AstraZeneca

Clinical Study Report Synopsis

Drug Substance	NKTR-118
Study Code	D3820C00011
Edition Number	1
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A Randomized, 2-Part, Crossover, Single Center Study to Evaluate Effect of Quinidine on the Pharmacokinetics of NKTR-118 and the Concomitant Effect of Quinidine and NKTR-118 on Morphine-induced Miosis

Study dates: First subject enrolled: 09 March 2012
Last subject last visit: 10 September 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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To investigate the effect of quinidine on the pharmacokinetics of NKTR-118 in healthy subjects	Part 1 : NKTR-118 C_{max}, t_{max}, $t_{1/2\lambda z}$, λ_z, AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, V_z/F Part 2: NKTR-118, morphine, morphine-3-glucuronide, and morphine-6-glucuronide AUC, $AUC_{(0-24)}$, C_{max}, and t_{max}
Secondary	Pharmacodynamic	To investigate the effect of coadministration of NKTR-118 and quinidine on morphine-induced miosis	Part 2: Change from baseline in pupillary measurements on both eyes at each time point postdose measured in 4 different conditions: dark (after the subject had been dark adapted to the room for 5 minutes), 0.04 lux (scotopic), 0.4 lux (low mesopic), and 4.0 lux (high mesopic)
	Safety	To investigate the safety and tolerability of NKTR-118 when administered alone and in combination with morphine and/or quinidine	Adverse events, vital sign measurements, Columbia-Suicide Severity Rating Scale assessments, physical examinations, clinical laboratory tests (clinical chemistry, hematology, and urinalysis), electrocardiogram recordings, and telemetry
Exploratory	Pharmacogenetic	To collect deoxyribonucleic acid samples for future exploratory research on genetic variations which may influence the clinical data generated from the main study (this was an optional part of the study and was not reported in the Clinical Study Report)	
	Biomarkers	To collect plasma samples for safety biomarker testing that will allow future assessment of safety biomarkers (this was an optional part of the study and was not reported in the Clinical Study Report)	

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Post hoc	Pharmacokinetic	To investigate the effect of morphine on the pharmacokinetics of NKTR-118 in healthy volunteers	AUC, $AUC_{(0-24)}$, and C_{max}

λ_z: terminal 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 time of the last quantifiable concentration; CL/F: apparent oral clearance from plasma; C_{max}: maximum observed plasma concentration; $t_{1/2\ \lambda z}$: 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 study was a double-blind (with regard to quinidine administration), randomized, 2-part, crossover, single-center study to evaluate effect of quinidine on pharmacokinetics of NKTR-118 and the effect of the coadministration of NKTR-118 and quinidine on morphine-induced miosis in healthy volunteers. Part 1 was conducted as a standard 2-period, 2-treatment crossover study. In Part 1, Period 1 on Day 1, volunteers received a single oral dose of NKTR-118 25 mg and quinidine placebo (Treatment A) or NKTR-118 25 mg and quinidine 600 mg (Treatment B). Following a minimum 7-day washout period between dose administration, volunteers received the alternate treatment on Day 1 of Period 2. The treatment sequences for Part 1 were AB or BA.

Following a washout period of at least 7 days, a subset of volunteers (at least 14 volunteers) returned to the clinic for Part 2 unless they met the individual stopping criteria. Part 2 was also conducted as a standard 2-period, 2-treatment crossover study. On Day 1 of Part 2, Period 3, volunteers were randomly assigned to receive either Treatment C (oral administration of NKTR-118 25 mg and quinidine placebo and intravenous administration of 5 mg/70 kg morphine) or Treatment D (oral administration of NKTR-118 25 mg and quinidine 600 mg and intravenous administration of 5 mg/70 kg morphine). Following a minimum 7-day washout period, volunteers received the alternate treatment on Day 1 of Period 4. The treatment sequences for Part 2 were CD or DC.

Target subject population and sample size

Healthy males and nonpregnant, nonlactating females 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.

From Part 1, at least 14 volunteers were to continueto participate in Part 2 such that there were at least 12 evaluable volunteers from Part 2. All pharmacodynamic analyses conducted in Part 2 of the study were exploratory in nature. The sample size for Part 2 was not powered to

detect a potential effect by quinidine on NKTR-118 with respect to pharmacokinetic or morphine-induced miosis.

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

Part 1: Treatment A consisted of a single oral dose of NKTR-118 25 mg and quinidine placebo. Treatment B consisted of a single oral dose of NKTR-118 25 mg and quinidine 600 mg.

Part 2: Treatment C consisted of a single, oral dose of NKTR-118 25 mg and quinidine placebo and an intravenous infusion of 5 mg/70 kg morphine. Treatment D consisted of a single, oral dose of NKTR-118 25 mg and quinidine 600 mg and an intravenous infusion of 5 mg/70 kg morphine.

Batch numbers:

- Morphine Sulfate 10mg/mL Lot: 05585LL
- Quinidine Sulfate 200 mg Lot: 450278M
- Placebo to match Quinidine Sulfate Lot: WK90863.003/Batch: 09-008132AZ
- NKTR-118 25mg Lot: WK90863.002/Batch: 17803.004
- Comparator: Not applicable.

Duration of treatment

The duration of the study for volunteers who only participated in Part 1 was approximately 49 days, including a screening period (Visit 1) of 28 days or less, 2 residential treatment periods (Visit 2 and 3) of 5 days (from check-in on Day -1 until discharge on Day 4), a washout period between residential periods of at least 7 days between doses, and a follow-up visit (Visit 4) 7 to 10 days after discharge.

Volunteers who continued on to Part 2 of the study did not perform the follow-up visit for Part 1. Part 2 added approximately 14 days to the study duration (total 63 days), which included 2 additional residential treatment periods (Visit 4 and 5) of 5 days (from check-in on Day -1 until discharge on Day 4), washout period between Part 1 and Part 2 and between each treatment period of at least 7 days between doses, and a follow-up visit 7 to 10 days after discharge (Visit 6). If new volunteers needed to be enrolled for Part 2, the length of study duration and visits was the same as for volunteers only participating in Part 1 of the study.

Statistical methods

The analyses of safety, tolerability, pharmacokinetic, and pharmacodynamic data were summarized descriptively by treatment including tables, listings, and graphs, as appropriate.

The effect of quinidine 600 mg on NKTR-118 25 mg was assessed by comparing the pharmacokinetic parameters [AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, and C_{max}] of NKTR-118 from the treatment of NKTR-118 25 mg administered with quinidine 600 mg (test, Treatment B) to that of NKTR-118 25 mg plus quinidine placebo (reference, Treatment A) in Part 1 of the study using a linear mixed-effects model. The effect of quinidine on NKTR-118 was assessed in the presence of morphine in Part 2 of the study using the same methodology and C_{max} as the primary pharmacokinetic parameter. In addition, the effect of morphine 5 mg/70 kg on NKTR-118 25 mg was assessed in the presence of morphine by comparing Treatment C to Treatment A using the same methodology and AUC, $AUC_{(0-24)}$, and C_{max} as the pharmacokinetic parameters.

The pupillometry measurements and change-from-baseline results from Part 2 of the study were listed and summarized descriptively by treatment for each eye, light condition, and all assessed time points. An exploratory comparison of the effect of quinidine on NKTR-118 in the presence of morphine on the pupillometry results was conducted by analyzing the change from baseline in a mixed-effects repeated-measures model. For individual and overall time points, results were based on change from baseline pupillometry measurements.

Subject population

Part 1: The 38 volunteers had a mean age of 30 years (range 18 to 55 years), a mean height of 174.4 cm (range 160.1 to 188.1 cm), a mean weight of 73.6 kg (range 50.5 to 96.2 kg), and a mean body mass index of 24.11 kg/m^2 (range 18.28 to 29.65 kg/m^2). There were 29 (76.3%) males and 9 (23.7%) females. Twenty-four (63.2%) volunteers were white; 12 (31.6%) volunteers were black; 1 (2.6%) volunteer was American Indian or Alaska native; and 1 (2.6%) volunteers was Asian. Two (5.3%) volunteers reported their ethnicity as Hispanic or Latino. All volunteers were considered healthy and no concomitant medications were reported for ongoing medical conditions.

Thirty-six (94.7%) of the 38 volunteers received all planned doses of IP. Two volunteers were discontinued from IP after receiving Treatment B in Period 1; 1 volunteer was withdrawn for a positive urine drug screen and 1 volunteer was lost-to-follow-up. All 38 (100%) volunteers were included in the safety analysis set.

Part 2: The 19 volunteers had a mean age of 31 years (range 18 to 55 years), a mean height of 174.6 cm (range 160.1 to 188.1 cm), a mean weight of 74.2 kg (range 53.1 to 96.2 kg), and a mean body mass index of 24.24 kg/m^2 (range 19.96 to 29.17 kg/m^2). There were 15 (78.9%) males and 4 (21.1%) females. Fifteen (78.9%) volunteers were white; 4 (21.1%) volunteers were black; and 1 (5.3%) volunteer reported their ethnicity as Hispanic or Latino. All volunteers in Part 2 were considered healthy and no concomitant medications were reported for ongoing medical conditions.

Fifteen (78.9%) of the 19 volunteers received all planned doses of IP. One volunteer discontinued investigational product due to an adverse event and 2 (10.5%) volunteers discontinued investigational product due to sponsor decision. One volunteer did not complete Period 4 in Part 2 but completed end-of-study procedures for participation in Part 1.

In Part 1, plasma concentration-time data were available for 36 volunteers in Treatment A and 38 volunteers in Treatment B. The data for 2 volunteers receiving Treatment A were excluded from the calculation of pharmacokinetic and pharmacodynamic parameters because of vomiting postdose close to NKTR-118 t_{max}. In Part 2, plasma concentration-time data were available for 17 volunteers in Treatment C and 17 volunteers in Treatment D. The data for 2 volunteers receiving Treatment D were excluded from the calculation of pharmacokinetic parameters because of vomiting postdose close to NKTR-118 t_{max}. Plasma pharmacokinetic concentrations and pharmacokinetic parameters were listed but not summarized.

Summary of pharmacokinetic results.

Coadministration with quinidine resulted in higher mean NKTR-118 plasma concentrations from 30 minutes up to 4 hours postdose. After the 4-hour time point, a steeper decline in mean NKTR-118 concentrations during Treatment B could be seen. When coadministered with morphine, NKTR-118 plasma concentrations were similar to when NKTR-118 was administered alone. Following intravenous administration, exposure of morphine and its metabolites (morphine-3-glucoronide and morphine-6-glucoronide) was observed in plasma.

Quinidine did not appear to have a consistent effect on NKTR-118 t_{max}; median t_{max} was 1.02 hours in the presence of quinidine (range: 0.48 to 3.02 hours) compared to 1.50 hours with NKTR-118 alone. Geometric mean NKTR-118 half-life decreased from 6.14 hours (NKTR-118 alone) to 2.42 hours upon quinidine coadministration.

The geometric least-squares means of primary pharmacokinetic parameters of NKTR-118 as well as the ratio of the treatment geometric least-squares means and their confidence intervals are shown in Table S2. In Part 1, in the presence of quinidine, NKTR-118 AUC was 1.39-fold as that of NKTR-118 alone and NKTR-118 C_{max} was 2.47-fold as that of NKTR-118 alone. For AUC and C_{max}, the upper and lower bounds of the 90% confidence interval for the ratios of the point estimates of geometric LS means for volunteers receiving Treatment B (NKTR-118 25 mg plus quinidine 600 mg) compared to volunteers receiving Treatment A (NKTR-118 25 mg plus quinidine placebo) were completely outside the prespecified bioequivalence limits of 80.00% to 125.00%. Based on these results, a statistically significant effect of quinidine on the PK of NKTR-118 could be concluded. In study Part 2, C_{max} was 1.70-fold that of NKTR-118 alone. The upper and lower bounds of the 90% confidence interval for the ratios of the point estimates of geometric LS means for volunteers receiving Treatment D (NKTR-118 25 mg plus morphine 5 mg/70 kg intravenous plus quinidine 600 mg) compared to volunteers receiving Treatment C (NKTR-118 25 mg plus morphine 5 mg/70 kg intravenous plus quinidine placebo) were completely outside the prespecified bioequivalence limits of 80.00% to 125.00%. A similar comparison between Treatment C and Treatment A to assess the effect of morphine on NKTR-118 PK showed that administration of intravenous morphine within 15 minutes of an oral dose of NKTR-118 did not have a clinically relevant effect on NKTR-118 PK although the confidence interval of the geometric least squares mean ratios were not entirely contained within the bioequivalence limits.

Table S2 Statistical comparison of NKTR-118 plasma pharmacokinetic parameters

					Comparisons		
Parameter	Trt [a]	n	Geometric LS mean	95% CI	Pair	Ratio (%)	90% CI
AUC	A	36	185.9	(168.2, 205.5)	B/A	138.72	(131.37, 146.48)
(ng·h/mL)	B	34	257.9	(233.1, 285.3)			
C_{max}	A	36	43.45	(38.26, 49.36	B/A	246.61	(219.10, 277.57)
(ng/mL)	B	36	107.2	(94.36, 121.7)			
C_{max}	C	17	37.75	(31.00, 45.98)	D/C	170.46	(146.39, 198.49)
(ng/mL)	D	15	64.35	(52.54, 78.83)			
$AUC_{(0-24)}$	A	15	193.2	(156.4, 238.6)	C/A	96.03	(83.29, 108.14)
(ng·h/mL)	C	15	185.5	(150.2, 229.2)			
C_{max}	A	15	40.05	(32.94, 48.71)	C/A	96.42	(78.15, 118.97)
(ng/mL)	C	15	38.62	(31.76, 46.97)			

[a] Treatment A: NKTR-118 25 mg plus quinidine placebo.
Treatment B: NKTR-118 25 mg plus quinidine 600 mg.
Treatment C: NKTR-118 25 mg plus morphine 5 mg/70 kg iv plus quinidine placebo.
Treatment D: NKTR-118 25 mg plus morphine 5 mg/70 kg iv plus quinidine 600 mg.

CI confidence interval; iv intravenous; LS least-squares; Trt treatment

Summary of pharmacodynamic results

Change-from-baseline pupil diameter data showed that there was a decrease in mean pupil diameter upon morphine administration during both treatments, NKTR-118 plus morphine plus quinidine placebo (Treatment C) and NKTR-118 plus morphine plus quinidine (Treatment D). The peak miotic effect was similar during both treatments with peak decrease in pupil diameter of 1.09 mm during Treatment C (overall dark eye exam range 0.460 to 2.38 mm) and 1.16 mm during Treatment D (overall dark eye exam range 0.0500 to 4.10 mm). While a statistically significantly greater miotic response during quinidine coadministration was observed at 0.5 and 1 hour, the finding was not adjusted for multiplicity. The changes in pupil diameter at 0.5 and 1 hour were in opposite direction to that expected from an antagonism of the miosis effect and were considered not clinically relevant. In addition, there is no statistically significant overall treatment effect (D vs C) when evaluated across all time points.

Summary of safety results

Part 1: there were no deaths or other significant adverse events reported. One volunteer (Treatment B) experienced a serious adverse event of tendon rupture/laceration 3 days after receiving NKTR-118 25 mg and quinidine 600 mg on Day 15; this event was considered by the Investigator to be not causally related to investigational product. One volunteer

(Treatment A) had an adverse event of blood creatine phosphokinase increased that was severe in intensity and considered by the Investigator to be not causally related to investigational product.

Overall, 32 (84.2%) volunteers experienced at least 1 adverse event during Part 1; 15 (41.7%) had adverse events during NKTR-118 25 mg plus quinidine placebo (Treatment A treatment); and 29 (76.3%) volunteers had adverse events during NKTR-118 25 mg plus quinidine 600 mg (Treatment B) treatment.

Part 2: there were no deaths, serious adverse events, other significant adverse events, or adverse events of severe intensity reported. One volunteer (Treatment C) was discontinued from investigational product due to an adverse event of urinary tract infection; this event was considered mild in intensity and not causally related to investigational product.

Overall, 19 (100%) volunteers experienced at least 1 adverse event during Part 2; 16 (94.1%) had adverse events during the NKTR-118 25 mg plus morphine 5 mg/70 kg intravenous plus quinidine placebo (Treatment C) treatment; and 17 (100%) had adverse events during the NKTR-118 25 mg plus morphine 5 mg/70 kg intravenous plus quinidine 600 mg (Treatment D) treatment.

Part 1 and Part 2: There were no clinically relevant changes or trends noted in mean or median laboratory variables. Adverse events were reported for 3 volunteers for abnormal laboratory values. (1 volunteer for blood creatine phosphokinase increased; 1 volunteer for anemia; and 1 volunteer for serum creatinine increased). The blood creatine phosphokinase increased was assessed by the Investigator as severe in intensity and not related to investigational product. The anemia and serum creatinine increased were assessed by the Investigator as mild in intensity and not related to investigational product.

Part 1 and Part 2: There were no trends or clinically relevant changes noted in mean or median vital sign values. Adverse events were reported for 4 volunteers for vital sign findings (2 volunteers for hypotension and 2 volunteers for orthostatic hypotension, all assessed as related to quinidine).

There was an increase in mean QTcF values for the NKTR-118 plus quinidine treatment (Treatment B) and the NKTR-118 plus quinidine and morphine treatment (Treatment D). This increase was not observed in the NKTR-118 alone (Treatment A) and NKTR-118 plus morphine (Treatment C) treatments.

Thirty-eight (100%) volunteers during the NKTR-118 plus quinidine treatment and 17 (100%) volunteers during the NKTR-118 plus quinidine and morphine treatment had QTcF outlier values compared to no volunteers during the NKTR-118 alone and NKTR-118 plus morphine treatments.