding 90% CIs for NKTR-181 Tablets

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

Tablet Fed/Tablet Fasted LSM ratios for C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-inf)}$ 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} , $AUC_{(0-last)}$ and $AUC_{(0-inf)}$ 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} , $AUC_{(0-last)}$ and $AUC_{(0-inf)}$ were observed (Table 4).

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

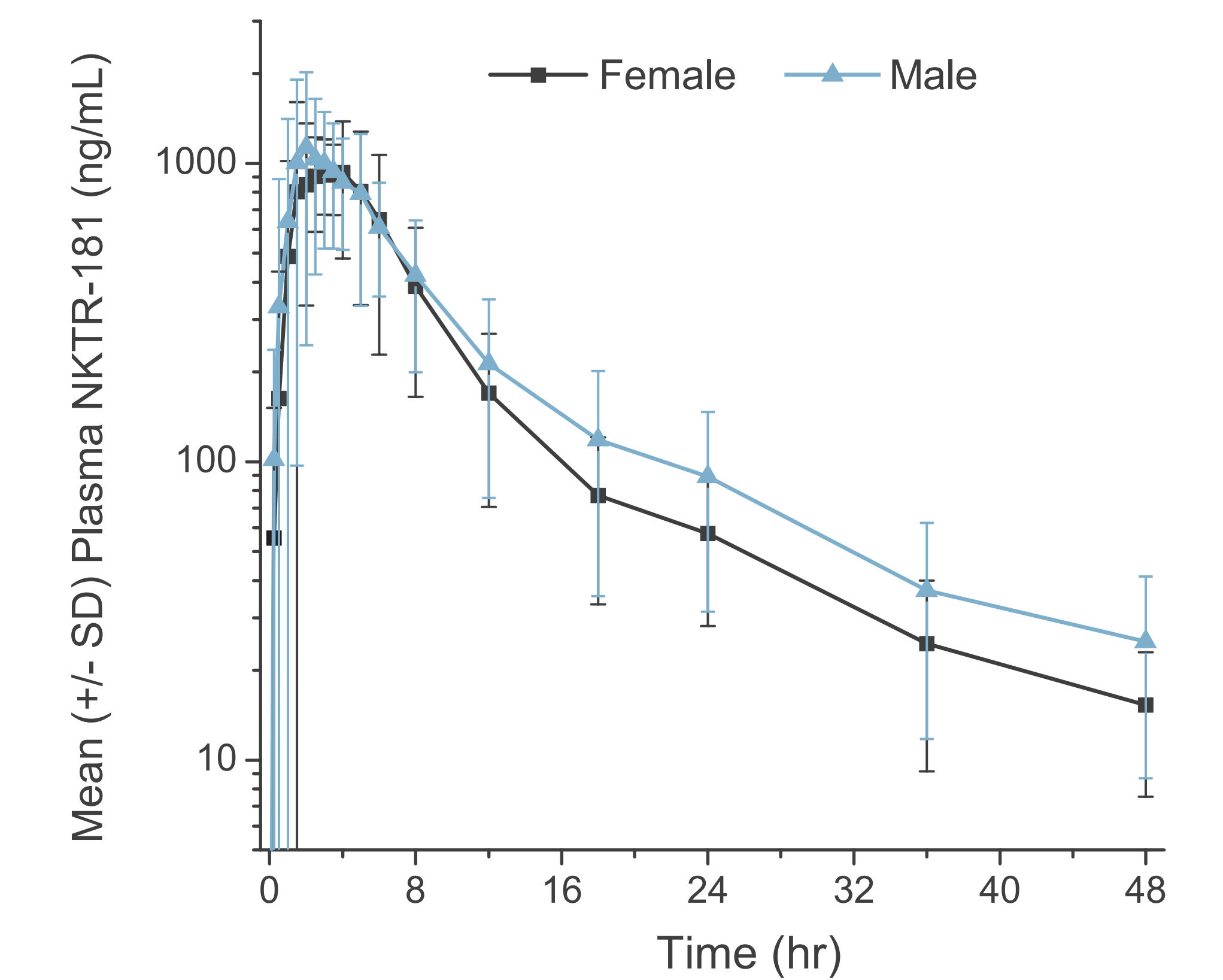


Table 4: Comparison of C_{max} and AUC Between Male and Female Subjects Receiving NKTR-181 Tablets With Food

Gender	PK Parameter (Mean (SD))		
	C_{max} (ng/mL)	$AUC_{(0-last)}$ (ng·hr/mL)	$AUC_{(0-inf)}$ (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.