AstraZeneca

Clinical Study Report Synopsis

Drug Substance NKTR-118

Study Code D3820C00020

A Phase I, Randomised, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of NKTR-118 following single and multiple ascending oral dose administration in healthy young and elderly Japanese subjects, and An Open, Randomised, Crossover Study to Investigate the Effect of Food on the Pharmacokinetics after single oral doses of NKTR-118 in healthy male young Japanese subjects

Study dates: First subject enrolled: 23 March 2011
Last subject last visit: 23 July 2011

Phase of development: Clinical pharmacology (1)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

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 safety and tolerability of NKTR-118 following single and multiple ascending oral doses of NKTR-118 in healthy young and elderly Japanese subjects under fasting and fed conditions.	Adverse events Laboratory variables Physical examination ECG Vital signs	Safety
Secondary	**Secondary**	
To characterise the pharmacokinetics (PK) of NKTR-118 following single and multiple dosing of NKTR-118 in healthy young and elderly Japanese subjects under fasting conditions.	After single dose: AUC, $AUC_{(0-t)}$, CL/F, C_{max}, t_{max}, $t_{1/2\lambda z}$, V_z/F, CL_R, A_e, f_e% After multiple doses: AUC_{ss}, $AUC_{(0-t),ss}$, $AUC_{\tau,ss}$, $CL/F_{,ss}$, $C_{max,ss}$, C_{trough}, $t_{max,ss}$, $t_{1/2\lambda z,ss}$, $V_z/F_{,ss}$, $R_{ac(AUC)}$, $R_{ac(Cmax)}$, time dependency of the pharmacokinetics evaluated by $AUC_{\tau,ss}/AUC$ (single dose), $CL_{R,ss}$, $A_{e,ss}$, $f_{e,\ ss}$%	PK
To evaluate the effects of food, in comparison to fasting condition, on pharmacokinetics of NKTR-118 following single oral administration of NKTR-118 in healthy male Japanese subjects.		PK
Explorative	**Explorative**	
To collect and store DNA for possible future exploratory research into genes/genetic variation that may influence response (ie, PK properties and safety) to NKTR-118 (participation was optional for all subjects and data were not included in this CSR).	Blood samples for optional genetic exploratory research	PGx*

*: No genotyping results are presented in this CSR.

Study design

This study consisted of two study parts, ie, a single and multiple ascending dose part (S+MAD part: Panels 1-5) and cross-over study part to investigate the effect of food (Effect of food part: Panel 6).

S+MAD part:

S+MAD part was a, Randomised, Double-Blind, Placebo-Controlled Study to assess the safety, tolerability and pharmacokinetics of NKTR-118 following single and multiple oral dose administration in healthy young and elderly Japanese subjects.

Four dose levels for young subjects and one dose level for elderly subjects were planned. A total of 40 subjects were randomised in this part. Each panel consisted of 8 healthy Japanese subjects with 6 subjects receiving active drug and 2 receiving placebo.

Effect of food part:

Effect of food part was an Open, Randomised, Two-treatment (dosing condition), 2-period, 2-sequence crossover study with single oral administration to healthy male young Japanese subjects.

A total of 10 subjects were randomised in this part. The subjects received single investigational product (IP) under the two different conditions (fed versus fasting) in a randomised order.

Target subject population and sample size

Healthy male young Japanese subjects aged 20 to 45 years, and elderly male and postmenopausal female Japanese subjects aged 65 to 80 years.

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

NKTR-118 12.5 mg tablet (batch number: 17802.002) or its placebo (batch number: 17805.001) was orally administered.

S+MAD part:

Young subjects received a single dose of 12.5, 25, 50 and 100 mg of NKTR-118/placebo at Day 1, followed by 8-day once daily multiple doses (during Days 3 - 10).

Elderly subjects received a single dose of 25 mg of NKTR-118/placebo at Day 1, followed by 8-day once daily multiple doses (during Days 3 - 10).

Effect of food part:

Young subjects received 25 mg of NKTR-118 as a single dose under the two different conditions (fed versus fasting) in a randomised order. Two single dose administrations (one in each of the two consecutive treatment periods) were separated by a washout period of at least 7 days between the two dosing.

Duration of treatment

S+MAD part:

Residential period: from Day -1 until Day 12, which was 12 nights and 13 days.

Follow-up: between 5 to 9 days after the last dose.

Effect of food part:

Residential period: 2 study session, from Day -1 until Day 3 in each session, there was a washout period of at least 7 days between the two dosing.

Follow-up: between 5 to 9 days after the last dose.

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of safety, tolerability and PK data were summarised descriptively including tables, listings and graphs.

Subject population

A total of 50 Japanese healthy volunteers, consisting of 40 healthy volunteers from the S+MAD part and 10 healthy volunteers from the effect of food part, were randomised to the study at one centre in Japan. All 50 randomised healthy volunteers completed the study. No major protocol deviations were found in this study. None of the healthy volunteers were excluded from the safety or PK analysis sets.

For young male healthy volunteers receiving NKTR-118 in the S+MAD part, overall, mean age was 27.8 years old; mean weight, 60.7 kg; and mean body mass index (BMI), 21.2 kg/m^2. The treatment groups were demographically similar to each other in terms of mean age, weight and BMI.

For elderly healthy volunteers consisting of 3 male and 3 female receiving NKTR-118 in the S+MAD part, overall, mean age was 71.2 years old; mean weight, 52.8 kg; and mean BMI, 21.7 kg/m^2.

For young male healthy volunteers in the effect of food part, mean age was 23.4 and 24.2 years old; mean weight, 67.8 and 70.8 kg; and mean BMI, 22.8 and 23.3 kg/m^2 in Sequence 1 (fed-fasted order) and Sequence 2 (fasted-fed order), respectively.

Summary of pharmacokinetic results

S+MAD part:

Following single dose administration of 12.5 to 100 mg NKTR-118 to young healthy volunteers or 25 mg NKTR-118 to elderly healthy volunteers, the median t_{max} was between 0.50 and 1.50 hours. Large inter-subject variability was seen in the C_{max} and AUC. In young healthy volunteers, the geometric means of AUC and C_{max} increased with ascending dose of

12.5 to 100 mg NKTR-118 with AUC of 81.9 to 731 h·ng/mL and C_{max} of 18.3 to 254 ng/mL, respectively. The AUC and C_{max} increased approximately dose proportionally. Elderly healthy volunteers showed geometric mean value of 174 h·ng/mL for AUC and 48.8 ng/mL for C_{max} after 25 mg NKTR-118, respectively.

The geometric mean apparent terminals half-life ($t_{½\lambda z}$) after single dosing was between 5.75 and 7.24 hours in young healthy volunteers, and was 6.63 hours in elderly healthy volunteers, respectively. The corresponding geometric mean CL/F was between 137 and 163 L/h in young healthy volunteers, and was 144 L/h in elderly healthy volunteers, respectively.

Following once daily administration of NKTR-118 starting on Day 3, steady state was reached within 5 to 6 days (Day 8 or Day 9) at the latest, as supported by NKTR-118 pre-dose plasma concentration values. The geometric means of $AUC_{\tau,ss}$ and $C_{max,ss}$ on Day 10 (the last dosing day) increased with ascending dose of 12.5 to 100 mg NKTR-118 in young healthy volunteers with $AUC_{\tau,ss}$ of 83.0 to 769 h·ng/mL and $C_{max,ss}$ of 18.7 to 416 ng/mL, respectively. The $AUC_{\tau,ss}$ increased dose proportionally, whereas the $C_{max,ss}$ increased slightly more than proportionally to the dose. Elderly healthy volunteers showed geometric mean values of 230 h·ng/mL for $AUC_{\tau,ss}$ and 68.6 ng/mL for $C_{max,ss}$ after 25 mg NKTR-118, respectively. The geometric mean $C_{max,ss}$ and $AUC_{\tau,ss}$ values seen in elderly healthy volunteers were slightly greater than those obtained in young healthy volunteers at the same dose level.

The median $t_{max,ss}$ was between 0.50 and 0.75 hours after multiple dosing. The geometric mean $t_{½\lambda z,ss}$ ranged from 6.69 to 9.83 hours in young healthy volunteers, and was 10.9 hours in elderly healthy volunteers, respectively. The corresponding geometric mean CL/F_{ss} was between 130 and 158 L/h in young healthy volunteers, and was 109 L/h in elderly healthy volunteers, respectively.

The steady state exposure to NKTR-118 on Day 10 was as expected from single-dose data on Day 1 in young healthy volunteers, but slightly higher than expected from single-dose data in elderly healthy volunteers. However, the systemic exposure to NKTR-118 appeared to be time-independent and accumulation was negligible for AUC_{τ} or minimal for C_{max}.

The geometric mean fraction of NKTR-118 excreted unchanged in urine within 48 hours after single and multiple dosing of 25 mg NKTR-118 was approximately 4 to 6%. The majority of the amount of NKTR-118 excreted in urine was collected within 24 hours. The geometric mean renal clearance (CL_R) accounted for approximately 1/20 of total plasma clearance, CL/F.

<u>Effect of food part:</u>

Following single dose administration of 25 mg NKTR-118 in the fasted and fed state, the shape of the plasma concentration-time curves in the effect of food part was generally similar to that in the S+MAD part, although the peak of the mean profile was higher when NKTR-118 was administered in the fed state than that after fasted administration.

The overall exposure to NKTR-118 (AUC) after administration of NKTR-118 in the fed state was approximately 1.5-fold greater compared to that in the fasted state and 90% CIs were not

contained within the standard bioequivalence limits (0.80-1.25). An increase in peak exposure (C_{max}) was seen for fed compared to fasted administration (40% increase in mean ratio; upper limit of 90% CI was above the 0.80 to 1.25 range).

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of IP due to adverse events (DAEs), adverse event caused subject to withdraw from study, or any other significant adverse event (OAEs) in the S+MAD part during the study. A total of 4 healthy volunteers receiving NKTR-118 (1 each in the 25 mg and the 50 mg, 2 in the 100 mg group) experienced at least 1 AE in the S+MAD part during the study. Of them, 1 young healthy volunteer receiving NKTR-118 100 mg had at least 1 causally related AE. A total of 7 AEs (1 each in the 25 mg and the 50 mg, 5 in the 100 mg group) were reported in the S+MAD part during the study. All AEs were of mild intensity. Of them, 3 AEs (2 events of muscular weakness and 1 event of dizziness) were considered related to the IP by the investigators, and were reported in the same healthy volunteer receiving NKTR-118 100 mg. Orthostatic hypotension was reported in 3 healthy volunteers associated with blood pressure (BP) decreased at standing position. All the cases were mild in intensity and were considered not related to the IP by the investigators. No adverse events were reported in the effect of food part during the study.

There were no clinically relevant changes or trends in any laboratory values in both the S+MAD part and the effect of food part during the study. All of laboratory values outside the reference range were considered within range of individual physiological changes and not to be abnormalities by the investigators.

A trend toward lower mean systolic blood pressure (SBP) compared with placebo was observed in the NKTR 118 100 mg dosing group. No clear trends relative to placebo were observed in the other dosing groups.

There were no abnormal findings in ECG evaluation in both the S+MAD part and the effect of food part during the study. There was no evidence for QT prolongation in both the S+MAD part and the effect of food part in this study.

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