AstraZeneca

Clinical Study Report Synopsis

Drug Substance	NKTR-118
Study Code	D3820C00015
Edition Number	1
Date	13 September 2012

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

Study dates:	First subject enrolled: 05 March 2012
	Last subject last visit: 25 May 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 rifampin on the pharmacokinetics of NKTR-118 in healthy subjects	C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $AUC_{(0-8)}$,$t_{1/2\lambda z}$, λ_z, $AUC_{(0-24)}$, CL/F, V_z/F	Pharmacokinetic
Secondary	**Secondary**	
To assess the safety and tolerability of NKTR-118 when administered alone and in combination with rifampin	Adverse events, clinical laboratory assessments (clinical chemistry, hematology, and urinalysis), vital signs, physical examinations, 12-lead electrocardiograms, and Columbia-Suicide Severity Rating Scale assessments	Safety
Exploratory	**Exploratory**	
To collect plasma samples for potential NKTR-118 metabolite analysis	To collect plasma samples for potential NKTR-118 metabolite analysis	Pharmacokinetic
To collect and store deoxyribonucleic acid samples for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) in the presence or absence of rifampin	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; $AUC_{(0-8)}$ area under the plasma concentration-versus-time curve from zero (predose) to 8 hours; $AUC_{(0-24)}$ 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 center to assess the effect of rifampin on the pharmacokinetics of NKTR-118 in healthy volunteers. In Period 1, a single 25-mg dose of NKTR-118 (Treatment A) was administered orally on the morning of Day 1 followed by a 2-day washout (Days 2 and 3). In Period 2, once-daily doses of 600-mg rifampin (Treatment B) were administered from Days 4 through Day 12. In Period 3, a single dose of 600-mg rifampin plus a single dose of 25-mg NKTR-118 (Treatment C) was administered on the morning of Day 13. Serial blood samples for the determination of NKTR-118 pharmacokinetics were collected up to 72 hours following NKTR-118 dosing on Days 1 and 13. Volunteers were admitted to the clinic on Day -1 and remained confined until completion of Day 16 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 17803.004), was administered orally after a fasting period of at least 10 hours on Days 1 and 13.

Rifampin 300-mg capsules (batch number 69025B) were sourced locally and were administered on the mornings of Days 4 through 12. On Day 13, rifampin was administered in combination with NKTR-118 following a minimum 10-hour fast; there were no food restrictions when rifampin was administered alone.

Duration of treatment

The total duration of the study was approximately 54 days, including a screening period (Visit 1) of 28 days or less, 1 residential treatment period (Visit 2) of 17 days (from check-in on Day -1 until discharge on Day 16), and a follow-up visit (Visit 3) 7 to 10 days after discharge.

Statistical methods

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

The effect of rifampin on the pharmacokinetics of NKTR-118, utilizing data from NKTR-118 plus rifampin administration (Treatment C) as test and 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}, and an additional parameter $AUC_{(0-8)}$ on logarithmic-scale. Treatment was included as a fixed effect and the 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 19 to 55 years), a mean height of 177.3 cm (range 163.5 to 192.8 cm), a mean weight of 79.4 kg (range 62.5 to 104.3 kg), and a mean body mass index of 25.2 (kg/m^2). There were 19 (86.4%) males and 3 (13.6%) females. The race for 11 (50.0%) volunteers was white; for 10 (45.5%) volunteers was black; and for 1 (4.5%) volunteer was American Indian or Alaska Native. One (4.5%) volunteer reported their ethnicity as Hispanic or Latino. All volunteers were considered healthy with no concomitant medication given for ongoing medical conditions.

Twenty-one (95.5%) volunteers received all planned doses of investigational product with 1 (4.5%) volunteer discontinuing on Day 11 (Period 2, Treatment B) after receiving 1 dose of 25-mg NKTR-118 and 8 doses of 600-mg rifampin. All 22 volunteers enrolled in the study were included in the pharmacokinetic and safety analysis sets, and there were no important protocol deviations.

Summary of pharmacokinetic results

There was a significant decrease in NKTR-118 exposure parameters, AUC and C_{max}, and an increase in CL/F following a single dose of NKTR-118 in the presence of the potent *CYP3A4* inducer and P-glycoprotein efflux inducer, rifampin.

Table S2 sumarizes key NKTR-118 pharmacokinetic parameters in the presence and absence of rifampin.

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

Treatment[a]	AUC (ng·h/mL)	$AUC_{(0-8)}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max}[b] (h)	$t_{½λz}$ (h)	CL/F (L/h)
Treatment A	172	143	45.2	1.00	6.69	145
(N=22)	26.8	27.6	36.0	(0.25, 4.00)	51.2	26.7
Treatment C	18.7	17.9	11.1	0.50	1.83	1330
(N=21)	27.3	26.6	52.8	(0.25, 1.50)	20.8	27.3

CV% geometric coefficient of variation
[a] Treatment A: NKTR-118 25 mg on Day 1.
Treatment C: Rifampin 600 mg plus NKTR-118 25 mg on Day 13
[b] t_{max} presented as median (range)

As shown in Table S3, in the presence of rifampin, geometric least-squres mean NKTR-118 AUC decreased approximately 89% while C_{max} decreased approximately 76%.

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	171.8	(153.2, 192.6)			
(ng·h/mL)	C	21	18.72	(16.65, 21.05)	C/A	10.90	(9.54, 12.45)
C_{max}	A	22	45.20	(37.61, 54.32)			
(ng/mL)	C	21	11.06	(9.160, 13.36)	C/A	24.47	(19.63, 30.51)
$AUC_{(0-8)}$[b]	A	22	142.6	(127.1, 160.0)			
(ng·h/mL)	C	21	17.93	(15.94, 20.17)	C/A	12.57	(11.01, 14.36)

CI confidence interval; LS least squares
[a] Treatment A: NKTR-118 25 mg on Day 1
Treatment C: Rifampin 600 mg plus NKTR-118 25 mg on Day 13
[b] $AUC_{(0-8)}$ was added as an additional PK parameter to the analysis

Summary of safety results

There were no deaths or serious adverse events reported during study conduct. One volunteer (E0001053) discontinued the study during Treatment B (rifampin only) due to adverse events of elevated gamma-glutamyl transferase and alanine aminotransaminase. Adverse events were reported in 13 (59.1%) volunteers with the majority during the rifampin (6 [27.3%] volunteers) only or rifampin plus NKTR-118 (7 [33.3%] volunteers) treatments as compared to the NKTR-118 only (1 [4.5%] volunteers) treatment. There were no adverse events of moderate or severe intensity and no other significant adverse events during the study.

The most frequently occurring adverse event was headache in 7 (31.8%) volunteers overall; occurring in no volunteers during Treatment A, 3 (13.6%) volunteers during Treatment B, and 4 (19%) volunteers during Treatment C. Adverse events occurring in 2 (9.1%) volunteers included nausea, upper respiratory infection, and dizziness. Nausea occurred in 1 volunteer during Treatment B and 1 volunteer during Treatment C. Upper respiratory infection occurred in 2 volunteers during Treatment C; and dizziness occurred in 2 volunteers during Treatment B.

Adverse events (mild in intensity) were reported for 2 volunteers for clinical laboratory findings of thrombocytopenia and elevated gamma-glutamyl transferase and alanine aminotransaminase. The thrombocytopenia was assessed as not related to investigational product. The elevated gamma-glutamyl transferase and alanine aminotransaminase were assessed as related to investigational product (rifampin).

There were no trends or clinically relevant changes in vital sign, electrocardiogram, or Columbia-Suicide Severity Rating Scale findings following dosing.