AstraZeneca

Clinical Study Report Synopsis

Drug Substance NKTR-118

Study Code D3820C00009

An Open-Label, Parallel-Group, Phase I Study to Compare the Pharmacokinetics of NKTR-118 Following a Single Oral Dose in Subjects with Renal Impairment and Subjects with Normal Renal Function

Study dates: First subject enrolled: 30 June 2011
Last subject last visit: 30 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 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the pharmacokinetics of a single oral dose 25-mg NKTR-118 in subjects with renal impairment compared to that in subjects with normal renal function	The primary variables were NKTR-118 AUC and C_{max} Secondary variables were NKTR-118 $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, V_z/F, t_{max}, and $t_{1/2}$; urine NKTR-118 A_e, f_e, and CL_R; and dialysate f_D and CL_D	Pharmacokinetic
Secondary	**Secondary**	**Safety**
To assess the safety and tolerability of NKTR-118 in subjects with renal impairment and normal renal function	Adverse events, vital signs, clinical laboratory measures, physical examination, Columbia-Suicide Severity Rating Scale, and electrocardiogram	
Exploratory	**Exploratory**	
To collect blood samples for potential pharmacogenetic testing that will allow future investigation of the influence of genotype on drug disposition and safety	These data do not form part of the main report for this study.	Pharmacogenetic
To reserve collected plasma, urine, and dialysate samples for potential metabolite analysis	These data do not form part of the main report for this study.	Pharmacokinetic

A_e cumulative amount of unchanged drug excreted into urine from time 0 to 72 h; 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 h; CL_D hemodialysis clearance; CL/F apparent systemic plasma clearance; CL_R renal clearance; C_{max} maximum plasma concentration; f_D fraction of dose extracted unchanged into the dialysate over the hemodialysis period; f_e fraction of drug excreted in urine; $t_{½}$ 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, single-dose, parallel-group study to investigate the pharmacokinetics, safety, and tolerability of NKTR-118 in subjects with renal impairment and subjects with normal renal function. The study was performed in subjects with either moderate or severe renal impairment, or end-stage renal disease (requiring hemodialysis), and

a group of subjects with normal renal function matched in demographic baseline characteristics to all 3 groups with renal impairment.

Grouping of subjects into renal function groups was based on estimated glomerular filtration rate calculated from serum creatinine values using the Modification of Diet in Renal Disease equation (see Table S2).

Table S2 Classification of renal function based on estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation

Group	Description	Estimated glomerular filtration rate (mL/min/1.73m^2)
Group 1	Normal renal function	≥80
Group 2	Moderate renal impairment	30 to 59 (inclusive)
Group 3	Severe renal impairment	less than 30
Group 4	End-stage renal disease	requiring hemodialysis

Each subject in Groups 1 to 3 participated in 1 treatment period during which they received a single oral dose of 25-mg NKTR-118. Subjects in Group 4 participated in 2 treatment periods and received 2 single doses of 25-mg NKTR-118, ie, 1 in each treatment period, with a washout period of at least 7 days between the doses. The first dose for Group 4 was administered approximately 1 to 2 hours after completion of a hemodialysis session, and the second dose was administered 2 hours before start of hemodialysis. In all groups, pharmacokinetic samples were collected for 72 hours after each dose administration. The subjects were resident at the clinic for at least 48 hours after dosing. After 48 hours, the subjects remained resident at the clinic or visited the clinic as outpatients for each sampling at the discretion of the Investigator. Safety was assessed throughout the study. A follow-up visit was conducted 7 to 10 days after the last pharmacokinetic sampling (Day 4).

Target subject population and sample size

Groups 2, 3, and 4: Male and female subjects with moderate or severe renal impairment, or end-stage renal disease on hemodialysis, aged 18 to 80 years. Recruitment aimed to include at least 2 males and 2 females in each of the renal impairment groups (Groups 2 to 4) and attempted to include 2 subjects with an estimated glomerular filtration rate less than 15 and not on hemodialysis in the severe renal impairment group (Group 3).

Group 1: Male and female subjects with normal renal function aged 18 to 80 years. The demographics of the subjects with normal renal function were matched for age ±10 years, and body mass index ±15%, to the mean age and body mass index of subjects across the 3 renal impairment groups. Sex was matched to achieve similar distribution between male and female subjects.

Two subjects were misclassified into the Normal renal function group (ie, estimated glomerular filtration rate of 80 mL/min/1.73m^2 or greater) when one of the clinics used an incorrect calculator versus the agreed upon calculator. The subjects were enrolled as Normal based on estimated glomerular filtration rate values of 84.9 and 85.7 mL/min/1.73m^2 with the clinic's formula, respectively. When the Sponsor-preferred formula was used, estimated glomerular filtration rate was calculated as 74 and 76 mL/min/1.73m^2, respectively. For purposes of analyses, the primary analysis for pharmacokinetic correlation with estimated glomerular filtration rate was presented twice - once excluding the 2 subjects and once including the 2 subjects.

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

NKTR-118, 25 mg, white film-coated tablet (Batch Number 17803.004), administered by oral route after a fasting period of at least 4 hours

Subjects in Groups 1, 2, and 3 received a single oral dose of 25-mg NKTR-118 on Day 1.

Subjects in Group 4 participated in 2 treatment periods and received a single oral dose of 25 mg-NKTR-118 on Day 1 of each treatment period. The single dose in the first treatment period was given after hemodialysis and the single dose in the second treatment period was given before hemodialysis.

There was no comparator.

Duration of treatment

The duration of each subject's participation was approximately 6 to 7 weeks, including a screening period of up to 29 days, 1 or 2 treatment periods each consisting of up to 5 days and 4 nights, and a follow-up visit 7 to 10 days after Day 4 of the last treatment period.

Statistical methods

Tabulations and listings of all safety data were presented by renal function group.

In addition to the estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation, creatinine clearance was also calculated by the Cockcroft-Gault equation using serum creatinine for further analysis and report purposes.

Plasma concentration data at each sampling time point and all pharmacokinetic parameters were summarized using descriptive statistics by renal function group. The relationship between renal impairment and the pharmacokinetics of NKTR-118 was assessed statistically based on plasma AUC and C_{max} using appropriate regression models. Each of the groups with renal impairment was compared to the group with normal renal function using an appropriate analysis of variance model on the plasma AUC and C_{max}. While this study was not statistically powered to claim no effect of renal impairment on NKTR-118 exposure, interpretation of the effect of renal impairment was based on point estimates of ratios and associated 90% confidence intervals. Additionally, comparisons of pharmacokinetic

parameters for subjects in Group 4 with end-stage renal disease on a nonhemodialysis day to those on a hemodialysis day were performed using a paired t-test (C_{max} and AUC). Interpretation of results from all analyses above was based on the groups with renal impairment studied and no extrapolation was made for the renal population excluded from the study.

Subject population

There were 32 study participants (8 subjects per renal function group) and all subjects completed the study. Overall, there were 17 men (53.1%) and 15 women (46.9%) enrolled in the study. Twenty subjects were white (62.5%), 10 subjects were black or African American (31.3%), and 2 subjects were Asian (6.3%). The mean age of all study participants was 57 ±11 years (range from 36 to 78 years); mean height was 168 ±12 cm; mean weight was 83.0 ±19.4 kg; and mean BMI was 29 ±4 kg/m^2. Subjects in the normal renal function group were considered healthy and without significant ongoing medical conditions. Subjects in the renal impairment groups demonstrated moderate or severe renal impairment or end-stage renal disease, based on the estimated glomerular filtration rates on Day -1.

Summary of pharmacokinetic results

This study shows that compared to normal controls, geometric mean AUC and C_{max} values were higher in subjects with moderate and severe renal impairment. Overall exposure of NKTR-118 in ESRD subjects appeared to be similar to that for normal renal function while maximum exposure was 29% lower compared to subjects with normal renal function.

Results from a linear regression analysis of exposure (AUC and C_{max}) versus eGFR showed that there was no apparent linear relationship of exposure of NKTR-118 (AUC or C_{max}) with increasing renal impairment. The increased exposure observed in subjects with moderate and severe renal impairment may be due to high exposure from 2 subjects in each group with others (n=6/group) having a similar exposure range as normal controls.

Table S3 Statistical comparison of NKTR-118 exposure parameters between renal groups for per-protocol subjects (per-protocol pharmacokinetic analysis set)

				Comparison to normal renal function group	
Parameter	**Renal Group[a]**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
AUC	Normal	6	281.4		
(ng*h/mL)	Moderate	8	487.1	173.06	(101.20, 295.94)
	Severe	8	611.8	217.39	(127.12, 371.76)
	ESRD	8	270.1	95.98	(56.12, 164.13)
C_{max}	Normal	6	80.54		
(ng/mL)	Moderate	8	89.43	111.04	(71.39, 172.71)
	Severe	8	148.2	184.01	(118.31, 286.20)
	ESRD	8	57.18	70.99	(45.64, 110.41)

CI confidence interval; ESRD end-stage renal disease; LS least squares.
Results based on analysis of variance model with terms for renal impairment group. ESRD, end-stage renal disease, Period 1 data are from ESRD subjects who received a single dose approximately 1 to 2 hours after completion of a hemodialysis session.

[a] Normal renal function: estimated glomerular filtration rate greater than or equal to 80 mL/min/1.73m^2
Moderate renal impairment: estimated glomerular filtration rate 30 to 59 mL/min/1.73m^2 inclusive
Severe renal impairment: estimated glomerular filtration rate less than 30 mL/min/1.73m^2
ESRD: requiring hemodialysis

Table S4 Key NKTR-118 pharmacokinetic parameters by renal group

Parameter		**Normal (n=6)**	**Moderate (n=8)**	**Severe (n=8)**	**ESRD[a] (n=8)**
t_{max}	Median	1.25	2.00	1.50	1.25
(h)	(min,max)	(0.50, 2.50)	(0.50, 3.00)	(0.50, 2.00)	(0.50, 2.50)
$t_{½}$	Geo Mean	8.28	11.1	9.85	9.50
(h)	CV%	46.6	38.9	86.7	72.0
CL/F	Geo Mean	88.8	51.3	40.9	92.5
(L/h)	CV%	43.5	68.5	90.5	41.1
CL_R	Geo Mean	4.74	3.38	1.05	ND
(L/h)	CV%	64.6	33.2	57.8	ND
f_e	Geo Mean	5.22	6.43	2.40	ND
(%)	CV%	66.0	53.6	103.8	ND

[a] Subjects received a single 25-mg NKTR-118 dose 2 hours before start of hemodialysis; CV% geometric coefficient of variation; geomean geometric mean; n number of subjects; ND not determined

Median time of maximum concentration and mean elimination half lives did not appear to be affected by renal impairment and fell within the range reported in previous healthy volunteer studies. Plasma clearance and renal clearance of NKTR-118 decreased in subjects with moderate and severe renal impairment compared to normal controls. Plasma clearance in subjects with ESRD was similar to that of normal controls. Mean percent of NKTR-118 excreted in the urine was lowest in subjects with severe renal impairment.

NKTR-118 C_{max} and AUC values observed when NKTR-118 was administered 2 hours prior to start of a hemodialysis session were similar to those observed when NKTR-118 was administered 1 to 2 hours after completion of a hemodialysis session. During the 4-hour hemodialysis session, negligible amounts of NKTR-118 (1.20%) were recovered in the dialysate.

Summary of safety results

There were no deaths during the study. One subject with severe renal impairment experienced a post-study serious adverse event of myocardial infarction 10 days after follow-up, was hospitalized with multi-vessel coronary artery disease, underwent 5-vessel coronary by-pass surgery, and died suddenly 4 days after release from a 14-day hospital stay. The adverse event was assessed by the Investigator as not related to investigational product. No subjects were withdrawn from the study due to adverse events.

Following the first dose of investigational product, adverse events were reported for 3 subjects each in the moderate renal impairment, end-stage renal disease (dosing after dialysis), and end-stage renal disease (dosing before dialysis) groups. Adverse events were reported for 1 subject each in the normal renal function and severe renal impairment groups. The most frequent adverse events reported overall were headache in 3 subjects, diarrhea in 2 subjects, and flatulence in 2 subjects. Three (9.4%) subjects reported adverse events that were assessed by the Investigator as moderate in intensity. One (1.9%) subject had a post-study serious adverse event of severe intensity (myocardial infarction) that led to death.

NKTR-118 was generally well tolerated in renal impairment patients. Following dosing, there were no clinically relevant changes or trends in mean or median clinical laboratory, vital sign, or electrocardiogram variables measured in subjects exposed to NKTR-118. No suicidal ideation or behavior occurred during the study.

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