Clinical Study Report Synopsis

Drug Substance NKTR-118

Study Code D3820C00012

An Open-label, 1-sequence, 3-period, 3-treatment, Crossover Study to Assess the Effects of Ketoconazole on the Pharmacokinetics of NKTR-118 in Healthy Subjects

Study dates: First subject enrolled: 06 February 2012
Last subject last visit: 09 April 2012

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the effect of ketoconazole on the pharmacokinetics of NKTR-118 in healthy subjects	C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-24)}$, AUC, λ_z, $t_{1/2,\lambda z}$, CL/F, V_z/F	Pharmacokinetic
Secondary	**Secondary**	
To assess the safety and tolerability of NKTR-118 when administered alone and in combination with ketoconazole	Adverse events, laboratory assessments (clinical chemistry, hematology, and urinalysis), physical examination, 12-lead electrocardiograms, vital signs, and Columbia-Suicide Severity Rating Scale	Safety
Exploratory	**Exploratory**	
To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy)	These data do not form part of the main report for this study.	Pharmacogenetic
To collect blood samples for safety biomarker testing that will allow future assessment of safety biomarkers	These data do not form part of the main report for this study.	Biomarker

AUC area under the plasma concentration versus time curve from zero (predose) extrapolated to infinity; $AUC_{(0-t)}$ area under the plasma concentration versus time curve from zero (predose) to time of last quantifiable concentration; $AUC_{(0-24)}$ area under the plasma concentration versus time curve from time zero (predose) to 24 hours; CL/F apparent systemic plasma clearance; C_{max} maximum plasma concentration; λ_z terminal rate constant; $t_{1/2,\lambda z}$ apparent terminal half-life; t_{max} time of maximum concentration; V_z/F apparent volume of distribution.

Study design

This was an open-label, nonrandomized, fixed-sequence study conducted at a single study center to assess the effect of ketoconazole on the pharmacokinetics of NKTR-118 in healthy volunteers. A single dose of 25 mg NKTR-118 was administered on Day 1 (Treatment A) followed by a 2-day washout (Days 2 and 3). Once-daily doses of 400 mg ketoconazole were administered from Days 4 through Day 6 (Treatment B) and on Days 7 and 8 with coadministration of 25 mg NKTR-118 on Day 7 (Treatment C). Serial blood samples for the determination of NKTR-118 pharmacokinetics were collected up to 72 hours following

NKTR-118 dosing on Days 1 and 7. Volunteers were admitted to the clinic on Day -1 and remained confined until completion of Day 10 procedures. A follow-up visit was conducted 7 to 10 days following clinic discharge.

Target subject population and sample size

Healthy males and females of nonchildbearing potential (nonpregnant and nonlactating) between the ages of 18 and 55 years, inclusive, with a minimum weight of 50 kg and a body mass index between 18 and 30 kg/m^2, inclusive, were eligible for study participation.

Up to 22 volunteers were to be enrolled to assure a minimum of 18 volunteers completed the study.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

NKTR-118, a 25-mg, white, film-coated tablet (Batch Number WK90885.001), was administered orally after a fasting period of at least 10 hours on 2 occasions (Day 1 and Day 7).

Ketoconazole was sourced locally from the same production lot. Once-daily oral doses of 400 mg ketoconazole were administered on the mornings of Days 4 through 8. On Day 7, ketoconazole was administered in combination with NKTR-118 following a minimum 10-hour fast; there were no food restrictions when ketoconazole was administered alone.

Duration of treatment

The duration of the study for each volunteer was up to 48 days, including a screening period (Visit 1) of 28 days or less, a residential treatment period of 11 days (from check-in on Day -1 until discharge on Day 10), and a follow-up visit 7 to 10 days after clinic discharge.

Statistical methods

Pharmacokinetic variables (NKTR-118 plasma concentrations and pharmacokinetic parameters) were summarized by treatment using appropriate descriptive statistics.

The effect of ketoconazole on the pharmacokinetics of NKTR-118, utilizing data from NKTR-118 plus ketoconazole administration (Treatment C) as test and treatment NKTR-118 administered alone (Treatment A) as reference, were assessed using an analysis of variance model for the primary pharmacokinetic parameters AUC and C_{max} on logarithmic-scale. Treatment was included as a fixed effect and volunteer was included as a random effect in the model.

Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities and summarized by treatment. Clinical laboratory parameters and vital signs were summarized using descriptive statistics. Electrocardiograms and physical examination findings as well as the Columbia-Suicide Severity Rating Scale assessments were presented in listings.

Subject population

The 22 volunteers in this study had a mean age of 34 years (range 18 to 55 years), a mean height of 177.6 cm (range 158.3 to 195.9 cm), a mean weight of 83.7 kg (range 64.2 to 108.6 kg), and a mean body mass index of 26.41 kg/m^2 (range 21.80 to 30.00 kg/m^2). There were 21 (95.5%) men and 1 (4.5%) woman. The race for 13 (59.1%) volunteers was black and for 9 (40.9%) volunteers was white. One (4.5%) volunteer reported their ethnicity as Hispanic or Latino. All volunteers were considered healthy and no concomitant medications were reported during the study.

All volunteers received all planned doses of investigational product; 21 volunteers completed all study procedures and 1 volunteer was lost to follow-up (no adverse events were reported for this volunteer during study conduct). All 22 volunteers were included in the pharmacokinetic and safety analysis sets and there were no important protocol deviations.

Summary of pharmacokinetic results

There was a significant increase in NKTR-118 exposure parameters, AUC and C_{max}, and a decrease in CL/F following a single dose of NKTR-118 in the presence of the potent *CYP3A* inhibitor, ketoconazole. This indicated that the *CYP3A4*-mediated metabolism of NKTR-118 was inhibited by ketoconazole. Ketoconazole did not appear to have a consistent effect on NKTR-118 t_{max}. NKTR-118 median t_{max} was 1.50 hours in the presence of ketoconazole (range: 0.50 to 3.00 hours) compared to 1.00 hour when NKTR-118 was administered alone (range: 0.25 to 5.02 hours).

Table S2 summarizes key NKTR-118 pharmacokinetic parameters in the presence and absence of ketoconazole.

Table S2 Summary of geometric mean (CV%) NKTR-118 pharmacokinetic parameters

Treatment[a]	AUC (ng·h/mL)	$AUC_{(0-t)}$ (ng·h/mL)	$AUC_{(0-24)}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max}[b] (h)	$t_{1/2,\lambda z}$ (h)	CL/F (L/h)
Treatment A	167	164	161	39.2	1.00	6.36	150
(N=22)	(43.5)	(43.2)	(41.7)	(46.9)	(0.25-5.02)	(56.8)	(43.5)
Treatment C	2140	2140	2080	376	1.50	9.19	11.7
(N=22)	(25.7)	(25.7)	(25.2)	(29.6)	(0.50-3.00)	(25.0)	(25.7)

CV geometric coefficient of variation.

[a] Treatment A: NKTR-118 25-mg tablet administered orally once on the morning of Day 1.
Treatment C: Ketoconazole 400-mg tablet on Days 7 and 8 plus NKTR-118 25-mg tablet administered orally on the morning of Day 7.

[b] t_{max} presented as median (range).

As shown in table S3, in the presence of ketoconazole, Geometric least-squares mean NKTR-118 AUC was 12.85-fold that of NKTR-118 administered alone (ratio%, 90% CI: 1285.44%, 1130.64 to 1461.44). In the presence of ketoconazole, Geometric least-squares

mean NKTR-118 C_{max} was 9.58-fold that of NKTR-118 administered alone (ratio%, 90% CI: 957.67, 809.60 to 1132.83).

Table S3 Statistical comparison of NKTR-118 primary pharmacokinetic parameters

					Comparisons		
Parameter	Treatment[a]	n	Geometric LS mean	95% CI	Pair	Ratio (%)	90% CI
AUC	A	22	166.8	(143.6,193.6)	C/A		
(ng·h/mL)	C	22	2144	(1846, 2489)	C/A	1285.44	(1130.64, 1461.44)
C_{max}	A	22	39.23	(33.35,46.14)	C/A		
(ng/mL)	C	22	375.7	(319.4, 441.9)	C/A	957.67	(809.60, 1132.83)

CI confidence interval; LS least-squares.

[a] Treatment A: NKTR-118 25-mg tablet administered orally once on the morning of Day 1.
Treatment C: Ketoconazole 400-mg tablet on Days 7 and 8 plus NKTR-118 25-mg tablet administered orally on the morning of Day 7.

Summary of safety results

There were no deaths, serious adverse events, or adverse events leading to study discontinuation. Overall, 10 (45.5%) volunteers experienced at least 1 adverse event during the study: 4 (18.2%) volunteers during NKTR-118 alone (Treatment A), 3 (13.6%) volunteers during ketoconazole alone (Treatment B), and 6 (27.3%) volunteers during the combination therapy (Treatment C). There were no adverse events of severe intensity and no other significant adverse events during the study.

The most frequently occurring adverse event was headache in 3 (13.6%) volunteers overall; occurring in 1 volunteer each during all treatments. Adverse events occurring in 2 (9.1%) volunteers overall included abdominal pain, nausea, and dizziness. Abdominal pain occurred in 1 volunteer during Treatment A and in 1 volunteer during Treatment C; nausea occurred in 1 volunteer during Treatment A and 1 volunteer during Treatment C; and dizziness occurred in 1 volunteer during Treatment B and 1 volunteer in Treatment C. There was 1 adverse event of nausea assessed as moderate in intensity; otherwise, all reported adverse events were of mild intensity.

No trends or clinically relevant changes were noted following dosing in mean or median clinical laboratory or vital sign parameters. Apart from a finding consistent with an adverse event of mild catheter site phlebitis, there were no changes in physical examinations following dosing. No volunteers displayed any suicidal ideation or behavior following dosing as determined by the Columbia-Suicide Severity Rating Scale assessment.

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