AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6140/Ticagrelor
Study Code	D5130C00030
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A Randomised, Double-Blind, Outpatient, Crossover Study of the Anti-platelet Effects of AZD6140 Compared with Clopidogrel in Patients with Stable Coronary Artery Disease Previously Identified as Clopidogrel Non-responders or Responders [RESPOND]

Study dates: First patient enrolled: 19 May 2008
Last patient completed: 25 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 10 centres in the United States (US), the United Kingdom (UK), Denmark, and Canada.

Publications

None at the time of writing this report.

Objectives

This study was designed to test the hypothesis that ticagrelor produces greater and more consistent IPA when compared with clopidogrel in patients previously identified as either responsive or non-responsive to clopidogrel.

The primary objective of this study was to assess the effect of ticagrelor (formerly known as AZD6140) on inhibition of platelet aggregation (IPA) compared with clopidogrel in patients previously identified as non-responsive to clopidogrel.

The secondary objectives of this study were:

- To compare IPA, platelet aggregation, and biomarker expression in clopidogrel non-responsive patients when directly switched from clopidogrel to ticagrelor, as opposed to continuing treatment with clopidogrel without interruption
- To compare IPA, platelet aggregation, and biomarker expression in clopidogrel responsive patients when directly switched from ticagrelor to clopidogrel, as opposed to continuing treatment with ticagrelor without interruption
- To assess the general tolerability of a direct switch from clopidogrel to ticagrelor without a washout

Study design

This study was a multi-centre, randomised, double-blind, double-dummy crossover study comparing the anti-platelet effects of ticagrelor with clopidogrel in patients with stable coronary artery disease (CAD) previously identified as clopidogrel non-responders or responders. Identification of non-responders/responders was based on the light transmittance aggregometry (LTA) method. During this period they received a single dose of 300 mg clopidogrel. Platelet aggregation in response to 20 μM ADP was determined pre-dose and again 6 to 8 hours following clopidogrel administration.

- Non-responder definition: patients with an absolute difference of less than or equal to 10% between baseline and post-treatment platelet aggregation (maximum extent) with 20 μM ADP used as the agonist

- Responder definition: patients with an absolute difference greater than 10% between baseline and post-treatment platelet aggregation (maximum extent) with 20 μM ADP used as the agonist

Where absolute difference in platelet aggregation (%) = baseline aggregation (%) - post treatment aggregation (%).

This study consisted of 2 treatment periods. During each period patients received 1 of 2 possible treatments. There was no washout period between the 2 treatments.

Treatment A: clopidogrel 600 mg loading dose followed by 75 mg once daily (od) for 2 weeks

Treatment B: ticagrelor 180 mg loading dose followed by 90 mg twice daily (bd) for 2 weeks

All treatments were administered in a double-blind, double-dummy design. Matching placebo ticagrelor tablets and clopidogrel capsules were given (ie, all patients received both tablets and capsules daily). All patients received 75 to 100 mg od ASA, which was maintained at a constant dose throughout the study period. Patients continuing on the same treatments in both study periods did not receive loading doses of study drug during Period 2.

Non-responders were assigned to 1 of 2 sequences (AB or BA) as follows:

- Approximately half of the non-responders received Treatment A for 14±2 days during Period 1, then received Treatment B for an additional 14±2 days during Period 2.

- Approximately half of the non-responders received Treatment B for 14±2 days during Period 1, then received Treatment A for an additional 14±2 days during Period 2.

Responders were randomly assigned to 1 of 4 sequences (AA, AB, BB, or BA) as follows:

- Approximately half of the responders received Treatment A for 14±2 days during Period 1. Half of these patients continued to receive Treatment A for an additional 14±2 days during Period 2 and the other half received Treatment B for 14±2 days during Period 2.

- Approximately half of the responders received Treatment B for 14±2 days during Period 1. Half of these patients continued to receive Treatment B for an additional 14±2 days during Period 2 and the other half received Treatment A for 14±2 days during Period 2.

Subject population and sample size

Male and female patients, at least 18 years of age and with documented stable CAD were eligible for enrolment. It was planned to randomise 80 patients to study treatment; 32 previously identified as clopidogrel non-responders and 48 previously identified as clopidogrel responders. The study actually enrolled 98 patients in total. There were 2 cohorts: non-responders (N=41) and responders (N=57).

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

Ticagrelor 90 mg tablets and matching placebo tablets were used in the study together with over-encapsulated clopidogrel 75 mg and matching placebo capsules. Batch numbers for ticagrelor 90 mg tablets were: KDN509, KDN516, and KDN518 and for ticagrelor placebo tablets was KA205. The batch numbers for over-encapsulated clopidogrel 75 mg were: A07316, A07165, A07165 and for matching clopidogrel placebo capsules was A08028.

Duration of treatment

The screening period was up to 28 days including a 14 day minimum washout period for patients who were on clopidogrel prior to receiving first dose of study drug. The total duration of treatment was approximately 28 days for each subject. Each treatment sequence was 14±2 days with no washout period between treatments. The duration of the study was approximately 7 weeks for each subject.

Criteria for evaluation - Pharmacodynamics

Primary outcome variable: Proportion of clopidogrel non-responders who respond to anti-platelet therapy as measured by 20 μM IPA (final extent) at 4 hours post dose at steady state. The primary definition of response to treatment in this trial is final extent %IPA >10%. A secondary definition of response to treatment is final extent %IPA >50%. A posthoc analysis also examined response at the >30% final extent IPA level, as well the absolute % change in platelet aggregation at the >10%, >30%, and >50% levels.

Secondary outcome variables: Secondary variables included IPA induced by 5 μM ADP by light transmittance aggregometry (LTA); IPA induced by 2 μg/ml collagen and 2 mM arachidonic acid (AA); platelet aggregation induced by 5 μM and 20 μM ADP; flow cytometry variables including P-selectin, (GP) IIb/IIIa receptor, and VASP-P; thromboelastography (TEG®) variables; and $P2Y_{12}$ analysis by VerifyNow™ assay.

Criteria for evaluation - safety

The safety and tolerability of clopidogrel and ticagrelor before and after an immediate switch to the other agent was assessed. Safety was assessed via the following variables: adverse events (AEs) (including bleeding events), safety labs (clinical chemistry, haematology and urinalysis), 12-lead electrocardiograms (ECG), physical examination, and vital signs (blood pressure, pulse and respiratory rate).

Statistical methods

The primary and secondary analyses were conducted in clopidogrel non-responder cohort. The comparison was the proportion of responders in each treatment (ticagrelor - clopidogrel) using McNemar's test in 20 μM ADP-stimulated IPA (final extent) measured at 4 hours post-dose, using 10 and 50% IPA following treatment as the definition for responder. Third and fourth analyses were conducted in clopidogrel responder cohort, to examine the effects switching from ticagrelor to clopidogrel and clopidogrel to ticagrelor on IPA. The contrast of interest was ticagrelor - clopidogrel LS means and a 2-sided 95% CI post switch at steady state (Day

14, 4 hrs post dose). The switching effects were analyzed using analysis of covariance (ANCOVA) model with fixed effect of centre, treatment, and steady state IPA values in Period 1 as a covariate.

All tests were conducted at the 2-sided 5% Type I error level. In order to control the Type I error rate, the tests were conducted in order. No further testing results could claim significance following the first non-statistically significant result.

Patient population

The first patient signed informed consent on 19 May 2008 and the last patient completed the study on 25 March 2009. A total of 98 patients were randomised to treatment (41 non-responders and 57 responders) while 88 patients completed the study. A sufficient number of patients were recruited and dosed to assess the endpoints described in the study objectives.

Summary of pharmacokinetic results

Mean T_{max}, C_{max} and AUC_{0-8} of ticagrelor following 2-week maintenance doses were similar between clopidogrel responders and non-responders. The PK of ticagrelor administered after the crossover from clopidogrel was unchanged compared with the PK of ticagrelor administered in Period 1, and was not affected by patient responsiveness to clopidogrel.

Summary of pharmacodynamic results

The primary analysis measured the effect of ticagrelor vs clopidogrel (20 µM ADP induced final extent %IPA) in non-responders (see Table S1).

Table S1 Number and percent of patients achieving specified %IPA and %PA thresholds on Day 14, 4 hrs - Non-responders (ITT analysis set)

Response criteria (20µM ADP)	Ticagrelor (N=32)		Clopidogrel (N=32)		Difference[a]		McNemar's test	
	n (%)	95% CI	n (%)	95% CI	%	95% CI	N[b]	p-value
%IPA >10%	32 (100)	89.1–100	30 (93.8)	79.2–99.2	6.1	-5.4–17.5	31	0.157
%IPA >30%	31 (96.9)	83.8–99.9	19 (59.4)	40.6–76.3	36.4	17.6–55.1	31	<0.001
%IPA >50%	27 (84.4)	67.2–94.7	8 (25.0)	11.5–43.4	57.6	37.9–77.2	31	<0.001
%PA >10%	32 (100)	89.1–100.0	28 (87.5)	71.0–96.5	12.1	-1.4–25.7	31	0.046
%PA >30%	28 (87.5)	71.0–96.5	12 (37.5)	21.1–56.3	48.5	28.0–69.0	31	<0.001
%PA >50%	19 (59.4)	40.6–76.3	3 (9.4)	2.0–25.0	48.5	29.0–68.0	31	<0.001

[a] Difference is the %difference in proportion of subjects (ticagrelor – clopidogrel).
[b] Only subjects with paired data available were used in McNemar's test.
Note: Results of %IPA >10%, >30% or >50% are calculated from the timepoints of 4 hours after the morning dose on Day 14, Period 1 and 4 hours after the morning dose on Day 1, Period 2.
ADP Adenosine diphosphate; CI Confidence interval; IPA Inhibition of platelet aggregation; ITT Intent to treat.

An analysis of 20µM ADP-induced IPA (ITT) on Day 14 is presented in Table S2.

Table S2 Analysis of Final Extent 20 µM ADP-induced %IPA –Non-reponders on Day 14 (ITT Analysis set)

	Ticagrelor			Clopidogrel			LS Mean Difference[a]	
Protocol time	n	LS mean	95% CI	n	LS mean	95% CI	Point estimate	95% CI
Day 14								
0 hours	35	56.6	49.4–63.8	34	23.3	16.0–30.5	33.3	26.6–40.1
2 hours	31	69.0	61.6–76.5	33	32.4	25.0–39.8	36.6	29.8–43.4
4 hours	32	68.0	60.6–75.5	32	33.6	26.2–41.0	34.5	27.7–41.2
8 hours	33	63.4	56.1–70.8	32	36.8	29.4–44.2	26.6	19.9–33.3

[a] Difference is ticagrelor – clopidogrel.
ADP Adenosine diphosphate; CI Confidence interval; IPA Inhibition of platelet aggregation; ITT Intent to treat; LS Least squares

The difference in the proportion of non-responders on ticagrelor versus clopidogrel who achieved >10% final extent %IPA was not statistically significant (McNemar's test). However, the nominal p-values for this difference at the >30% and >50% IPA levels were both <0.001 (see Table S1). A post hoc analysis showed that 12.1%, 48.5% and 48.5% more non-responders taking ticagrelor achieved decreases from baseline in %PA of >10%, >30%, and >50% versus clopidogrel (see Table S1). At steady state (Day 14), the response (%IPA) to ticagrelor was consistently higher compared with clopidogrel at all post dose assessments (see Table S2) with nominal p-values <0.05 for all assessments. Switching of non-responders to ticagrelor resulted in higher and more consistent IPA (Day 14 LS mean increases of 26.6% to 36.6%).

Responders switching from clopidogrel to ticagrelor at steady state (PD analysis set, Day 14, Period 2) had a LS mean 26.4% increase in IPA. Responders switching from ticagrelor to clopidogrel had a LS mean 24.5% decrease in %IPA (Day 14, Period 2). Ticagrelor effects substantially higher IPA compared with clopidogrel in both non-responders and responders, and patients can switch directly from clopidogrel to ticagrelor without any interruption of antiplatelet effects.

Summary of pharmacokinetic/pharmacodynamic relationships

High E_{max} values in both the non-responder (73.1% to 99.2%) and responder (94.9% to 99.7%) cohorts suggest that ticagrelor can completely inhibit platelet aggregation within this dosing range in responders and can also overcome nonresponsiveness to clopidogrel in non-responders. Ticagrelor's effect on platelet aggregation was not greatly affected by patient responsiveness to clopidogrel. Trough plasma concentrations of ticagrelor were at least 2-fold higher than EC_{50} estimates for ticagrelor, indicating that the plasma concentrations at the end of the 90 mg bid dosing interval were sufficient to maintain high IPA during the dosing interval.

Summary of safety results

Overall, ticagrelor was generally well tolerated, with more AEs reported during ticagrelor treatment compared with clopidogrel treatment but no increase in AEs observed during the 24-hour switching period. There were more bleeding events during ticagrelor treatment compared with clopidogrel treatment but no increase in events during the switching period for either treatment. There were few DAEs (n=6) and a total of 5 SAEs during the study but only 2 SAEs were considered treatment related. Several OAEs of dyspnoea were reported but the vast majority occurred early in the study, resolved without intervention, and did not result in discontinuation. There was 1 death that occurred 28 days after stopping study treatment and it was confirmed by the investigator to be unrelated to study treatment.