AstraZeneca

Clinical Study Report Synopsis

Drug Substance NKTR-118

Study Code D3820C00025

A Phase I, Open-label, Randomized, Balanced, Single-dose, 2-part Study to Assess the Relative Bioavailability of NKTR-118 in 3 Formulations under Fasted (3-Way Cross-over) and Fed (2-Way Cross-over) Conditions in Male and Non-fertile Female Volunteers

Study dates: First subject enrolled: 10 June 2011
Last subject last visit: 5 August 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 assess the relative bioavailability of 2 new NKTR-118 oxalate formulations to the new NKTR-118 Phase III formulation following single oral dose administration in healthy adult volunteers under fasted conditions	C_{max}, AUC, t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F	Pharmacokinetic
Secondary	**Secondary**	
To assess the relative bioavailability of new NKTR-118 oxalate Formulation 1 to Formulation 2 following single oral dose administration in healthy adult volunteers under fasted conditions	C_{max}, AUC, t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F	Pharmacokinetic
To assess the effect of food on the PK of the new NKTR-118 oxalate Formulation 1 and the NKTR-118 Phase III formulation following single oral dose administration in healthy male and non-fertile female volunteers	C_{max}, AUC, t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F	Pharmacokinetic
To investigate the safety and tolerability of NKTR-118 in male and non-fertile female healthy volunteers when given either formulation under either food intake condition	Adverse events, laboratory assessments, vital signs, physical examination, C-SSRS, 12-lead ECG	Safety
Exploratory	**Exploratory**	
To collected blood samples for potential pharmacogenetic testing that will allow future assessment of genotypes and safety biomarkers	Not applicable	Pharmacogenetic
To collect blood samples for safety biomarker testing that will allow future assessment of safety biomarkers	Not applicable	Pharmacogenetic
To reserve blood samples for potential metabolite analysis	Not applicable	Pharmacogenetic

λ_z: terminal elimination rate constant; AUC: area under the plasma concentration-time curve from zero (pre-dose) extrapolated to infinity; $AUC_{(0-24)}$: area under the plasma concentration-time curve from zero to 24 hours; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; C-SSRS: Columbia-Suicide Severity Rating Scale; CL/F: apparent oral clearance; C_{max}: maximum observed plasma concentration; CSP: Clinical Study Protocol; ECG: electrocardiogram; $t_{1/2\lambda z}$: apparent terminal half-life; t_{max}: time of maximum observed plasma concentration; V_z/F: apparent volume of distribution during the terminal phase.

Study design

This was a Phase I, open-label, randomized, balanced, cross-over, single-dose, 2-part study to investigate the relative bioavailability of 2 NKTR-118 oxalate formulations with different release characteristics (fast oxalate Formulation 1 and slow oxalate Formulation 2), compared to the Phase III formulation (white film-coated Formulation 3), and to assess the effect of food on the PK of 1 of the oxalate formulations of NKTR-118 (Formulation 1) and the Phase III formulation (Formulation 3).

Each volunteer was to receive a single oral dose of 25 mg NKTR-118 on Day 1 of each of 5 treatment periods with safety monitoring and serial blood sample collections for PK evaluation throughout the period of admission. Following a screening period of up to 30 days, Part A was conducted by administration of the 3 formulations under fasted conditions with a 3-way cross-over design. Each volunteer received a single oral 25 mg dose of NKTR-118 of each formulation with a wash-out period of at least 7 days between each dose. Part B, the 2-way cross-over design to assess the effect of food on NKTR-118 PK commenced after completion of Part A. Volunteers returned for a follow-up visit, 7 to 10 days after discharge from the study center in Period 5.

Target subject population and sample size

A sufficient number of healthy male and non-fertile female volunteers between the ages of 18 and 55 years old, inclusive volunteers were to be enrolled to allow for a total of 18 evaluable male and non-fertile female healthy volunteers to complete Part A of the study.

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

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
NKTR–118 IR Variant Fast Oxalate (Formulation 1)	Tablet, 25 mg, oral	AstraZeneca	11-000764AZ
NKTR–118 IR Variant Slow Oxalate (Formulation 2)	Tablet, 25 mg, oral	AstraZeneca	11-000441AZ
NKTR–118 (reference, WFC Tablet, F13775, Formulation 3)	Tablet, 25 mg, oral	Pharmaceutical International, Inc	17803.002

Duration of treatment

Part A: 3 single 25 mg doses in each of 3 treatment periods separated by a wash-out period of at least 7 days (calculated from the time of the previous dose to the next dose).

Part B: 2 single 25 mg doses in each of 2 treatment periods separated by a wash-out period of at least 7 days (calculated from the time of the previous dose to the next dose).

Statistical methods

This was an exploratory study and the sample size was not based on statistical power. A sample size of 24 volunteers was chosen for a minimum of 18 volunteers to complete the study and provide a reliable estimate of the ratio of the test Formulations 1 and 2 to the reference Formulation 3 (Phase III tablets).

Study conduct, safety, and PK data were summarized using descriptive statistics, as appropriate. To make an assessment of the primary objective of the study the NKTR-118 immediate release (IR) fast oxalate tablet (Formulation 1) and the slow oxalate tablet (Formulation 2) were compared to the reference white film-coated (WFC) Phase III tablet (Formulation 3) statistically after completion of Part A of the study. Relative bioavailability in the fasted state was estimated using an analysis of variance (ANOVA) model with the logarithm of AUC and C_{max} for NKTR-118 as the response variable, treatment, period, and sequence as fixed effects and volunteer within sequence included as a random effect in the model. A comparison of the 2 test formulations (Formulation 1 versus Formulation 2) when administered under fasted conditions was also made from this model using the same methodology.

To make an assessment of the effect of food on the NKTR-118 Formulations 1 and 3, the pharmacokinetic (PK) parameters (AUC and C_{max}) from fed arm in Part B of the study were compared to that of the fasted arm in Part A. The comparisons (fed Formulation 1 versus fasted Formulation 1; fed Formulation 3 versus fasted Formulation 3) were made using an ANOVA model for each of the formulations with fed or fasted state as a fixed effect and subject as a random effect.

An additional comparison of the exposures of NKTR-118 via Formulations 1 and 3 when administered under fed conditions in Part B was made retrospectively utilizing a similar statistical model as employed in Part A of the study.

Subject population

Planned: 24 volunteers

Enrolled: 24 volunteers

Completed: 21 volunteers

All volunteers were included in the safety and PK analysis data sets. The age of volunteers ranged from 19 to 53 years (mean 31 years and median 27 years) and the body mass index (BMI) ranged from 19.90 to 29.95 kg/m^2 (mean 24.20 kg/m^2 and median 23.61 kg/m^2) in accordance with the inclusion criteria.

Summary of pharmacokinetic results

The mean NKTR-118 plasma concentrations versus time profiles following administration of Formulations 1, 2, and 3 in the fasted state were superimposable. Across all treatments, absorption was rapid with peak concentrations in plasma being achieved within 1.5 to 2 hours postdose (median values). Following C_{max} the decline in NKTR-118 mean plasma concentration was rapid with a terminal elimination phase that had a geometric mean $t_{1/2\lambda z}$ of 8.31, 6.60, and 7.74 hours for Formulations 1, 2, and 3, respectively.

In contrast, exposure to NKTR-118 was higher after food administration for both formulations (Formulations 1 and 3) when compared to their respective fasted reference treatments. Time to maximum concentration was not affected by food administration with peak concentrations in plasma being achieved within 1.74 to 1.99 hours postdose (median values). In the fed state, for Formulations 1 and 3, the geometric mean $t_{1/2\lambda z}$ was increased to 9.09 and 9.83 hours, respectively, which is likely due to the fact that NKTR-118 concentrations remained quantifiable (lower limit of quantification [LLOQ] = 0.1 ng/mL) for a longer sampling period. Since in the fasted and fed states $AUC_{(0-t)}$ accounted for the majority (97% to 99%) of the AUC, the slightly longer $t_{1/2\lambda z}$ estimates were not considered to be of clinical relevance .

The results of the statistical comparisons from Part A of the study are presented in Table S3. Under fasted conditions, the 90% confidence intervals (CIs) of the ratios of least squares (LS) geometric means of the new 25 mg NKTR-118 oxalate tablet formulations (Formulation 1 and 2) to the reference WFC tablet (Formulation 3) and of the new Formulation 1 to Formulation 2 were all contained within the 20% standard bioequivalence range of 80% to 125% for both AUC and C_{max}. These results indicate that the new 25 mg oxalate tablet Formulations 1 and 2 are equally bioavailable, when administered orally under fasted conditions, when compared to the reference WFC tablet and to each other.

Table S3 Statistical comparison of primary PK parameters for Formulations 1, 2, and 3 (fasted state)

						Comparisons		
Param	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC	Form 1	Fasted	22	161.3	(137.3, 189.4)	Form 1/Form 3	106.46	(97.29, 116.50)
(ng·hr/mL)	Form 2	Fasted	24	156.2	(133.3, 183.0)	Form 2/Form 3	103.12	(94.41, 112.64)
	Form 3	Fasted	23	151.5	(129.1, 177.7)	Form 1/Form 2	103.24	(94.36, 112.96)
C_{max}	Form 1	Fasted	22	33.77	(27.62, 41.30)	Form 1/Form 3	99.98	(88.26, 113.25)
(ng/mL)	Form 2	Fasted	24	32.93	(27.03, 40.12)	Form 2/Form 3	97.48	(86.28, 110.14)
	Form 3	Fasted	23	33.78	(27.67, 41.23)	Form 1/Form 2	102.56	(90.56, 116.15)

CI confidence interval; Geo geometric; LS least squares; Param parameters; Tmt treatment

[a] Form 1: 25 mg NKTR-118 IR Variant Fast Oxalate (Formulation 1)
Form 2: 25 mg NKTR-118 IR Variant Slow Oxalate (Formulation 2)
Form 3: 25 mg NKTR-118 (reference, WFC tablet, F13775, Formulation 3)

The results of statistical comparison of primary PK parameters of Formulations 1 and 3 in fed state (Part B) to fasted state (Part A) are shown in Table S4. The 90% CI of the ratios of LS geometric means in fed state to fasted state for Formulations 1 and 3 were contained completely outside of the 20% standard bioequivalence range of 80% to 125% for AUC while the lower limits were slightly lower than 125% for C_{max}. The results indicate that administration with food increased the bioavailability of NKTR-118 from the new fast oxalate tablet (Formulation 1) and the reference WFC tablet (Formulation 3) relative to administration after an overnight fast. For Formulation 1 the AUC and C_{max} increased by approximately 42% and 35%, respectively (as reflected by the point estimates of the geometric LS mean of fed/fasted ratios). Similarly, for Formulation 3 the AUC and C_{max} increased by approximately 56% and 47%, respectively.

Table S4 Statistical comparison of primary PK parameters for Formulations 1 and Formulation 3 (fed versus fasted state)

						Comparisons		
Param	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC	Form 1	Fasted	22	161.0	(138.7, 187.0)			
(ng·hr/mL)		Fed	20	228.1	(195.4, 266.4)	Fed/Fasted	141.69	(129.27, 155.31)
	Form 3	Fasted	23	150.5	(127.6, 177.5)			
		Fed	21	234.0	(197.5, 277.2)	Fed/Fasted	155.47	(137.84, 175.36)
C_{max}	Form 1	Fasted	22	33.26	(28.25, 39.16)			
(ng/mL)		Fed	20	44.79	(37.68, 53.24)	Fed/Fasted	134.65	(113.81, 159.30)
	Form 3	Fasted	23	33.38	(27.16, 41.03)			
		Fed	22	48.96	(39.72, 60.35)	Fed/Fasted	146.66	(124.76, 172.42)

CI confidence interval; Geo geometric; LS least squares; Param parameters

[a] Form 1: 25 mg NKTR-118 IR Variant Fast Oxalate (Formulation 1)
Form 2: 25 mg NKTR-118 IR Variant Slow Oxalate (Formulation 2)
Form 3: 25 mg NKTR-118 (reference, WFC tablet, F13775, Formulation 3)

A comparison to evaluate the relative bioavailability of the new fast oxalate variant of NKTR-118 (Formulation 1) versus the reference WFC tablet (Formulation 3) in the fed state was made retrospectively. The 90% CI for AUC geometric LS mean ratio was entirely contained within the 80% to 125% bounds while the lower limit of the CI for the C_{max} geometric LS mean ratio was slightly lower than 80% (Table S5) indicating that the NKTR-118 fast oxalate tablet formulation and the reference WFC tablet formulation had similar exposures when administered orally under fed conditions..

Table S5 Statistical comparison of primary PK parameters for Formulation 1 versus Formulation 3 (fed state)

						Comparisons		
Param	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC (ng·hr/mL)	Form 1	Fed	20	227.2	(199.5, 258.9)	Form 1 (Fed)/Form 3(Fed)	95.40	(89.97, 101.17)
	Form 3	Fed	21	238.2	(209.4, 271.0)			
C_{max} (ng/mL)	Form 1	Fed	20	44.72	(37.91, 52.74)	Form 1 (Fed)/Form 3(Fed)	90.31	(78.99, 103.24)
	Form 3	Fed	22	49.52	(42.34, 57.90)			

CI confidence interval; LS least squares; Param parameters
[a] Form 1: 25 mg NKTR-118 IR Variant Fast Oxalate (Formulation 1)
Form 2: 25 mg NKTR-118 IR Variant Slow Oxalate (Formulation 2)
Form 3: 25 mg NKTR-118 (reference, WFC tablet, F13775, Formulation 3)

Summary of safety results

No deaths or serious adverse events (SAEs) were reported. One volunteer was prematurely withdrawn from the study due to an adverse event (AE), vessel puncture site pain (considered not related to the investigational product by the Investigator).

The majority of volunteers did not report any AEs. The highest number of volunteers with at least 1 AE was reported after Formulation 1 (fasting): 7 volunteers (31.8%), of which only 1 AE was considered related to the investigational product by the Investigator (flatulence).

Based on the reported AEs, laboratory measurements, vital signs, electrocardiogram (ECG) evaluations, physical examination findings, and Columbia-Suicide Severity Scale (C-SSRS), NKTR-118 was generally well tolerated when administered as 3 different formulations under fasting and fed conditions in healthy volunteers.

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