Clinical Study Report Synopsis

Drug Substance   Ticagrelor

Study Code   D5130C00076

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An Open-label, Randomised, 3-Period, 3-Treatment, Crossover, Single-centre, Single-dose, Bioavailability Study with Alternative Methods of Administration of Crushed Ticagrelor Tablets, 90 mg, Compared to Whole Ticagrelor Tablets, 90 mg, in Healthy Volunteers

Study dates: First volunteer enrolled: 1 July 2013

                              Last volunteer last visit: 11 September 2013

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	PK	To evaluate the bioavailability of the crushed ticagrelor tablets when administered orally or dispersed tablets through nasogastric tubes, compared to whole ticagrelor tablets given orally by assessment of the AUC and C_{max} for both ticagrelor and AR-C124910XX, the active metabolite of ticagrelor	The following PK parameters were calculated for ticagrelor and its metabolite AR-C124910XX in plasma: C_{max}, and AUC
Secondary	Safety	To examine the safety and tolerability of ticagrelor when administered as dispersed tablets orally, dispersed tablets via nasogastric tube and as whole tablet orally by assessment of AEs, safety laboratory variables, physical examination, ECG and vital signs	AEs, laboratory variables, vital signs, physical examination, and 12-lead ECG
	PK		The following PK parameters were calculated for ticagrelor and its metabolite AR-C124910XX in plasma: t_{max}, $AUC_{(0-t)}$, $t_{1/2}$ Additionally, metabolite to parent ratios (AR-C124910XX:ticagrelor) was computed for C_{max}, $AUC_{(0-t)}$, and AUC

AE: Adverse event; AUC: Area under plasma concentration-time curve from zero (predose) extrapolated to infinity; $AUC_{(0-t)}$: Area under plasma concentration-time curve from zero (predose) to the last quantifiable concentration; C_{max}: Maximum plasma concentration; ECG: Electrocardiogram; PK: Pharmacokinetic; $t_{1/2}$: Apparent terminal half-life; t_{max}: Time of maximum concentration

Study design

This was a single-centre, open-label, randomised, 3-period, 3-treatment crossover study in which healthy volunteers received single doses of ticagrelor in 3 different ways (Treatment A, B, and C). The 3 treatments were:

- Treatment A: Ticagrelor 90 mg (whole) tablet administered as a single oral dose

- Treatment B: Ticagrelor 90 mg tablet crushed and suspended in water (test product)

- Treatment C: Dispersed ticagrelor 90 mg tablet suspended in water and administered through a nasogastric tube into the stomach (test product)

There were 3 treatment periods of 4 days each, with each period separated by a washout period of at least 7 days between investigational product administrations. For each treatment period, healthy volunteers were admitted to the study centre the evening of Day -1. Investigational product was administered on Day 1 and volunteers were discharged 48 hours after administration of the investigational product on Day 3. The follow-up procedures were performed 5 to 10 days after the last dose in Treatment Period 3.

Target subject population and sample size

Up to 36 healthy male and female volunteers aged 18 to 50 years (inclusive) who had a body mass index between 18 and 30 kg/m^2 (inclusive) and weighed at least 50 kg (110 pounds) and no more than 100 kg (220 lbs).

A total of 36 healthy volunteers were randomised and all 36 received treatment and completed the study.

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

Table S2   Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
Ticagrelor	90 mg tablets	AstraZeneca	13-001169AZ

Duration of treatment

Each healthy volunteer received a single dose of ticagrelor in 3 different ways.

The study consisted of screening 28 days prior to administration of the first dose of the investigational product. There were 3 treatment periods of 4 days each, each period separated by a washout period of at least 7 days between investigational product administrations. The follow-up procedures were performed 5 to 10 days after the last investigational product administration in Treatment Period 3.

Statistical methods

Plasma concentrations and pharmacokinetic parameters for ticagrelor and AR-124910XX were summarised using appropriate descriptive statistics by treatment.

Ticagrelor and AR-C124910XX PK parameters AUC and C_{max} were analysed using a mixed-effects model with fixed effects for sequence, period, and treatment with volunteer nested within sequence as a random effect. AUC and C_{max} was natural log transformed prior to analyses. The results were back transformed and presented as geometric least-squares means (95% CIs) and the ratios of geometric least-squares means (90% CIs). The treatment comparisons were test (Treatments B or C) versus reference (Treatment A). The PK parameters AUC and C_{max} for ticagrelor were the primary PK variables.

Additionally, concentrations at time points 0.5 hours, 1 hour and 2 hours postdose were compared between treatments for both ticagrelor and AR-C124910XX, using the above analysis of variance (ANOVA) model.

Subject population

A total of 36 healthy volunteers were randomised and all of them received the investigational product as per the randomisation scheme. All 36 enrolled healthy volunteers completed the study.

The age of the healthy volunteers ranged from 20 to 49 years (mean 31 years) and the BMI from 19.42 to 29.55 kg/m^2 (mean 24.41 kg/m^2), in accordance with the inclusion criteria. Most of the volunteers were male (77.8%); weight ranged from 55.2 kg to 94.0 kg, in accordance with inclusion criteria.

Summary of pharmacokinetic results

Mean concentrations were higher for Treatments B and C than Treatment A at 0.5 h and 1 h for ticagrelor and 0.5 hour, 1 hour, and 2 hours for AR-C124910XX .

The median t_{max} for ticagrelor was shorter for Treatments B and C in comparison to Treatment A. Exposure [C_{max}, AUC and AUC$_{(0-t)}$] and the calculated $t_{1/2}$ were similar across all the 3 treatments.

The median time to maximum concentration (t_{max}) for AR-C124910XX was similar between the 3 treatments. Similarly, exposure [C_{max}, AUC and AUC$_{(0-t)}$] and calculated $t_{1/2}$ were similar across all the 3 treatments.

The statistical comparison of key pharmacokinetic parameters for ticagrelor and AR-124910XX are presented in Table S3.

Table S3   Statistical comparison of key pharmacokinetic parameters (Pharmacokinetic analysis set)

Analyte	Parameter (unit)	Trt[a]	n	Geometric LS mean	Geometric LS mean 95% CI	Pair-wise comparisons		
						Pair	Ratio (%)	90% CI
Ticagrelor	AUC (ng*h/mL)	A	36	2886	(2491, 3344)			
		B	36	3093	(2670, 3583)	B/A	107.18	(102.53, 112.04)
		C	36	3054	(2637, 3538)	C/A	105.82	(101.23, 110.62)
	C_{max} (ng/mL)	A	36	506.3	(448.0, 572.2)			
		B	36	528.7	(467.9, 597.5)	B/A	104.42	(97.47, 111.87)
		C	36	546.9	(483.9, 618.0)	C/A	108.00	(100.81, 115.71)
AR-C124910XX	AUC (ng*h/mL)	A	36	1385	(1265, 1516)			
		B	36	1431	(1307, 1567)	B/A	103.33	(99.49, 107.31)
		C	36	1457	(1331, 1596)	C/A	105.23	(101.32, 109.29)
	C_{max} (ng/mL)	A	36	164.8	(150.6, 180.3)			
		B	36	166	(151.8, 181.7)	B/A	100.78	(93.89, 108.17)
		C	36	174.5	(159.5, 190.9)	C/A	105.90	(98.66, 113.67)

CI: Confidence intervals; LS: Least-squares; Trt: treatment.
Results based on linear mixed-effects model with sequence, period and treatment as fixed effects and volunteer nested within sequence as a random effect.
a   Treatment A: Ticagrelor 90 mg (whole) tablet administered as a single oral dose (without chewing)
    Treatment B: Ticagrelor 90 mg tablet crushed and suspended in water (test product)
    Treatment C: Dispersed ticagrelor 90 mg tablet suspended in water and administered through a nasogastric tube into the stomach (test product).

Source: Table 11.2.5

For ticagrelor, the 90% confidence intervals of the geometric mean ratios comparing AUC and C_{max} for Treatment B versus Treatment A and for Treatment C versus Treatment A were entirely contained within the interval for bioequivalence (80.00% to 125.00%).

For AR-C124910XX, the 90% confidence intervals of the geometric mean ratios comparing AUC and C_{max} for Treatment B versus Treatment A and for Treatment C versus Treatment A were entirely contained within the interval for bioequivalence (80.00% to 125.00%).

Summary of safety results

- There were no deaths, serious adverse events, or AEs leading to discontinuation of the investigational product reported in this study

- Overall 16 (44.4%) volunteers reported at least 1 AE. The number of volunteers reporting at least 1 AE was higher after Treatment B (11 [30.6%] volunteers) than after Treatment A (3 [8.3%] volunteers) or Treatment C (5 [13.9%] volunteers)

- Two volunteers reported at least 1 AE of oral herpes after receiving Treatment B. Both events were not considered to be related to administration of the investigational product

- Three volunteers reported AEs which were considered to be causally related to the investigational product. Volunteer E0001055 reported an AE of dizziness after Treatment B. After Treatment C, Volunteer E0001062 reported an AE of dry mouth and Volunteer E0001027 reported an AE of menorrhagia. All these AEs were considered to be mild in intensity by the Investigator and resolved

- Most of the AEs reported were considered by the Investigator to be of mild intensity except for an AE of tooth infection reported by Volunteer E0001038, after receiving Treatment B and an AE of migraine reported by Volunteer E0001058, also after receiving Treatment B. Both these AEs were considered to be moderate in intensity by the Investigator and resolved without intervention

- Variations, but no trends, were observed over time and between treatments in mean and median laboratory values. Although a number of abnormal laboratory values were reported, none of the laboratory values were considered to be clinically significant by the Investigator. No changes in laboratory measurements were considered clinically significant by the Investigator or reported as AEs. The mean change from baseline in the clinical laboratory variables was similar after Treatment A, Treatment B and Treatment C. Although abnormal urinalysis results were reported, none of these values were considered to be clinically significant by the Investigator

- Variation, but no relevant trends, over time and between treatments were observed in the vital signs measurements. No clinically important changes in vital signs were recorded

- No abnormal clinically significant ECG measurements were reported

- No abnormal physical examination findings were reported in the study