**Clinical Study Report Synopsis**

Drug Substance NKTR-118

Study Code D3820C00014

# A Single Center, Randomized, Double-blinded, Placebo-controlled, Open-label, Positive-controlled, 4-way Cross-over Study to Assess the Effect of a Single Oral Dose NKTR-118 Administration on QTc Interval Compared to Placebo, Using AVELOX™ (moxifloxacin) as a Positive Control, in Healthy Male Volunteers

**Study Dates:** First subject enrolled: 5 April 2011
Last subject last visit: 28 July 2011

**Phase of Development:** Clinical Pharmacology (1)

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 evaluate the effect of a single dose of NKTR-118 25 mg (therapeutic dose) and 150 mg (supratherapeutic dose) on the change in time-matched QTcF intervals compared with placebo | QTcF | Pharmacodynamic |
| **Secondary** | **Secondary** | |
| To evaluate the effect of a single oral dose of moxifloxacin 400 mg on the changes in time-matched QTcF intervals compared with placebo, which will be used as supporting data | QTcF | Pharmacodynamic |
| To investigate the effect of NKTR-118 on additional ECG variables (RR, PR, QRS, QT, and QTcB) | HR, RR, PR, QRS, QT, and QTcB | Pharmacodynamic |
| To assess the safety of NKTR-118 25 mg and 150 mg in healthy male volunteers | Adverse events, safety laboratory assessments (clinical chemistry, hematology, and urinalysis), vital signs (blood pressure and pulse rate), safety ECGs, physical examinations, telemetry, and Columbia-Suicide Severity Rating Scale | Safety |
| To describe the PK of single dose NKTR-118 25 mg and 150 mg and moxifloxacin 400 mg in healthy volunteers | $AUC_{(0-t)}$, $C_{max}$, and $t_{max}$ | Pharmacokinetic |
| **Exploratory**[a] | **Exploratory** | |
| To explore the relationship between plasma concentrations and changes in QTcF parameters if clinically meaningful changes in QTcF are observed | To be performed if the results of QTc prolongation analysis is positive | NA |

**Table S1 Primary and secondary objectives and outcome variables**

| Objectives | Outcome variables | Type |
|---|---|---|
| To collect and store deoxyribonucleic acid (DNA) samples for future exploratory research into genes/genetic variation that may influence response, that is, PK, tolerability, and safety of NKTR-118 and that may explain some of the variability observed in the QTcF interval of NKTR-118 and moxifloxacin | NA | NA |
| To reserve PK samples for further exploratory research per AstraZeneca's further decision based on the human absorption, distribution, metabolism, and excretion (ADME) study | NA | NA |
| To analyze biological samples (that is, human plasma) for circulating biomarkers from consenting volunteers prior to administration of the investigational product | NA | NA |

a To be reported separately from the Clinical Study Report, if performed.

$AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; $C_{max}$: maximum observed plasma concentration; ECG: electrocardiogram; HR: heart rate; NA: not applicable; PD: pharmacodynamic; PK: pharmacokinetic; PR: ECG interval measured from the onset of the P wave to the onset of the QRS complex; QRS: ECG interval measured from the onset of the QRS complex to the J point; QT: ECG interval measured from the onset of the QRS complex to the end of the T wave; QTcB: QT interval corrected for heart rate using Bazett's formula; QTcF: QT interval corrected for heart rate using Fridericia's formula; RR: time between corresponding points on 2 consecutive R waves on ECG; $t_{max}$: time of maximum plasma concentration.

## Study design

This study was a randomized, 4-period, 4-treatment single dose cross-over study. The study consisted of 6 visits. During each 2-day treatment period, each volunteer received 1 of the 4 treatments in 1 of 4 treatment sequences in a double-blind fashion determined by a randomization schedule. The wash-out time between the treatment periods was at least 5 days.

The following treatments were administered in this study:

- Treatment A: NKTR-118 25 mg (1 x 25 mg tablet + 5 x placebo tablets)
- Treatment B: NKTR-118 150 mg (6 x 25 mg tablets)
- Treatment C: NKTR-118 placebo (6 x placebo tablets)

- Treatment D: moxifloxacin 400 mg (1 x 400 mg tablet)

**Target subject population and sample size**

Approximately 52 healthy male volunteers, aged 18 to 50 years (inclusive) were to be randomized to ensure 44 evaluable volunteers.

**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 | Tablet, 25 mg, oral | AstraZeneca Pharmaceuticals International, Inc | WK90644.001 |
| Avelox® (moxifloxacin) | Tablet, 400 mg, oral | Bayer AG | 540215X |
| Placebo matched to NKTR-118 | Tablet, 0 mg, oral | AstraZeneca Pharmaceuticals International, Inc | WK90644.002 |

**Duration of treatment**

Four single doses in four 2-day treatment periods, separated by a wash-out period of at least 5 days between visits.

**Statistical methods**

Digital electrocardiogram variables (heart rate, RR, PR, QRS, QT, QTcF, and QTcB) and their corresponding change-from-baseline values were listed and summarized by treatment group using appropriate descriptive statistics. The baseline value was defined as the predose value on Day 1 of each treatment period.

Analyses of change-from-baseline QTcF and QTcB were carried out using a repeated measures linear mixed model adjusting for volunteer, period, treatment, time, and interaction of treatment by time and including baseline as covariate. At each of the postdose electrocardiogram nominal times, the least-squares means and the 2-sided 90% confidence interval for the treatment compared to placebo for the change in QTcF and QTcB were estimated. To test the treatment effect for each treatment (NKTR-118 25 mg, NKTR-118 150 mg, and moxifloxacin 400 mg), the upper bounds of the 2-sided 90% confidence interval were evaluated against the 10 ms threshold under an inter-section-union test. To conclude that a dose showed no effect on the QTcF interval, all upper confidence bounds needed to be less than 10 ms.

The analysis for assay sensitivity was to compare the moxifloxacin and placebo treatments using the analysis model above considering the mean QTcF at all time points between 1 and 4 hours, inclusive. The lower bound of the 2-sided 90% confidence interval was evaluated against the 5 ms threshold.

Pharmacokinetic variables (NKTR-118 25 mg, NKTR-118 150 mg, and moxifloxacin 400 mg plasma concentrations and pharmacokinetic parameters) were summarized using appropriate descriptive statistics.

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

**Subject population**

Planned: 52 volunteers

Enrolled: 52 volunteers

Completed: 45 volunteers

All 52 volunteers were included in the safety, PK, and PD analysis data sets. The age of volunteers ranged from 18 to 50 years (mean 28 years, median 25 years) and the body mass index (BMI) from 18.63 $kg/m^2$ to 29.93 $kg/m^2$ (mean 24.57 $kg/m^2$, median 24.29 $kg/m^2$).

**Summary of pharmacodynamic results**

QTcF was analyzed as the primary variable in this study. QTcF was adequately corrected for the RR interval. Assay sensitivity was confirmed as the lower limit of the 2-sided 90% confidence interval for the difference of moxifloxacin versus placebo in change from baseline of QTcF over the interval of 1 to 4 hours postdose was greater than 5 ms at 9.3 ms.

In the primary comparisons of QTcF for NKTR-118 25 mg (therapeutic dose) and NKTR-118 150 mg (supratherapeutic dose) versus placebo, the upper bound of the 2-sided 90% confidence interval did not exceed 10 ms at any time point postdose. The largest placebo-corrected mean change-from-baseline in QTcF occurred at 1.5 (for 150 mg NKTR-118) to 2 hours postdose (for 25 mg NKTR-118), where the upper bounds of the 2-sided 90% confidence interval were 4.9 ms and 2.9 ms for NKTR-118 150 mg and NKTR-118 25 mg, respectively.

There were no QTcF intervals greater than 450 ms nor were there any QTcF interval changes from baseline greater than 30 ms after a single oral dose of NKTR-118 150 mg and NKTR-118 25 mg.

Similar to QTcF, the upper bounds of the 2-sided 90% confidence intervals for comparison of change-from-baseline QTcB for NKTR-118 150 mg and NKTR-118 25 mg versus placebo did not exceed 10 ms at any time point postdose.

Changes in RR, PR, and QRS intervals were consistent between placebo and a single oral dose of NKTR-118 150 mg or NKTR-118 25 mg. No clinically important changes in T wave morphology were observed in the study.

**Summary of pharmacokinetic results**

The observed exposures ($C_{max}$ and $AUC_{(0-t)}$) for NKTR-118 25 mg and moxifloxacin were similar to those observed in previous clinical studies. The supratherapeutic dose of NKTR-118 (150 mg) tested in this study resulted in an approximately dose proportional increase in systemic exposure from NKTR-118 25 mg, the anticipated therapeutic dose. Thus, an adequate exposure range to NKTR-118 was included in this study to demonstrate lack of clinically relevant cardiac repolarization changes in healthy volunteers.

**Summary of safety results**

There were no deaths, other serious adverse events (SAEs), or discontinuation due to adverse events (AEs) reported in the study. One AE of interest, feeling of relaxation, was reported after the NKTR-118 150 mg administration in Period 1 for Volunteer E0001058.

The most frequently reported AEs were headache and excoriation. Headache was reported after administration of all 4 treatments and mostly on the same day as the investigational product administration. Most of the AEs were considered to be not related to the investigational product by the Investigator.

No other safety concerns, based on the reported AEs, laboratory measurements, vital signs, electrocardiogram (ECG) evaluations, physical examination findings, and Columbia-Suicide Severity Rating Scale (C-SSRS), were reported.