AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	Ticagrelor (AZD6140)
Study Code	D5130C00027
Edition Number	1
Date	8 April 2013
ClinicalTrials.gov ID	NCT01294462

A Randomised, Double-blind, Double-dummy, Parallel Group, International (Asian), Multicenter, Phase 3 Study to Assess Safety and Efficacy of AZD6140 on top of low dose Acetyl Salicylic Acid (ASA) versus Clopidogrel on top of low dose ASA in Asian/Japanese Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS) for whom PCI is planned

Study dates: First subject enrolled: 28 February 2011
Last subject last visit: 31 July 2012

Phase of development: Therapeutic confirmatory (III)

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

Study centre(s)

This study was conducted in approximately 110 investigational centres in Japan, South Korea, and Taiwan. A total of 801 subjects were randomised to study treatment.

The majority of sites recruited 10 or more subjects.

Publications

None at the time of writing this report.

Table S1 Objectives and outcome variables for PHILO study

Objective	Outcome Variable
Primary safety:	
To assess short and long term safety and tolerability (especially bleeding) of AZD6140 90 mg bd compared with clopidogrel 75 mg od in Asian/Japanese patients with non-ST or ST elevation ACS for whom PCI was planned	Primary endpoint: The time to first occurrence of any total major bleeding event (to be adjudicated using PLATO[1] criteria) Secondary endpoint: Bleeding events (to be adjudicated using PLATO criteria) - Total, non-procedure-related, coronary procedure-related[a] and non-coronary procedure-related major bleeding events - Total, non-procedure-related, coronary procedure-related[a] and non-coronary procedure-related minor bleeding events - Combined major and minor bleeding events for each of the categories - Total minimal bleeding events Adverse events (AEs), laboratory values, physical examination, 12 lead electrocardiogram (ECG), Holter ECG and vital signs.

Table S1 Objectives and outcome variables for PHILO study

Objective	Outcome Variable
Primary efficacy: To evaluate effect of AZD6140 90 mg bd in the prevention of vascular events compared with clopidogrel 75 mg od in Asian/Japanese patients with non-ST or ST elevation ACS for whom PCI was planned	The time to first occurrence of : Primary endpoint: - Any event from the composite of death from vascular causes, myocardial infarction (MI) or stroke Secondary endpoint: - Any event from the composite of all-cause mortality, MI or stroke - Any event from the composite of death from vascular causes, MI (including silent MI by ECG), stroke, recurrent cardiac ischaemia, transient ischemic attack (TIA) or other arterial thrombotic events - Each component of the primary composite efficacy endpoint individually in the order of MI, death from vascular causes and then stroke - All-cause mortality
Secondary PK objective: To investigate the population PK of AZD6140 in this patient population - To assess the effect of demographics, concomitant therapies and disease state on PK of AZD6140 - To assess relationship between steady-state exposure of AZD6140 and AR-C124910XX (active metabolite) and various safety and efficacy outcomes To investigate efficacy of AZD6140 in this patients population in comparison with efficacy in total patients and Asian cohort from study D5130C05262 (PLATO) To investigate safety of AZD6140 in this patients population in comparison with safety in total patients and Asian cohort from study D5130C05262 (PLATO)	Plasma concentrations of AZD6140 and AR-C124910XX
Secondary efficacy objective: To investigate the efficacy of AZD6140 in this patient population in comparison with efficacy in total patients and Asian cohort from study D5130C05262 (PLATO)	See description of primary efficacy variable.
Secondary safety objective: To investigatet the safety of AZD6140 in this patients population in comparison with safety in total patients and Asian cohort from study D5130C05262 (PLATO)	See description of primary efficacy variable.

Table S1 Objectives and outcome variables for PHILO study

Objective	Outcome Variable
Secondary PK objective:	
To investigate population PK of AZD6140 in this patient population in comparison with the results in Caucasian cohorts total patients and Asian cohort from study D5130C05262 (PLATO)[b]	Maximum plasma drug concentration at steady state ($C_{ss,max}$), minimum plasma drug concentration at steady state ($C_{ss,min}$), average plasma concentration at steady state ($C_{ss,av}$), time to reach peak or maximum concentration or maximum response following drug administration at steady state ($T_{ss,max}$), half-life ($t_{1/2}$) and area under plasma concentration-time curve at steady state (AUC_{ss}) for AZD6140 and AR-C124910XX [c] The relationship between predicted individual $C_{ss,max}$ or AUC_{ss} and outcome events [c]
Secondary PK/PD objective:	
To compare IPA of AZD6140 treated patients with IPA in clopidogrel treated patients, and establish PK/PD relationship for AZD6140, in a subpopulation of patients[d]	IPA: Final extent at each assessment points
Exploratory PGX objective: To collect and store DNA for potential future exploratory research into genes/genetic variation that may influence response to AZD6140 and/or co-medications and/or clopidogrel (ie, distribution, safety, tolerability and efficacy) and susceptibility to and prognosis of cardiovascular disease	Genotype

PLATO is the pivotal Phase III study, D5130C05262, compared AZD6140 (90 mg bd) and clopidogrel (75 mg od) for the prevention of cardiovascular events (a composite of death from vascular causes, MI, or stroke) in 18624 patients with an ACS.

a Coronary procedure-related includes coronary artery bypass graft (CABG), PCI and coronary angioplasty
b Population subgroup form PLATO study was changed to Caucasian patients instead of total patients before unblinding of the study data, see Table 9 in Section 5.8 for details.
c PK parameters for this objective were changed before unblinding of the study data, see Table 9 in Section 5.8 for details.
d It was decided to evaluate PA instead of IPA for this objective before unblinding of the study data, see Table 9 in Section 5.8 for details.

Optional: Exploratory objectives

To collect and store deoxyribonucleic acid (DNA) for potential future exploratory research into genes/genetic variation that may influence response to AZD6140 and/or co-medications and/or clopidogrel (ie, distribution, safety, tolerability and efficacy) and susceptibility to and prognosis of cardiovascular (CV) disease.

Study design

This study (PHILO) is a randomised, double-blind, double-dummy, parallel group, international, multicentre, Phase III study to assess the efficacy and safety of AZD6140 on top of low dose acetyl salicylic acid (ASA) versus clopidogrel on top of low dose ASA in Asian/Japanese patients with non-ST or ST-elevation ACS for whom PCI is planned.

Target subject population and sample size

Male and female patients aged 20 years and over, with documented evidence of non-ST or ST-segment elevation ACS in the 24 hours before randomisation, and for whom PCI is planned, were eligible for enrolment.

In addition to the target population, results from PHILO and subgroups were compared to results from the PLATO study, ie, PLATO All and select subgroups: PLATO All patients (N=18624), PLATO Asian cohort (n=1056), PLATO Asian PK, PLATO Caucasian PK

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

Patients were randomized in a 1:1 ratio to blinded study medication to one of two treatment groups below:

AZD6140 (ticagrelor) 90 mg (tablets) taken twice daily, orally, with an initial loading dose of 180 mg (batches: KA205, ML155); or matching placebo tablets (batches: KD518, ML550)

Clopidogrel 75 mg (over-encapsulated) taken once daily, orally, with an initial 300 mg loading dose for clopidogrel-naïve patients (batches: A08028/XG37D1, B10337, B11151); or matching placebo tablets (A09322, A11032/A10340, A11159).

In addition to randomised study medication, all patients were required to be treated with concomitant ASA 75 to 100 mg daily during the treatment period according to local practice

Duration of treatment

Patients were randomised to treatment no later than 24 hours after the most recent symptoms of the onset of their index event; there was no run-in period. The duration of treatment for an individual patient was estimated to be at least 6 months up to a maximum of 12 months (depending on the time of entry to the study).

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 in the full analysis set. 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 in the prespecified safety analysis set.

Subject population

In total, 817 patients were enrolled from 3 countries (Japan, South Korea and Taiwan). Of the randomised patients, most patients were Japanese (723 [90.3%]).

Table S 2 presents a summary of the study patient population and disposition.

Table S 2 PHILO Subject population and disposition

		All patients				Japanese patients			
Parameter		**AZD6140 90mg bd**		**Clopidogrel 75 mg od**		**AZD6140 90mg bd**		**Clopidogrel 75 mg od**	
Disposition									
N randomised (%)		401	(100%)	400	(100%)	363	(100%)	360	(100%)
N (%) of subjects who	Completed	335	(83.5%)	337	(84.3%)	305	(84.0%)	305	(84.7%)
	Discontinued	66	(16.2%)	63	(15.8%)	58	(16.0%)	55	(15.3%)
Patients included in the full analysis set		401 [a]		400		363 [a]		360	
Patients included in the safety analysis set		387		380		349		340	
Patients included in the PK analysis set		324		-		291		-	
Patients included in the PK/PD sub study analysis set		14		11		14		11	
Patients included in the Holter analysis set		48		53		48		53	
Demographic characteristics									
n		400		400		362		360	
Sex (n and % of subjects)	Female	95	(23.7%)	93	(23.3%)	82	(22.6%)	83	(23.1%)
	Male	305	(76.1%)	307	(76.8%)	280	(77.1%)	277	(76.9%)
Age (years)	Mean	67		66		67		67	
	SD	12		11		11		11	
	Median	68		67		68		67	
	Min - Max	35 - 93		34 - 91		38 - 93		36 - 91	
Ethnic group (n and % of subjects)	Chinese	16	(4.0%)	19	(4.8%)	0		0	
	Japanese	361	(90.0%)	360	(90.0%)	361	(99.4%)	360	(100.0%)
	Korean	23	(5.7%)	21	(5.3%)	1	(0.3%)	0	
Final diagnosis									
Unstable angina		119	(29.7%)	109	(27.3%)	107	(29.5%)	103	(28.6%)
STEMI		205	(51.1%)	210	(52.5%)	202	(55.6%)	203	(56.4%)

Table S 2 PHILO Subject population and disposition

Parameter	All patients				Japanese patients			
	AZD6140 90mg bd		Clopidogrel 75 mg od		AZD6140 90mg bd		Clopidogrel 75 mg od	
NSTEMI	66	(16.5%)	74	(18.5%)	45	(12.4%)	49	(13.6%)
Other	10	(2.5%)	7	(1.8%)	8	(2.2%)	5	(1.4%)
Unstable angina /NSTEMI	185	(46.1%)	183	(45.8%)	152	(41.9%)	152	(42.2%)

bd: Twice daily, od: Once daily, NSTEMI: Non-ST elevation myocardial infarction, SD: Standard deviation, STEMI: ST elevation myocardial infarction.
a Most data for Patient E4370007 were unavailable due to withdrawal of consent.

- The overall demographic and baseline characteristics for PHILO Japanese patients were representative of Japanese patients with ACS for whom PCI was planned.
- In both PHILO All patients and PHILO Japanese patients, treatment groups were well balanced across analysis sets with respect to disposition, protocol deviations, demographic characteristics, concomitant medications and treatment compliance.
- Despite randomisation, there was imbalance between treatment groups in PHILO Japanese patients and PHILO All patients. Conventional coronary risk factors, including hypertension, diabetes and dyslipidaemia were more prevalent among patients in the ticagrelor group compared with the clopidogrel group. This consistent imbalance with higher risk characteristics in the ticagrelor group may reflect normal variation within the limited sample size of PHILO.
- Demographic and baseline characteristics (including ACS-related baseline characteristics) in PHILO Japanese patients differed somewhat from PLATO All patients, but were consistent with PLATO Asian patients and representative for ACS patients in a Japanese registry study.

Summary of efficacy results

- Efficacy data from Japanese patients in this study are limited due to the small number of major adverse cardiovascular events (MACE); numerically more events were observed with ticagrelor compared to clopidogrel (ticagrelor 34 patients [10.3%/year], clopidogrel 24 patients [8.5%/year], hazard ratio [HR, ticagrelor/clopidogrel]=1.44, 95% confidence interval [CI] 0.85 to 2.43). The HR for MACE was in the high end of the range observed in the PLATO All patients analysis by country
- In the medical literature, peri-procedural MI does not confer increased risk of subsequent death, whereas spontaneous MI strongly predicts subsequent mortality. In PHILO, peri-procedural MI comprised 62% of the primary endpoint events. There was no large difference between ticagrelor and clopidogrel in the event rate

of the composite of spontaneous MI/stroke/CV deaths, although the number of events was small. Hazard ratio for Japanese patients in this study for the post-hoc composite of spontaneous MI/stroke/CV death fell within the range observed in the PLATO analysis by country.

- For the event rate of the composite of CV death/total MI/stroke/recurrent cardiac ischemia/transient ischemic attack/other arterial thrombotic events in PHILO Japanese patients, there was no large difference between ticagrelor and clopidogrel (ticagrelor 36 patients [10.9%/year], clopidogrel 31 patients [10.9%/year], HR=1.17, 95% CI 0.73 to 1.90,).

Summary of pharmacokinetic results

In the population pharmacokinetic analysis, plasma concentrations of ticagrelor were well represented by a 2-compartment model with first order absorption, and plasma concentrations its active metabolite AR-C124910XX were described by a 2-compartment model. Age was a statistically significant covariate on apparent clearances of ticagrelor and AR-C124910XX. Its impacts on systemic exposures was 60% higher for ticagrelor in patients aged 83 years than 46 years (corresponding to 95th and 5th percentiles of the distribution of age in the analysis population, respectively), and 55% higher for AR-C124910XX. Sex and body weight were also statistically significant against the metabolite clearance. The systemic exposure of AR-C124910XX was 25% lower in patients weighing 88 kg than 46 kg (corresponding to 95th and 5th percentiles of the distribution of body weight in the analysis population, respectively), and 47% higher in females than males. These moderate changes were not considered to be clinically meaningful. Unexplainable inter-patient variability (CV) for ticagrelor and AR-C124910XX was small and estimated to 42.3% and 32.4%, respectively. No ethnic differences in the average plasma concentrations of ticagrelor and AR-C124910XX at the steady-state were identified between PHILO Japanese and PHILO non-Japanese Asian. In the comparison of PLATO data, the systemic exposures in PHILO Japanese were similar to those in PLATO Asian PK subgroup, but approximately 40% higher than those in PLATO Caucasian PK subgroup.

Summary of pharmacodynamic results

In the small PD substudy, platelet aggregation in patients taking ticagrelor 90 mg twice daily was approximately 25%, compared with approximately 50% in patients taking clopidogrel 75 mg daily. These data are consistent with the Phase II data from Japan, the global Phase II development program and the PD substudy in PLATO.

Summary of exposure-response results

The systemic exposures of ticagrelor and/or AR-C124910XX in patients with bleeding events overlapped with those in patients without bleeding events. The distributions of exposures were comparable between patients with and without bleeding events. No clear exposure-response relationships were observed for bleeding events against systemic exposures of ticagrelor and/or AR-C124910XX at 90 mg bd of ticagrelor. No exposure-response

relationship was observed for the primary clinical efficacy endpoints. Overall, the exposure-response findings were consistent with those observed in PLATO.

Summary of pharmacogenetic results

A total of 380 Japanese patients participated in the PHILO genetic substudy. The distribution of 2C19 and ABCB1 genotypes was similar to published reports for Japanese populations.

Numbers of major bleeding and CV events among patients in the PHILO genetic substudy were small. Overall there was no significant evidence to suggest that PHILO outcomes are dependent on genotype, a finding consistent with PLATO.

Summary of safety results

- Major bleeding data in PHILO (PHILO All patients: HR [ticagrelor/clopidogrel]=1.54; 95% CI 0.94 to 2.53, PHILO Japanese patients: HR=1.41; 95% CI 0.83 to 2.38) are consistent with those in PLATO, ie., in PHILO Japanese patietns, the HR for major bleeding was within the range observed in the PLATO All patients analysis by country. In PLATO All patients and in the PLATO Asian cohort, major bleeding with ticagrelor was similar to that observed in the clopidogrel group (PLATO All patients: HR=1.04; p=0.4336, PLATO Asian cohort: HR=1.07; p=0.7219). Major + minor bleeding was more frequent with ticagrelor.

- The non-bleeding adverse event (AE) profile of ticagrelor in PHILO Japanese and all patients was generally similar to that of clopidogrel.

  - The total number of drug-related AEs (ticagrelor 11.7%, clopidogrel 16.8% in PHILO Japanese), serious AEs (SAEs) (ticagrelor 23.8%, clopidogrel 31.2% in PHILO Japanese) and AEs leading to discontinuation (DAEs) (ticagrelor 5.2%, clopidogrel 9.4% in PHILO Japanese) was slightly lower with ticagrelor.

- The safety profile in PHILO is consistent with that of PLATO.

  - Dyspnoea in PHILO was more frequent with ticagrelor, but overall less frequent in PHILO (7% vs.3%) than in PLATO (14 vs.8%)
  - No ventricular pauses were observed with ticagrelor

-