Clinical Study Report Synopsis

Drug Substance NKTR-118

Study Code D3820C00001

A Phase I, Open-Label, Single-Centre Study to Assess Absorption, Distribution, Metabolism and Excretion (ADME) after [^{14}C]-labelled Oral Administration of NKTR-118 to Healthy Male Volunteers

Study Dates: First subject enrolled: 21 June 2011
Last subject last visit: 7 September 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 characterise the ADME of a single oral dose of 25 mg [^{14}C]-labelled NKTR-118 in healthy male volunteers	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F for NKTR-118 and [^{14}C] radioactivity in plasma and whole blood; A_e and f_e of [^{14}C] radioactivity in urine and faeces and of NKTR-118 in urine; plasma NKTR-118/plasma [^{14}C] radioactivity ratios and whole blood [^{14}C] radioactivity to plasma [^{14}C] radioactivity ratios; distribution into red blood cells	Pharmacokinetic
Secondary	**Secondary**	
To further describe the safety and tolerability of a single oral dose of 25 mg [^{14}C] NKTR-118 in healthy male volunteers	Adverse events, laboratory assessments, vital signs, physical examination, C-SSRS, 12-lead ECG	Safety
Exploratory	**Exploratory**	
To identify and profile the metabolites in selected samples of urine, faeces, and plasma following a single oral dose of [^{14}C] NKTR-118	NA	Pharmacokinetic[a]
To collect and store DNA for future exploratory research into genes that may influence the PK profile and safety of NKTR-118	NA	Pharmacogenetic[a]

[a] Results from the metabolite and pharmacogenetic analyses, if performed, are not reported in this Clinical Study Report.

ADME: absorption, distribution, metabolism, and excretion; A_e: amount excreted; AUC: area under the plasma concentration-time curve from zero (predose) to infinity; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero (predose) 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; DNA: deoxyribonucleic acid; ECG: electrocardiogram; f_e: fraction (percent) excreted; NA: not applicable; PK: pharmacokinetic(s); $t_{1/2}$: apparent terminal half-life; t_{max}: time of maximum observed plasma concentration; V_z/F: apparent volume of distribution.

Study design

This was a Phase I, open-label, non-comparative, single dose, single centre study. Six healthy male volunteers were studied as a single group. The study consisted of 3 visits: Visit 1 (screening); Visit 2 (Day -1 to Day 11 with optional 5-day extension); and Visit 3 (follow-up).

If significant radioactivity was still being recovered, additional 24 hour collections of urine and/or faeces was to continue on an out-patient basis up to a maximum of an additional 5 days.

Each volunteer received a single oral dose of 27 mg (3.43 MBq ±10%) [^{14}C] NKTR-118 on Day 1.

Target subject population and sample size

Six healthy male volunteers aged 50 to 65 years (inclusive) with a body mass index (BMI) of ≥18.0 and ≤30.0 kg/m^2.

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	Route of administration, dosage form, and strength	Manufacturer	Batch number
[^{14}C] NKTR-118	Oral solution, 27 mg containing 3.43 MBq in 10 mL 0.1 M citrate buffer	AstraZeneca	P8481

Based on the Analytical Summary Document for Drug Product of the [^{14}C] NKTR-118 solution, the nominal total dose was to be 25 mg (3.20 MBq ± 10% [78-95 µCi ± 10%]). The release data however showed 108% of label claim which was within the acceptance criterion. The content was verified by Covance Laboratories to be 27 mg (3.43 MBq) and the 6 volunteers were thus each administered 27 mg of investigational product. Hence in this Clinical Study Report, the actual dose administered is referred to as 27 mg and used for all analyses.

Duration of treatment

Single dose

Statistical methods

Pharmacokinetic (PK) and safety data were summarised using descriptive statistics comprising arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, and/or coefficient of variation as appropriate. NKTR-118 and [^{14}C] radioactivity exposure and recovery were graphically presented.

Subject population

Planned: 6 volunteers

Enrolled: 6 volunteers

Completed: 6 volunteers

The age of volunteers ranged from 50 to 63 years (mean 56 years and median 55 years) and the BMI ranged from 20.6 to 26.7 kg/m^2 (mean 24.6 kg/m^2 and median 26.0 kg/m^2) in

accordance with the inclusion criteria. All volunteers were included in the safety and PK populations.

Summary of pharmacokinetic results

Mean recovery of total radioactivity in urine and faeces combined as percent of dose was 84.2% and ranged from 74.9% to 93.2% of the dose. Approximately 80% of the total dose, on average, was excreted within the first 144 hours. Most of the recovered radioactivity was found in faeces (67.7%) with 16.0% found in urine. The average percentage of NKTR-118 dose recovered in urine was 5.90% indicating that the majority of the radioactivity in urine may be attributed to NKTR-118 metabolites.

Key PK parameters for NKTR-118 in plasma, radioactivity in plasma, and radioactivity in whole blood are summarised in Table S3.

NKTR-118 was absorbed with peak concentrations being achieved at a median time of 1.74 hour for plasma NKTR-118 and 2.23 hour and 2.20 hour for radioactivity in plasma and whole blood, respectively. Mean plasma radioactivity equivalent concentrations were greater than mean NKTR-118 plasma concentrations at all sampling times indicating the presence of metabolic products in the systemic circulation. The ratio of NKTR-118 to plasma radioactivity equivalent concentrations was time dependent and decreased during the time-course from an average of approximately 90% at 0.25 hours, 70% at 0.5 hours to approximately 9 to 22% by 16 hours postdose. The whole blood to plasma radioactivity ratios indicate that ^{14}C radioactivity does not distribute into erythrocytes to any meaningful extent.

Table S3 Summary of key NKTR-118 and plasma and whole blood radioactivity PK parameters

Parameter	n	Statistic	NKTR-118 plasma	Plasma radioactivity	Whole blood radioactivity
AUC [a] (ng*h/mL)	6	Geo. Mean (CV%)	233 (61.9)	710 (49.2)	392 (44.2)
C_{max} [a] (ng/mL)	6	Geo. Mean (CV%)	51.1 (38.3)	84.8 (40.3)	57.5 (40.8)
t_{max} (h)	6	Median (min, max)	1.74 (0.25, 3.02)	2.23 (0.50, 4.02)	2.20 (0.50, 4.02)
$t_{1/2}$ (h)	6	Geo. Mean (CV%)	7.88 (46.4)	7.28 (41.4)	3.66 (27.5)
CL_R (L/h)	6	Geo. Mean (CV%)	6.92 (25.6)	5.83 (29.3)	
C_{max}(PL)/ C_{max}(PR)	6	Geo. Mean (CV%)	0.602 (7.0)	-	-
AUC(PL)/ AUC(PR)	6	Geo. Mean (CV%)	0.327 (30.2)	-	-
C_{max}(WBR)/ C_{max}(PR)	6	Geo. Mean (CV%)	-	-	0.678 (3.9)
AUC(WBR)/ AUC(PR)	6	Geo. Mean (CV%)	-	-	0.551 (11.1)

CV% geometric coefficient of variation in percent; Geo. Mean geometric mean; PL NKTR-118 plasma; PR plasma radioactivity; WBR whole blood radioactivity

[a] For radioactivity AUC units are ngEq·h/mL and C_{max} units are ngEq/mL

Summary of safety results

No deaths, serious adverse events (SAEs), discontinuations due to adverse events (DAEs), or other significant adverse events (OAEs) were reported. At least 1 adverse event (AE) was reported for 2 volunteers (33.3%). Based on the reported AEs, laboratory measurements, vital signs, electrocardiogram (ECG) evaluations, physical examination findings, and Columbia-Suicide Severity Rating Scale (C-SSRS), [^{14}C] NKTR-118 was generally well tolerated in healthy male volunteers.

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