AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor (formerly known as AZD6140)
Study Code	D5130C05262
Edition Number	1.0
Date	23 September 2009

A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of AZD6140 Compared with Clopidogrel for Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)
[PLATO – A Study of PLATelet inhibition and Patient Outcomes.]

Study dates:	First patient enrolled: 11 October 2006 Last patient completed: 27 February 2009
Phase of development:	Therapeutic confirmatory (III)

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 centres

This study was conducted in 862 investigational centres in 43 countries worldwide.

Publications

James S, Akerblom A, Cannon C, Emanuelssom H, Husted S, Katus, H, et al. Comparison of ticagrelor, the first reversible oral $P2Y_{12}$ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2009;157:599-605.

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held, C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361: 361-73.

Objectives

Primary objective

To test the hypothesis that ticagrelor (formerly known as AZD6140) is superior to clopidogrel for the prevention of vascular events in patients with non-ST or ST elevation ACS.

Secondary objectives

To assess the safety and tolerability of ticagrelor compared to clopidogrel.

To compare the efficacy and safety of ticagrelor with clopidogrel in those patients who underwent CABG surgery during the study and in relation to the timing of these interventions.

To the occurrence of arrhythmic episodes detected by Holter monitoring with ticagrelor compared with clopidogrel both during the initial period after randomisation and at 1 month, and the relation of these episodes to clinical outcomes.

ACS Acute coronary syndromes; CABG coronary artery bypass graft.

Study design

Randomised, double-blind, double-dummy, parallel group, international, multicentre study.

Target population and sample size

Both sexes, age ≥ 18 years with non-ST or ST segment elevation acute coronary syndromes (ACS) (index event) and high risk of secondary thrombotic event. 1780 events provide 90% power to detect a 13.5% relative risk reduction (RRR) at a 4.97% significance level (adjusted for 1 interim analysis). 18000 patients should provide this number of events over the planned study period.

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

Ticagrelor 180 mg loading dose (LD) followed by 90 mg twice daily (bd), with additional 90 mg LD if percutaneous coronary intervention (PCI) occurred >24 hours after randomisation. Clopidogrel 300 mg LD (unless concomitant medication at randomisation)

followed by 75 mg (over-encapsulated) once daily (od) with an additional 300 mg at PCI at the discretion of the investigator. Forty-three batches of ticagrelor and 19 batches of clopidogrel were used.

Duration of treatment

Six to 12 months with planned study completion at 6, 9 or 12 months depending on entry date.

Criteria for evaluation – efficacy (main variables)

Primary variable
Time from randomisation to first occurrence of death from vascular causes, MI, stroke
Secondary variables (analysed in the order presented using a hierarchical procedure)
Time from randomisation to first occurrence of death from vascular causes, MI, stroke and for the subgroup of patients intended for invasive management at randomisation
Time from randomisation to first occurrence of all-cause mortality, MI, or stroke
Time from randomisation to first occurrence of death from vascular causes, MI (including silent MI by ECG), stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, TIA or other arterial thrombotic events
Time from randomisation to first occurrence of MI. Time to first occurrence of death from vascular causes. Time to first occurrence of stroke.
Time from randomisation to occurrence of all-cause mortality

ECG Electrocardiogram; MI Myocardial infarction; TIA Transient ischaemic attack.

Criteria for evaluation - safety (main variables)

Additional secondary variables
Primary safety endpoint: Time from first dose of study drug to first occurrence of any total major bleeding event
Secondary safety endpoint: Time from first dose of study drug total, non-CABG, non-procedure-related, coronary procedure-related and non-coronary procedure-related major bleeding events
Secondary safety endpoint: Time from first dose of study drug total, non-CABG, non-procedure-related, coronary procedure-related and non-coronary procedure-related major + minor bleeding events

CABG Coronary artery bypass graft.

Statistical methods

The efficacy analysis of time from randomisation to first occurrence of centrally adjudicated events included all patients randomised to study drug, using the Cox proportional hazards model. The hierarchical test procedure included the hypothesis tests for the endpoints listed in criteria for evaluation – efficacy (main variables) above. This procedure was followed in order to control family-wise type I error. Primary and secondary safety endpoints ('Major' and 'Major + Minor' bleeding events, total and by category) were analysed as time from first dose of study drug to event using a Cox proportional hazards model.

Subject population

Table S 1 presents a summary of the study patient population and disposition.

Table S 1 Subject population and disposition

Parameter		Ticagrelor 90 mg bd		Clopidogrel 75 mg od		Total	
Disposition							
N randomised (%)		9333	(100%)	9291	(100%)	18624	(100%)
N (%) of subjects who	Completed	9026	(96.7%)	9036	(97.3%)	18062	(97.0%)
	Discontinued	307	(3.3%)	255	(2.7%)	562	(3.0%)
Patients in the full analysis set		9333		9291		18624	
Patients in the safety set		9235		9186		18421	
Patients in the safety lab analysis set		5610		5582		11192	
Demographic characteristics							
Sex (n and % of subjects)	Male	6678	(71.6%)	6658	(71.7%)	13336	(71.6%)
	Female	2655	(28.4%)	2633	(28.3%)	5288	(28.4%)
Age (years)	Mean (SD)	62.1	(11.21)	62.3	(11.21)	62.2	(11.21)
	Range	19 to 97		21 to 94		19 to 97	
Race (n and % of subjects)	Caucasian	8566	(91.8%)	8511	(91.6%)	17077	(91.7%)
	Black	115	(1.2%)	114	(1.2%)	229	(1.2%)
	Asian	542	(5.8%)	554	(6.0%)	1096	(5.9%)
	Other	109	(1.2%)	112	(1.2%)	221	(1.2%)
	Unknown	1	(0.0%)	0	(0.0%)	1	(0.0%)
Final diagnosis of index event							
Unstable angina		1549	(16.6%)	1563	(16.8%)	3112	(16.7%)
NSTEMI		4005	(42.9%)	3950	(42.5%)	7955	(42.7%)
STEMI		3496	(37.5%)	3530	(38.0%)	7026	(37.7%)

bd Twice daily; NSTEMI Non-ST elevation myocardial infarction; SD Standard deviation; STEMI ST elevation myocardial infarction; od Once daily.

- PLATO enrolled a broad and inclusive population of patients with ACS (UA [16.7%], NSTEMI [42.7%], or STEMI [37.7%]), including patients planned for invasive management (coronary angiography with PCI or CABG as indicated) (72%), as well as patients intended for a medical management strategy (28%). In total, 10.2% of all patients underwent CABG.

- A total of 6762 (73.2%) patients in the ticagrelor group and 6915 (75.3%) of patients in the clopidogrel group were exposed for >180 days to study treatment, and 3138 (34.0%) and 3184 (34.7%) had >360 days of exposure to the respective study treatments.

- PLATO enrolled a population generally representative of ACS patients globally with respect to demographic and disease characteristics at baseline.

- PLATO, like other ACS programmes, enrolled a predominantly Caucasian cohort (91.7%) (1.2% Blacks overall, 10% of North American cohort). Previous trials and registries document the predominance of Caucasian patients in ACS trials.

- Treatment groups were balanced across analysis sets with respect to: disposition; protocol deviations; demographic and baseline characteristics; pre-, post-, and concomitant medications; and treatment compliance.

- Treatment patterns in PLATO were generally consistent across regions and adhered to global ACS guidelines.

Summary of efficacy results

- Ticagrelor is superior to clopidogrel in reducing the rate of the composite efficacy endpoint of cardiovascular death, MI, or stroke after ACS events (RRR 16%, ARR 1.9%, HR 0.84 [95% CI 0.77, 0.92]; p=0.0003).

- Ticagrelor, compared to clopidogrel, reduces the rate of primary composite endpoint events in ACS patients planned for invasive management (RRR 16%, ARR 1.7%, HR 0.84 [95% CI 0.75, 0.94]; p=0.0025) and in ACS patients intended for medical management (RRR 15%, ARR 2.3%, HR 0.85 [95% CI 0.73, 1.00]; nominal p=0.0444).

  – Results support ticagrelor use to decrease the rate of clinically-important thrombotic events, those that represent major adverse cardiovascular events, in patients planned for invasive management and patients intended for medical management.

- Ticagrelor, compared to clopidogrel, decreases separately the rates of cardiovascular death (RRR 21%, ARR 1.1%, HR 0.79 [95% CI 0.69, 0.91]; p=0.0013) and of MI (RRR 16%, ARR 1.1%, HR 0.84 [95% CI 0.75, 0.95]; p=0.0045), but not that of stroke (1.5% vs. 1.3%; p=0.2249).

- Treating 54 patients with ticagrelor instead of with clopidogrel for 12 months will prevent 1 event in the primary outcome composite.

- A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined Major bleeding) supports the clinical benefit of ticagrelor compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

- The treatment effect of ticagrelor over clopidogrel appears consistent across multiple patient subgroups by demographic characteristics and by final index event diagnosis (UA, NSTEMI and STEMI).

- Ticagrelor, compared to clopidogrel, decreases the rate of the composite of all-cause mortality, MI, and stroke (RRR 16%, ARR 2.1%, HR 0.84 [95% CI 0.72, 0.92]; p-value=0.0001).

  – Although formal, hierarchical statistical testing of secondary endpoints concluded after stroke, there was an observed numerical reduction in all-cause mortality (RRR 22%, ARR 1.4%, HR 0.78 [95% CI 0.69, 0.89]; nominal p=0.0003) compared to clopidogrel.

- There were numerically fewer definite stent thromboses among patients treated with ticagrelor compared to clopidogrel (73 vs. 107, RRR 32%, ARR 0.6%, HR 0.68 [95% CI 0.51, 0.92]; nominal p=0.0123).

- Cessation of ticagrelor or clopidogrel results in similar numerical increases in the rates of events in the primary outcome composite in the 30 day follow-up period.

- Within the first 30 days of treatment, ticagrelor shows a statistically significant early benefit (RRR 12%). In those patients free of events and still in the trial during the first 30 days, evaluation of the primary endpoint in patients who continue following the first 30 days suggest that the KM curves continue to separate (RRR 19%). The benefit of ticagrelor treatment continues to accrue over 1 to 12 months, and suggest that it is appropriate to treat ACS patients with ticagrelor for at least 12 months.

Summary of safety results

Exposure

Study drug exposure was similar in both treatment groups: mean 248 days, median 277 days. Interruptions of study drug occurred for 15% of ticagrelor and 13.8% of clopidogrel patients.

Bleeding events

- PLATO-defined 'Total Major' bleeding (primary safety endpoint) for ticagrelor does not differ significantly from that of clopidogrel (HR 1.04 [95% CI 0.95, 1.13]; p=0.4336).

- Neither Fatal bleeding nor the rate of 'Major Fatal or life threatening' bleeding differed significantly between treatments.

- PLATO-defined 'Major + Minor' bleeding rates were significantly greater with ticagrelor compared to clopidogrel.

- PLATO-defined CABG-related 'Total Major' bleeding was similar between treatment groups.

- When CABG bleeding was removed from the analysis, it resulted in decreased rates of 'Total Major' bleeding in both treatment groups, but the rate for ticagrelor was significantly greater vs. clopidogrel.

  - There was also an increased rate for TIMI-derived Major and TIMI-derived Major + Minor with ticagrelor, which is similar to PLATO-defined 'Total Major'.

- Non-procedural PLATO-defined Fatal and 'Major Fatal/Life-threatening' bleeding were similar for ticagrelor and clopidogrel.

  - 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events occurred in 26 ticagrelor and 14 clopidogrel patients of which there were 11 Fatal events with ticagrelor and 1 with clopidogrel.

  - 'Major Fatal/Life-threatening' non-intracranial non-procedural bleeding events occurred in 77 ticagrelor and 81 clopidogrel patients, of which there were 2 Fatal events with ticagrelor and 11 with clopidogrel.

- Non-procedural 'Total Major' bleeding differed significantly between treatment groups; the rate was higher with ticagrelor.

  - Investigators reported numerically more 'Total Major' gastrointestinal non-procedural bleeding events with ticagrelor (124 events) compared to clopidogrel (94 events) of which there were no Fatal bleeding events with ticagrelor and 5 with clopidogrel. The increase in gastrointestinal bleeding observed with ticagrelor diminished with increasingly severe bleeding categories.

- Non-procedural PLATO-defined 'Major + Minor' bleeding rates were significantly greater with ticagrelor compared to clopidogrel ($p<0.0001$).
  - The increase in 'Minor' bleeding with ticagrelor was mostly due to epistaxis.
- No subgroup was identified as being at increased risk of 'Total Major' overall, or 'Total Major' non-CABG or non-procedural bleeding.
- Inherent to the pharmacodynamic effects of ticagrelor, with higher inhibition of platelet aggregation, the bleeding data above provide a clinically manageable profile.

Adverse events

Table S 2 presents the summary of all adverse events (AEs) during the treatment period (including and excluding bleeding events).

Table S 2 Summary of all adverse events during the treatment period

Category	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Including bleeding events		
Any adverse event	6714 (72.7%)	6398 (69.6%)
Serious adverse event	1864 (20.2%)	1866 (20.3%)
Adverse event leading to death	221 (2.4%)	285 (3.1%)
Serious adverse event other than death	1712 (18.5%)	1685 (18.3%)
Adverse event leading to discontinuation	687 (7.4%)	500 (5.4%)
SAE leading to study drug discontinuation	259 (2.8%)	218 (2.4%)
Excluding bleeding events		
Any adverse event	6337 (68.6%)	6120 (66.6%)
Serious adverse event	1633 (17.7%)	1694 (18.4%)
Adverse event leading to death	201 (2.1%)	266 (2.9%)
Serious adverse event other than death	1485 (16.1%)	1519 (16.5%)
Adverse event leading to discontinuation	486 (5.3%)	411 (4.5%)
SAE leading to study drug discontinuation	172 (1.9%)	174 (1.9%)

bd Twice daily; od Once daily; SAE Serious adverse event.

Ticagrelor was well tolerated. Overall safety profile was generally similar to that for clopidogrel. The treatment groups had similar numbers of patients with AEs, except in the categories of dyspnoea, bleeding, and renal.