AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6140/Ticagrelor
Study Code	D5130C00048
Date	13 July 2009

A Multi-centre Randomised, Double-blind, Double-dummy Parallel Group Study of the Onset and Offset of the Antiplatelet Effects of AZD6140 Compared with Clopidogrel and Placebo With Aspirin as Background Therapy in Patients with Stable Coronary Artery Disease with Additional Detailed Assessment of Cardiopulmonary Function

Study dates: First patient enrolled: 17 October 2007
Last patient completed: 05 March 2009

Phase of development: Therapeutic exploratory (2)

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

Study centre(s)

This study was conducted at 8 centres in the United States (US) and the European Union (EU).

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to determine the onset and offset of antiplatelet effect of ticagrelor (formerly AZD6140) compared with clopidogrel by evaluation of the percent inhibition of platelet aggregation (%IPA) by light transmittance aggregometry (LTA) at 2 hours after first dose of study drug; and the difference in slope of offset of the IPA effect curves for ticagrelor and clopidogrel by LTA after the last dose of study drug.

The secondary objectives of this study were to investigate if ticagrelor had any clinically significant cardiopulmonary effect compared with clopidogrel and placebo by assessment of cardiopulmonary function; assess safety and tolerability of ticagrelor compared with clopidogrel and placebo by evaluation of adverse events (AEs), laboratory testing, ECG, vital signs, and physical examination (PE); to evaluate the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of ticagrelor and its active metabolite AR-C124910XX by assessment of PK and PD parameters; and determine the effect on platelet aggregation of ticagrelor compared with clopidogrel with respect to onset and offset by measuring 5 μM and 20 μM adenosine diphosphate (ADP)-induced platelet aggregation.

Study design

This was a multi-centre, randomised, double-blind, double-dummy, parallel group study of the onset and offset of the antiplatelet effects of ticagrelor compared with clopidogrel and placebo with acetylsalicylic acid (ASA) as background therapy with additional detailed assessment of cardiopulmonary function in patients with stable coronary artery disease (CAD).

Target healthy volunteer population and sample size

Male and female patients, 18 years of age and over with documented stable CAD were eligible for enrolment. For inclusion in the study, patients had to have documented stable CAD fulfilled by any of the following: stable angina pectoris with objective evidence of CAD; previous myocardial infarction (MI) history; or previous revascularization history (ie, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]). Patients were also taking 75 to 100 mg ASA daily treatment:

It was planned that approximately 112 patients were to be randomised. A placebo group including approximately 12 patients was included as a reference group for the purpose of comparing the cardiopulmonary data with the ticagrelor group. With 50 patients per treatment group there was 90% power to detect a difference in median IPA values at onset of at least 15% using the Wilcoxon rank sum test. With 50 patients per treatment group, there was approximately 90% power to show a true difference in slopes of –0.45% per hour. The

calculations assume that the linear relationship in IPA offset will continue from the 4-hour to the72-hour timepoint.

Study drug and comparator(s): dosage, mode of administration, and batch numbers

Ticagrelor 90 mg tablets (batch nos. 06-010163AZ, KA511, KD517) and their matching placebo tablets (batch nos. HE202, IH204) were used in the study together with over-encapsulated clopidogrel 75 mg tablets (batch nos. A06317, A07340, A08025) and their matching placebo capsules (batch nos. A05348, B07165, A08028).

Duration of treatment

The total study duration was expected to be approximately 10 weeks per patient including the screening period; duration of treatment for an individual patient was approximately 6 weeks.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

The primary variable of the study to evaluate onset was IPA (final extent) induced by 20 μM ADP at 2 hours after first dose measured by LTA. The primary variable of the study to evaluate offset was slope of IPA (induced by 20 μM ADP, final extent, by LTA) effect curve from 4 to 72 hours after the last dose of study drug.

Secondary PD variables included %IPA induced by 5 μM ADP, 2 μg/ml collagen, and 2 mM arachidonic acid (AA) by LTA (final and maximum extent); %IPA induced by 20 μM ADP by LTA (maximum extent at all timepoints and final extent at all timepoints except for 2-hours after first dose); maximum inhibition of ADP-induced platelet aggregation (IPA_{max}) (final and maximum extent); time to maximum inhibition of ADP-induced platelet aggregation ($TIPA_{max}$) and $AUEC_{0-8}$ after first dose induced by 20μM ADP (final and maximum extent); platelet aggregation induced by 5 μM and 20 μM ADP by LTA (final and maximum extent); $P2Y_{12}$ reactivity ratio (vasodilator-stimulated phosphoprotein-phosphorylated [VASP-P]), P-selectin expression (CD62P), and activated glycoprotein (GP) IIb/IIIa receptor expression (PAC-1 and CD41a) by flow cytometry; thromboelastography (TEG®); platelet $P2Y_{12}$ receptor blockade measured by VerifyNow™ $P2Y_{12}$ assay.

The following PK parameters were calculated for ticagrelor and its active metabolite, AR-C124910XX: C_{max} (maximum plasma [peak] drug concentration after single dose administration [amount/volume]); t_{max} (time to reach peak or maximum concentration or maximum response following drug administration [time]); AUC_{0-8} (area under the plasma concentration-time curve from 0 to 8 hours); C_{min} (minimum plasma drug concentration over a dosing interval); and $t_{½}$ (half-life).

Criteria for evaluation - safety (main variables)

The secondary variables that addressed the safety objective of the study were: AEs (including bleeding events, vascular events, and dyspnoea); vital signs (blood pressure [BP], pulse, and respiratory rate [RR]); PE; 12-lead ECG; and safety laboratory analysis (clinical chemistry, haematology, and urinalysis). Investigation of cardiopulmonary effects compared with clopidogrel and placebo included measurement of several parameters (FEV_1, FVC, FEV_1/FVC

ratio, RV, V_E, V_T, and RR) at baseline, at the end of the 6-week treatment, and any time patients reported dyspnoea.

Statistical methods

The primary objective of this study, which was to determine the onset and offset of antiplatelet effect of ticagrelor compared with clopidogrel, was supported by the analyses of the onset of IPA at 2 hours after the first dose of ticagrelor compared with clopidogrel and the comparison of the slope of the offset portion of the IPA curves for ticagrelor and clopidogrel from 4 hours post-dose out to 72 hours post-dose. The onset treatment effects were analysed by the Wilcoxon rank sum test. The offset treatment effects were analysed by random coefficients model, which included terms of treatment, time, centre, treatment by time, centre by treatment, and random effects of patient and patient by time interaction. All other PD parameters were analysed using analysis of covariance (ANCOVA) model with fixed-effect of treatment group, centre, centre-by-treatment interaction, and baseline as covariate. For the PD analyses, comparisons were made between the ticagrelor and clopidogrel treatments. Sigmoid E_{max} model was used to analyse PK/PD relationship. Cardiopulmonary function analyses were performed using ANCOVA model for each cardiopulmonary function change from baseline with fixed-effect of treatment group, centre, centre-by-treatment interaction, and baseline value as covariate. Cardiopulmonary function comparisons were ticagrelor versus placebo, and ticagrelor versus clopidogrel treatments.

Patient population

A total of 123 patients were enrolled of which 57 were randomised to ticagrelor, 54 to clopidogrel, and 12 to placebo. Of the123 randomised patients, 114 completed the study and 9 patients discontinued. The rate of discontinuation was similar between groups; the most common reason for discontinuation was due to AEs. Demographic and baseline characteristics were comparable among the treatment groups and were typical for this study population of patients with stable CAD.

Summary of pharmacokinetic results

The AUC_{0-8} (geometric mean [CV%] of 5538.8 ng · h/mL [36.78] for ticagrelor after loading dose, and 1253.7 ng · h/mL [39.33] for AR-C124910XX), C_{max} (1197.2 ng/mL and 243.4 ng/mL for ticagrelor and its metabolite, respectively), t_{max} (median 2 hours), and $t_{1/2}$ (9.8 and 12.4 hours after last dose) values obtained in this study were comparable to those previously reported in healthy subjects.

Summary of pharmacokinetic/pharmacodynamic relationships

E_{max} values were all higher than 90% for final extent %IPA versus ticagrelor and AR-C124910XX plasma concentrations. These high E_{max} values suggest that the ticagrelor or its active metabolite can completely inhibit platelet aggregation with this dosing regimen in this patient population.

Summary of pharmacodynamic results

Table S1 summarizes the final extent %IPA induced by 20 μM ADP after the first dose of study medication (loading dose of ticagrelor 180 mg or clopidogrel 600 mg).

Table S1 Summary of final extent %IPA induced by 20 μM ADP after first dose (ITT analysis set)

	Ticagrelor (N=54)			Clopidogrel (N=50)			
Protocol-scheduled time	**n**	**Median**	**IQR**	**n**	**Median**	**IQR**	**p-value**
0.5 hours	49	45.39	3.0 – 66.4	47	4.71	0.0 – 14.8	<0.0001
1 hour	47	86.71	72.6 –99.4	47	15.83	0.0 – 32.5	<0.0001
2 hours	48	93.15	80.4 – 100.0	49	31.05	10.3 – 56.9	<0.0001
4 hours	49	98.39	84.2 – 100.0	48	40.87	16.6 – 69.3	<0.0001
8 hours	53	96.99	81.1 – 100.0	47	46.90	20.4 – 80.8	< 0.0001
24 hours	52	87.29	62.9 – 98.4	46	49.64	17.7 – 76.9	< 0.0001

ADP Adenosine diphosphate; IPA Inhibition of platelet aggregation; IQR Inner quartile range; ITT Intent to treat.

After the loading dose, more rapid onset of IPA occurred with ticagrelor compared with clopidogrel at 0.5, 1, and 2 hours. Higher IPA for ticagrelor was consistently maintained during maintenance therapy ($p<0.0001$ at all times). More patients in the ticagrelor group than in the clopidogrel group achieved >70% IPA (90% vs 16%) at 2 hours post dose; more ticagrelor patients achieved >70% IPA at all timepoints post loading dose.

A faster offset rate for IPA was observed after the last dose of ticagrelor than for clopidogrel from 4 to 72 h (slope [%IPA/h]: –1.037 vs. –0.482, $p<0.0001$). Mean IPA for ticagrelor at 72 hours post dose (Day 3) was comparable to clopidogrel at 120 hours (Day 5). Mean IPA on Day 5 for ticagrelor was similar to that for clopidogrel on Day 7, both of which were not statistically different from placebo ($p>0.05$). Mean IPA at 24 hours after the last dose was similar between ticagrelor and clopidogrel (difference of LS means estimate 8.97, 95% CI -2.41 to 20.34) suggesting IPA after a missed ticagrelor dose is comparable to clopidogrel IPA at steady state (trough levels).

Results for platelet aggregation and other markers of platelet activation such as VASP-P PRI, P-selectin and VerifyNow™ showed results highly concordant with IPA at onset and offset.

Summary of safety results

Ticagrelor treatment was associated with more AEs compared with clopidogrel or placebo. The most common AEs (>10%) were dyspnoea, increased tendency to bruise, and contusion for ticagrelor; and dyspnoea for clopidogrel. The majority of AEs were of mild or moderate intensity. Other significant AEs (dyspnoea, exertional dyspnoea, and/or gout) occurred in 17,

4, and 1 patients in the ticagrelor, clopidogrel, and placebo groups, respectively. There were no deaths or SAEs during randomized treatment, and few DAEs (4 [7%] ticagrelor patients and 1 [8.3%] placebo patient). There were more bleeding-related AEs for the ticagrelor group but most events were minimal bleeds and none resulted in discontinuation of study drug. No thrombotic events were reported during the study.

Ticagrelor showed no adverse effects on cardiopulmonary function. Dyspnoea was reported with a higher frequency on ticagrelor compared with clopidogrel group but was not linked to any change in cardiopulmonary function or changes in uric acid, and did not affect the rate of discontinuation. Dyspnoea was transient, of short duration, and resolved without intervention.

No safety concerns were raised based on clinical laboratory, vital signs, or ECGs evaluations. Increases in uric acid (<10%) were observed in ticagrelor patients, consistent with that observed in previous studies.