AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130C00015
Date	6 March 2009

A Single Dose, Non-Randomised, Open-Label, Parallel Group Study Comparing the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of AZD6140 in Patients with Renal Impairment to Volunteers with Normal Renal Function

Study dates: First healthy volunteer enrolled: 28 February 2007
Last healthy volunteer completed: 29 September 2008

Phase of development: Clinical pharmacology (1)

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

Drug substance(s):	Ticagrelor	**SYNOPSIS**	
Study code:	D5130C00015		
Date:	6 March 2009		

A Single Dose, Non-Randomised, Open-Label, Parallel Group Study Comparing the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of AZD6140 in Patients with Renal Impairment to Volunteers with Normal Renal Function

Study centre(s)

This study was conducted at 4 centres in the United States (US):

First healthy volunteer enrolled: 28 February 2007

Last healthy volunteer completed: 29 September 2008

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was:

To compare the pharmacokinetics (PK) of ticagrelor (formerly known as AZD6140) and its active metabolite, AR-C124910XX, in volunteers with severe renal impairment and in healthy volunteers with normal renal function by assessment of maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinity (AUC) of ticagrelor and AR-C124910XX.

The secondary objectives of the study were:

1. To examine the safety and tolerability of ticagrelor in volunteers with severe renal impairment and in healthy volunteers with normal renal function, by assessment of adverse events (AEs), vital signs, and laboratory parameters including clinical chemistry, haematology, and urinalysis.
2. To compare the pharmacodynamics (PD) of ticagrelor and AR-C124910XX in volunteers with severe renal impairment and in healthy volunteers with normal renal function by assessment of inhibition of platelet aggregation (IPA).

Study design

This was a single dose, non-randomised, open-label, parallel group study conducted at multiple centres in the US to examine the PK, PD, safety, and tolerability of ticagrelor and its

active metabolite, AR-C124910XX, in volunteers with severe renal impairment compared with healthy volunteers with normal renal function.

The study was to be conducted in 2 stages. Stage 1 of this study was conducted in volunteers with severe renal impairment (Cockcroft-Gault estimation of creatinine clearance [CrCL] of <30 mL/min) in Group 4 and in healthy volunteers with normal renal function (CrCL of ≥80 mL/min) in Group 1, matched by age (<65 years or ≥65 years), sex, and body weight (<75 kg or ≥75 kg). Stage 2 of this study would have been conducted in volunteers with mild renal impairment (Group 2, CrCL of ≥50 mL/min to <80 mL/min) and moderate renal impairment (Group 3, CrCL >30 mL/min to <50 mL/min). The results from Stage 1 demonstrated that severe renal impairment did not alter PK to an extent warranting dose adjustment; therefore, further dosing in volunteers with mild and moderate renal impairment in Stage 2 as outlined in the clinical study protocol was not pursued.

Target volunteer population and sample size

A total of 20 male and female volunteers greater than 18 years of age were enrolled to ensure the completion of at least 10 evaluable volunteers in each group.

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

Single oral dose of 180 mg ticagrelor (2 × 90 mg tablet [Batch #06-009508AZ; formulation number FDN334])

Duration of treatment

Volunteers were screened within 21 days of treatment and then admitted to the Clinical Pharmacology Unit on Day -2 and remained at the unit until the completion of the Treatment Period assessments on Day 4. The Follow-up Visit was 3 days after completion of the Treatment Period.

Criteria for evaluation - pharmacokinetics (main variables)

The C_{max}, AUC, time to reach maximum plasma concentration (t_{max}), mean terminal half life ($t_{1/2}$), fraction of total drug unbound (Fu), metabolite/parent C_{max} and AUC ratios of ticagrelor and AR-C124910XX, and apparent oral clearance (CL/F) of ticagrelor were estimated.

Criteria for evaluation - pharmacodynamics (main variables)

The degree of IPA (%IPA) was measured by optical aggregometry using 20 μM adenosine diphosphate (ADP) as the agonist. The time to peak inhibition of platelet aggregation ($TIPA_{max}$), peak IPA ($\%IPA_{max}$), and the area-under-the-effect curve (AUEC) were estimated for ADP-induced final extent and maximum extent IPA.

Criteria for evaluation – pharmacokinetics/pharmacodynamics (main variables)

The relationship between plasma concentrations of ticagrelor, AR-C124910XX, and ticagrelor + AR-C124910XX and IPA was assessed using a sigmoid maximum effect (E_{max}) model.

Criteria for evaluation - safety (main variables)

Safety and tolerability were assessed in terms of incidence and severity of AEs, vital signs, and laboratory assessments (clinical chemistry, haematology, and urinalysis).

Statistical methods

Pharmacokinetics

Following log-transformation, C_{max} and AUC data were analysed separately by a mixed-effect model with the stratification variables (gender, weight, and age) as random effects and renal group as a fixed effect. The difference in least square (LS) means (renal impairment-normal function) and 2-sided 90% confidence intervals (CIs) for the difference were estimated from the mixed-effect model for the log-transformed C_{max} and AUC, and exponentiated so that the geometric LS (GLS) mean ratio (renal impairment/normal function) and 2-sided 90% CIs for the ratio could be presented in the original linear scale.

Pharmacodynamics

AUEC from 0 to 24 hours ($AUEC_{0-24}$) and from 0 to 72 hours ($AUEC_{0-72}$) were analysed. The IPA_{max} data were also analysed assuming normality, if found to violate this assumption log transformation was considered. The IPA_{max}, $AUEC_{0-24}$, and $AUEC_{0-72}$ data were analysed separately by the mixed-effect model with the stratification variables (gender, weight, and age) as random effects and renal group as a fixed effect. LSmeans and 2-sided 95% CIs for the differences of interest (renal impairment - normal function) were presented.

Safety

No formal statistical hypothesis testing of the safety data was performed.

Volunteer population

All volunteers fulfilled the inclusion/exclusion criteria, and were enrolled and completed the study. The volunteer population consisted of 10 volunteers with severe renal impairment and 10 healthy volunteers with normal renal function matched by age (<65 years or ≥65 years), sex, and body weight (<75 kg or ≥75 kg). Demographic characteristics of the volunteers were suitable for the purposes of assessing study variables.

Summary of pharmacokinetic results

The mean $t_{1/2}$ and t_{max} values for both ticagrelor and AR-C124910XX were comparable between healthy volunteers and volunteers with severe renal impairment, indicating that impaired renal function has little effect on the absorption of ticagrelor or the elimination of ticagrelor and AR-C124910XX.

The observed AUC and C_{max} of ticagrelor were about 20% lower and AUC of AR-C124910XX was 17% higher for volunteers with severe renal impairment compared to healthy matched volunteers. However, the systemic exposures to ticagrelor and AR-C124910XX were highly variable, especially for AUC in the severe renal group (CV 64-74%). The slightly lower exposure and higher viabilities observed in volunteers with severe renal impairment were partially due to the lower C_{max} and AUC estimates for ticagrelor in the

3 subjects with CrCL < 20 ml/min as compared to the rest of the subjects with CrCL of 20-145 ml/min. The observed differences in exposure to ticagrelor and AR-C124910XX are relatively small compared to the high variability in AUC and C_{max}, which suggests that the overall C_{max} and AUC for both ticagrelor and AR-C124910XX were not much different between the volunteers with severe renal impairment and healthy matched volunteers.

The C_{max} and AUC metabolite/parent ratios were about 30-50% higher in the renal group. However, the apparent differences were confounded by the much higher viabilities in the renal group.

There was no difference in plasma protein binding between the 2 groups; with the mean unbound fractions of 0.16% in healthy volunteers versus 0.21% in volunteers with severe renal impairment for ticagrelor and 0.18% in healthy volunteers versus 0.20% for volunteers with severe renal impairment for AR-C124910XX. The unbound fractions appear to be more variable with decreasing total plasma ticagrelor or AR-C124910XX concentrations. The high variability observed at low ticagrelor and AR-C124910XX concentrations was most likely due to the analytical variability, as the free concentrations in plasma were low and close to the lower limit of quantification (LLOQ) for both ticagrelor and AR-C124910XX.

Statistical analysis of the PK parameters for ticagrelor and AR-C124910XX is summarised in Table S1.

Table S1 Statistical analysis of the PK parameters for ticagrelor and AR-C124910XX (PK evaluable volunteers)

Parameter	Healthy		Severe renal impairment		GLS mean ratio[a]		
	N	GLS Mean	N	GLS Mean	Point estimate	90% CI Lower	90% CI Upper
Ticagrelor							
C_{max} (ng/mL)	10	1341.58	10	1093.87	0.815	0.558	1.191
AUC_{0-t} (ng.h/mL)	10	9380.04	10	7545.52	0.804	0.533	1.214
AUC (ng.h/mL)	10	9584.16	10	7638.63	0.797	0.526	1.207
AR-C124910XX							
C_{max} (ng/mL)	10	349.38	10	363.59	1.041	0.815	1.329
AUC_{0-t} (ng.h/mL)	10	3463.05	10	4073.02	1.176	0.826	1.674
AUC (ng.h/mL)	10	3537.11	10	4141.13	1.171	0.819	1.674

[a] GLS mean ratio is severe renal impairment/healthy volunteer.
AUC Area under the plasma concentration-time curve from zero to infinity; AUC_{0-t} Area under the plasma concentration-time curve from zero until the time of the last concentration above the limit of quantification; C_{max} Maximum drug concentration after single dose administration; CI Confidence interval. GLS Geometric least square; PK Pharmacokinetic.

Summary of pharmacodynamic results

The LSmean differences in final and maximum $\%IPA_{max}$, $AUEC_{0-24}$, and $AUEC_{0-72}$ were not statistically significantly different between the volunteers with severe renal impairment compared with the healthy matched volunteers; however, responses in the volunteers with severe renal impairment displayed much greater variability of response. Overall, the results indicate the PD, as assessed by IPA, of ticagrelor was not different between the 2 groups.

Summary of pharmacokinetic/pharmacodynamic relationships

Overall, evaluation of the PK/PD relationship through E_{max} modelling showed similar concentration-effect profiles and PD model parameter estimates for both volunteers with severe renal impairment and healthy matched volunteers.

Summary of safety results

Ticagrelor was well tolerated in both volunteers with severe renal impairment and in healthy matched volunteers. There were no signals to indicate the safety or tolerability of ticagrelor in volunteers with severe renal impairment differs significantly from healthy volunteers.