AstraZeneca

Clinical Study Report Synopsis

Drug Substance NKTR-118

Study Code D3820C00010

An Open-label, Single Center Study to Assess the Pharmacokinetics of NKTR-118 in Patients with Impaired Hepatic Function and Healthy Volunteers with Normal Hepatic Function Following Administration of a Single Dose of 25 mg NKTR-118

Study dates: First subject enrolled: 1 August 2011
Last subject last visit: 9 November 2011

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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetics (PK)	To assess the PK of a single oral dose of 25 mg NKTR-118 in patients with impaired hepatic function (mild and moderate) compared to that in healthy volunteers with normal hepatic function	Primary variables: C_{max} and AUC Secondary variables: t_{max}, $t_{1/2}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F
Secondary	Safety	To examine the safety and tolerability of a single oral dose of 25 mg NKTR-118 in patients with impaired hepatic function and in healthy volunteers with normal hepatic function	Adverse events, laboratory assessments (clinical chemistry, hematology, and urinalysis), vital signs (blood pressure and pulse rate), 12-lead ECG, physical examination, and C-SSRS
Exploratory [a]	PK	To reserved collected plasma samples for the potential metabolite evaluation	Not applicable
	Pharmacogenetic	To collect blood samples for potential pharmacogenetics testing that will allow future investigation of the influence of genotype on drug disposition and safety	Not applicable

[a] Results from the exploratory objectives, if performed, are not reported in the clinical study report.
λ_z: terminal elimination rate constant; AUC: area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0-24)}$: area under the plasma concentration-time curve from time zero to 24 hours postdose; $AUC_{(0-t)}$: area under the plasma concentration-time curve from time zero to the last measurable concentration; CL/F: apparent oral clearance; C_{max}: maximum observed plasma concentration; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; $t_{1/2}$: apparent terminal half-life; t_{max}: time to maximum observed plasma concentration; V_z/F: apparent volume of distribution during the terminal phase

Study design

This was a single dose, nonrandomized, open-label, parallel group study to examine the PK, safety, and tolerability of NKTR-118 in patients with mild and moderate hepatic impairment and healthy volunteers with normal hepatic function (as control). Hepatic impairment was assessed based on the patients' Child-Pugh classification.

A total of 24 subjects (3 groups of 8 subjects each, based on hepatic impairment) were included in the study: 8 patients in the mild hepatic impairment group [Child Pugh Class A],

8 patients in the moderate hepatic impairment group [Child-Pugh Class B]), and 8 healthy volunteers in the normal hepatic function group.

Potential subjects were screened at Visit 1, within 28 days before Visit 2. Visit 2 was the treatment period and each subject was resident in the study center from Day -1 until Day 6 (after the Day 6 120 hours postdose assessments were completed). The investigational product was administered on Day 1. Visit 3, follow-up, occurred 7 to 10 days after discharge from the study center (after the Day 6 120 hours postdose assessments were completed).

Target subject population and sample size

Males or females aged 18 years or more with a weight of at least 50 kg and a body mass index (BMI) between 18 and 40 kg/m^2, inclusive. In order to avoid bias due to demographic differences between patients with hepatic impairment and healthy volunteers with normal hepatic function, the healthy volunteers with normal hepatic function were to be matched to the mean demographic characteristics of all the patients with hepatic impairment.

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

All subjects received a single dose of 25 mg NKTR-118 (tablet) on Day 1. Batch number: WK90775.001.

Duration of treatment

Single dose.

Statistical methods

The sample size of 8 subjects per group (minimum of 6 evaluable subjects per group) was based on experience from previous similar Phase I studies.

Tabulations and listings of all safety data were presented by hepatic impairment category. Plasma concentration data at each sampling time point and all PK parameters were summarized using descriptive statistics for each hepatic impairment group. To assess the potential effects of hepatic impairment on NKTR-118 25 mg PK, the primary PK parameters of AUC and C_{max} were analyzed using an analysis of variance (ANOVA) model, with hepatic impairment category as a fixed effect, following a natural logarithmic transformation. The geometric least squares (LS) means, the ratios of geometric LS means corresponding to the mildly impaired group over the healthy volunteer group, and the moderately impaired group over the healthy volunteer group and associated 90% confidence intervals (CIs) were reported. Interpretation of the results was based on the 90% CIs of the ratios of the geometric means of mildly impaired group over the healthy volunteer group and of moderately impaired group over the healthy volunteer group. No effect of hepatic impairment on the PK of NKTR-118 was to be indicated if these 90% CIs were completely contained within the 40% limits (60%, 167%).

As an exploratory analysis, the relationship between Child-Pugh score and AUC and C_{max} was analyzed using a linear regression model with the Child-Pugh score as a dependent variable and the logarithm of AUC (or C_{max}) as the independent variable. The intercept α and the slope β together with CIs (2-sided 95%) was estimated.

Subject population

Subjects with either mild or moderate hepatic impairment or with normal hepatic function were enrolled in the study. All 24 subjects who participated in the study (8 subjects in each group) received the investigational product and completed the study.

The demographic characteristics (age, BMI, and gender distribution) were similar for the 3 groups. Overall, there were 12 males (50.0%) and 12 females (50.0%) in the study with a mean age of 55 years (range from 37 to 63 years) and a mean BMI of 31 kg/m^2 (range from 21 to 38 kg/m^2). Healthy volunteers with normal hepatic function were considered to be healthy and without significant ongoing medical conditions. Patients included the hepatic impairment groups had mild or moderate hepatic impairment, as determined by their Child-Pugh scores.

There were no premature withdrawals and no important protocol deviations were reported during the study. No subjects or data were excluded from the safety or PK analysis sets.

Summary of pharmacokinetic results

Plasma concentration-time profiles amongst all cohorts tended to be bimodal with the 2 peaks separated by a time interval of approximately 1 to 2.5 hours. However, in patients with mild and moderate hepatic impairment the incidence of bimodality was progressively lower with the second, higher, peak disappearing in many patients. Hence, on average, peak concentration of NKTR-118 in plasma occurred earlier in patients with moderate hepatic impairment than in patients with mild hepatic impairment or in healthy volunteers. Table S2 summarizes key NKTR-118 PK parameters for the 3 hepatic function groups.

Table S2 Summary of NKTR-118 pharmacokinetic parameters

Hepatic group		AUC	C_{max}	t_{max}[a]	$t_{1/2}$	CL/F
		(ng*h/mL)	(ng/mL)	(h)	(h)	(L/h)
Mild	Geo mean	337	74.2	2.25	9.64	74.1
(n=8)	(CV%)	(57.0)	(52.1)		(81.3)	(56.8)
	min	127	31.9	0.50	5.20	33.5
	max	747	165	3.00	49.0	196
Moderate	Geo mean	335	78.4	0.55	7.52	74.7
(n=8)	(CV%)	(48.)	(72.4)		(48.9)	(48.0)
	min	230	41.6	0.50	3.97	28.7
	max	872	269	2.50	13.8	109
Normal	Geo mean	407	78.5	2.00	11.3	61.5
(n=8)	(CV%)	(55.3)	(40.4)		(65.6)	(55.3)
	min	191	47.7	0.50	4.48	33.4
	max	749	122	3.00	25.3	131

[a] t_{max} presented as median (range).
CV% geometric coefficient of variation; Geo geometric; Mild mild hepatic impairment – Child-Pugh Category A (Score 5-6); Moderate moderate hepatic impairment – Child-Pugh Category B (Score 7-9); Normal healthy volunteers with normal hepatic function.

In patients with mild hepatic impairment the geometric LS mean NKTR-118 AUC was modestly (17%) lower (ratio%: 82.87% and 90% CI: 53.82-127.60%) and C_{max} was similar (ratio%: 94.55 and 90% CI: 60.41-147.98) compared to healthy volunteers. In patients with moderate hepatic impairment the geometric LS mean NKTR-118 AUC was modestly (16%) lower (ratio%: 82.27% and 90% CI: 53.43-126.68%) and C_{max} was similar (ratio%: 99.90% and 90% CI: 63.83-156.36%) compared to healthy volunteers. The lower limit of the 90% CI for the geometric LS mean NKTR-118 ratios fell slightly outside the predefined no-effect range of 60% to 167% in both the mild and moderate hepatic impairment groups for AUC but not for C_{max}.

Geometric mean $t_{1/2}$ for mild and moderate hepatic impairment was shorter (9.64 and 7.54 hours, respectively) than in healthy volunteers (11.3 hours). Reduced enterohepatic recycling is a potential explanation for the decrease in AUC and $t_{1/2}$ in hepatic impairment groups. The median t_{max} was shorter 0.55 hour in patients with moderate hepatic impairment compared to 2.25 hours and 2.00 hours, respectively, in patients with mild hepatic impairment and healthy volunteers.

A relationship between NKTR-118 exposure (AUC or C_{max}) and increasing Child-Pugh score (ie, increasing hepatic impairment) could not be established based on the fit of a linear regression model.

Summary of safety results

No adverse events (AEs) leading to discontinuation of the investigational product were reported. Four healthy volunteers (50%) in the normal hepatic function group reported 4 AEs.

Three patients (37.5%) in the mild hepatic impairment group reported 4 AEs and 3 patients (37.5%) in the moderate hepatic impairment group reported 3 AEs.

One AE of mild hypotension, which occurred approximately 1 hour after the investigational product administration, was considered to be related to the investigational product by the investigator. This AE was asymptomatic throughout and resolved on the same day.

One patient in the moderate hepatic impairment group reported a serious AE (SAE) of severe rectal hemorrhage (8 days and 16 hours after the investigational product administration). The SAE was not considered to be related to the investigational product by the investigator and resolved by the time of database lock. Hospital records showed that the patient had a previous history of rectal bleeding.

All AEs were reported by 1 subject each, except for vessel puncture site hematoma which was reported by 2 healthy volunteers in the normal hepatic function group.

Based on the reported AEs, laboratory evaluations, vital signs, ECG evaluations, physical examination findings, and Columbia-Suicide Severity Rating Scale (C-SSRS) results, NKTR-118 was well tolerated in patients with hepatic impairment and healthy volunteers with normal hepatic function.