Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130C00054
Date	09 March 2009

A Two-Cohort, Open-Label, Single and Multiple Dose Pharmacokinetic Study of 90-mg and 180-mg Doses of AZD6140 in Healthy Chinese Volunteers Living in China

Study dates:	First healthy volunteer enroled: 02 July 2008 Last healthy volunteer completed: 11 August 2008
Phase of development:	Clinical pharmacology (I)
International Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	

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

Study centre

This was a single-centre study conducted at the Drug Clinical Trial Center, Beijing, China. The first healthy volunteer was enrolled on 02 July 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to characterise the pharmacokinetics (PK) of ticagrelor (formerly known as AZD6140) and its active metabolite AR-C124910XX after single and multiple (twice-daily) doses of ticagrelor 90 mg and 180 mg in healthy Chinese volunteers.

The secondary objective was to determine the safety and tolerability of single and multiple (twice-daily) 90 mg and 180 mg doses of ticagrelor by physical examination, clinical laboratory tests, vital signs, and collection of adverse events (AEs) in healthy Chinese volunteers.

Study design

This was a 2-cohort, open-label, single-centre, single- and multiple-dose PK study in healthy Chinese volunteers with sequential cohorts: a 90-mg cohort (Cohort A) and then a 180-mg cohort (Cohort B). For each cohort, the volunteers received a single dose on Day 1, no study medication on Days 2 and 3, doses twice a day on Days 4 to 9, and on Day 10, a single dose in the morning.

Target healthy volunteer population and sample size

The target population included healthy Chinese volunteers of either sex between 18 and 45 years old and with body mass index between 18 and 25 kg/m^2. Approximately 24 healthy Chinese volunteers were to be recruited to obtain at least 20 evaluable volunteers (10 per cohort).

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

Ticagrelor was provided in 90-mg tablets (Batch 07-011183AZ). No comparator was used. Ticagrelor 90 or 180 mg was taken orally as a single dose on Day 1, as twice-daily doses on Days 4 through 9, and as a single dose on Day 10.

Duration of treatment

The duration of study participation was 14 days confined in the study centre (1 day pre-study, 10 days on study, and 3 days post-treatment), not including the screening period (up to 28 days) and the follow-up period (up to 5 days).

Criteria for evaluation - pharmacokinetics (main variables)

Blood samples were collected to determine plasma concentrations of ticagrelor and its active metabolite, AR-C124910XX. PK parameters that were assessed included the following: maximum plasma drug concentration (C_{max}), time of maximum concentration (t_{max}), mean terminal elimination half life ($t_{1/2}$), area under the plasma concentration-time curve from time zero to selected time points, apparent oral clearance (CL/F), accumulation ratio, and degree of fluctuation (DF). Metabolite/parent ratios were also estimated.

Criteria for evaluation - safety (main variables)

Safety and tolerability were assessed by the nature and incidence of AEs, vital sign assessments, physical examinations, clinical laboratory assessments, and effects on electrocardiography parameters.

Statistical methods

The PK analysis set included all volunteers who received at least 1 dose of study medication, provided sufficient data to estimate the PK parameters, and had no deviations that would have interfered with absorption, distribution, metabolism, or excretion. The safety analysis set included all volunteers who received at least 1 dose of study medication.

PK parameters and plasma concentration data for ticagrelor and for AR-C124910XX were summarised using descriptive statistics. All data were presented by ticagrelor dose. Results from the 90 mg cohort were presented side-by-side with those from the 180 mg cohort, though the 2 cohorts were not compared using hypothesis testing methods.

For safety, AEs were summarised by System Organ Class and Preferred Term and were analysed using frequency distributions by ticagrelor dose. Separate listings of serious adverse events (SAEs), deaths, AEs leading to discontinuation, and other significant adverse events (OAEs) were presented. Clinical labs, vital signs, and electrocardiograms (ECGs) were analysed using descriptive statistics by ticagrelor dose and protocol time point.

Subject population

A total of 26 healthy Chinese volunteers between the ages of 21 and 44 were enrolled in this study: 12 volunteers in the 90 mg cohort and 14 volunteers in the 180 mg cohort. Most volunteers were male (66.7% in the 90 mg cohort and 78.6% in the 180 mg cohort). No differences in demography or baseline characteristics that were deemed clinically important were noted between the cohorts. There were no protocol deviations that would have interfered with absorption, distribution, metabolism, or excretion in this study. All 26 (100%) volunteers that received at least 1 dose of study drug were included in the PK and the safety analysis sets. Twenty four volunteers completed the study (83% of the 90 mg cohort and 100% of the 180 mg cohort). Two (17%) volunteers in the 90 mg cohort discontinued due to abnormal hepatic function and were excluded from the Day 10 analyses.

Summary of pharmacokinetic results

For single and twice-daily doses of ticagrelor 90 mg and 180 mg in healthy Chinese volunteers, the PK of ticagrelor was linear and stationary. By visual inspection, the steady-state concentrations for ticagrelor and AR-C124910XX were apparently achieved by the second day of dosing. Plasma levels were quantifiable at 0.5 to 1 hour post-dose for both ticagrelor and AR-C124910XX. Selected PK parameters are summarized in Table S1 and Table S2. Systemic exposures to ticagrelor and AR-C124910XX were approximately dose-proportional with a ticagrelor dose increase from 90 mg to 180 mg. The mean DF values for both ticagrelor and AR-C124910XX were comparable following multiple doses of ticagrelor 90 mg and 180 mg. Following single and multiple doses of ticagrelor 90 mg or 180 mg, metabolite/parent ratios for both C_{max} and AUC were comparable both for 90-mg and 180-mg doses and for single and multiple dosing. The mean daily accumulation ratios at 90-mg and 180-mg doses of ticagrelor were 1.8 and 2.1, respectively, for ticagrelor and were 1.8 and 2.0, respectively, for AR-C124910XX. Values of $t_{1/2}$, t_{max}, and CL/F for ticagrelor and of $t_{1/2}$ and t_{max} for AR-C124910XX were independent of ticagrelor dose over the course of 1 week of twice-daily dosing.

Table S1 Summary for ticagrelor PK parameters (PK evaluable volunteers)

			Day 1 (single dose)		Day 10 (steady state)	
PK parameter	**Statistic**	**Ticagrelor dose (mg)**	**n**	**Results**	**n**	**Results**
C_{max} (ng/mL)	Geometric mean (CV%)[a]	90	12	602.0 (32.28)	10	915.3 (31.77)
		180	14	1197.8 (29.82)	14	1972.6 (27.39)
C_{av} (ng/mL)	Geometric mean (CV%)[a]	90	0	NC	10	417.158 (28.89)
		180	0	NC	14	978.850 (36.44)
AUC (ng h/mL)	Geometric mean (CV%)[a]	90	12	3855.059 (30.81)	10	7168.381 (35.03)
		180	14	7737.978 (32.58)	14	18034.782 (45.59)
t_{max} (h)	Median (range)	90	12	2.00 (1.00 to 4.00)	10	2.00 (1.00 to 4.00)
		180	14	2.00 (1.00 to 4.00)	14	2.00 (0.83 to 4.00)
$t_{1/2}$ (h)	Geometric mean (CV%)[a]	90	12	10.943 (36.43)	10	13.179 (43.30)
		180	14	11.660 (28.12)	14	14.879 (17.61)
CL/F (L/h)	Geometric mean (CV%)[a]	90	12	23.346 (30.81)	10	17.979 (28.89)
		180	14	23.262 (32.58)	14	15.324 (36.44)

Table S1 Summary for ticagrelor PK parameters (PK evaluable volunteers)

			Day 1 (single dose)		Day 10 (steady state)	
PK parameter	**Statistic**	**Ticagrelor dose (mg)**	**n**	**Results**	**n**	**Results**
DF (%)	Geometric mean (CV%)[a]	90	0	NC	10	175.526 (27.58)
		180	0	NC	14	150.023 (24.47)
AR	Geometric mean (CV%)[a]	90	0	NC	10	1.795 (15.39)
		180	0	NC	14	2.053 (26.46)

[a] CV%=sqrt (exp [SD^2] - 1)*100, where SD denotes standard deviation of the log-transformed data.
Calculation of geometric mean and CV% are based on log transformed data.
Volunteers received a single dose on Day 1; twice-daily doses on Days 4 to 9, and a single dose on Day 10.
AR Accumulation ratio; AUC Area under the curve of plasma concentration against time from zero to infinity; C_{av} Mean plasma concentration during the dosing interval; CL/F Apparent oral clearance; C_{max} Maximum plasma drug concentration; CV% Coefficient of variation expressed as a percentage; DF Degree of fluctuation; n Number of volunteers meeting a criterion; NC Not calculated; PK Pharmacokinetic; SD Standard deviation; $t_{1/2}$ Half-life; t_{max} Time of maximum concentration.

Table S2 Summary for AR-C124910XX PK parameters (PK evaluable volunteers)

			Day 1 (single dose)		Day 10 (steady state)	
PK parameter	**Statistic**	**Ticagrelor dose (mg)**	**n**	**Results**	**n**	**Results**
C_{max} (ng/mL)	Geometric mean (CV%)[a]	90	12	182.6 (24.62)	10	310.6 (25.00)
		180	14	344.7 (24.63)	14	509.0 (19.57)
C_{av} (ng/mL)	Geometric mean (CV%)[a]	90	0	NC	10	174.134 (23.11)
		180	0	NC	14	312.696 (21.09)
AUC (ng h/mL)	Geometric mean (CV%)[a]	90	12	1796.558 (24.83)	10	3510.909 (30.70)
		180	14	2996.811 (24.67)	14	6471.340 (29.07)
t_{max} (h)	Median (range)	90	12	2.500 (1.00 to 4.00)	10	3.000 (1.00 to 4.00)
		180	14	2.000 (2.00 to 4.00)	14	3.000 (1.83 to 4.00)
$t_{1/2}$ (h)	Geometric mean (CV%)[a]	90	12	9.512 (28.58)	10	10.102 (31.64)
		180	14	9.118 (14.55)	14	11.896 (25.33)
DF (%)	Geometric mean (CV%)[a]	90	0	NC	10	120.469 (25.41)
		180	0	NC	14	101.745 (19.45)
AR	Geometric mean (CV%)[a]	90	0	NC	10	1.847 (13.47)
		180	0	NC	14	1.956 (19.38)

Table S2 Summary for AR-C124910XX PK parameters (PK evaluable volunteers)

			Day 1 (single dose)		Day 10 (steady state)	
PK parameter	**Statistic**	**Ticagrelor dose (mg)**	**n**	**Results**	**n**	**Results**
C_{max} ratio[b]	Geometric mean (CV%)[a]	90	12	0.30876 (28.45)	10	0.33930 (35.99)
		180	14	0.28776 (26.56)	14	0.25801 (25.36)
AUC ratio[b]	Geometric mean (CV%)[a]	90	12	0.47411 (30.51)	10	0.48978 (49.33)
		180	14	0.38729 (34.77)	14	0.35883 (35.81)

[a] CV%=sqrt (exp [SD^2] - 1)*100, where SD denotes standard deviation of the log-transformed data.
[b] Ratio calculated as value for metabolite (AR-C124910XX) divided by value for parent (ticagrelor).
Calculation of geometric mean and CV% are based on log transformed data.
Volunteers received a single dose on Day 1; twice-daily doses on Days 4 to 9, and a single dose on Day 10.
AR Accumulation ratio; AUC Area under the curve of plasma concentration against time from zero to infinity; C_{av} Mean plasma concentration during the dosing interval; C_{max} Maximum plasma drug concentration; CV% Coefficient of variation expressed as a percentage; DF Degree of fluctuation; n Number of volunteers meeting a criterion; NC Not calculated; PK Pharmacokinetic; SD Standard deviation; $t_{1/2}$ Half-life; t_{max} Time of maximum concentration.

Summary of safety results

Single and twice daily oral doses of ticagrelor 90 mg and 180 mg were generally well tolerated in healthy Chinese volunteers.

There were no deaths or SAEs during this study. Two volunteers discontinued the study due to abnormal hepatic function. OAEs included dyspnoea (3 volunteers) and bleeding (2 volunteers, epistaxis and gingival bleeding).

In the 90 mg cohort, 3 (25%) of the 12 volunteers experienced an AE; 7 (50%) of the 14 volunteers in the 180-mg cohort experienced an AE. Except for 2 AEs of hepatic function abnormal, all AEs were mild. AEs that occurred in more than a single volunteer were dyspnoea (3 volunteers), abdominal pain (2 volunteers), alanine aminotransferase (ALT) increased (2 volunteers), and hepatic function abnormal (2 volunteers).

No new clinically meaningful safety findings were observed from haematology, clinical chemistry, urinalysis, vital sign, ECG, or physical examination results. Elevated uric acid levels (both mean change versus baseline and 6 volunteers with levels above the upper limit of normal [ULN; maximum level approximately 1.2 times the ULN]) and ALT levels (6 volunteers with levels above the ULN [maximum approximately 3 times the ULN]) were noted in this study. Elevated uric acid levels in volunteers dosed with ticagrelor were expected based on observations in previous studies. For ALT, the observed elevations cannot establish causality, because there is no placebo group for comparison. In addition, other factors affect liver function test results during confinement.