AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6140
Study Code	D5130C00065
Edition Number	1
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A Randomised, Double-Blind, Parallel Group, International (Asian), Multicenter Study, to Assess Pharmacokinetic and Pharmacodynamic Profile of 2 Doses of AZD6140 on Low Dose Acetyl Salicylic Acid Therapy on Platelet Aggregation in Japanese and Asian Patients with Stable Coronary Artery Disease

Study dates: First patient enrolled: 22 April 2010
Last patient last visit: 22 March 2011

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

15 sites from 2 countries (Japan and Philippines)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	PD
To investigate effect of two doses of AZD6140 (45 mg and 90 mg bid) on IPA in Japanese patients with stable coronary artery disease	IPA final extent at each assessment points	
Secondary	**Secondary**	
To investigate PK profile of AZD6140 in Japanese patients in comparison with Non-Japanese Asian patients	Exposure of AZD6140 and AR-C124910XX (C_{max}, $AUC_{0\text{-}tau}$, t_{max}, $t_{1/2}$ for AZD6140 and its active metabolite AR-C124910XX, accumulation ratios)	PK
To investigate PK profile in Japanese patients in comparison with profile from the study D5130C00008 (DISPERSE)	Exposure of AZD6140 and AR-C124910XX (C_{max}, $AUC_{0\text{-}tau}$, t_{max}, $t_{1/2}$ for AZD6140 and its active metabolite AR-C124910XX, accumulation ratios)	PK
To compare relationship of AZD6140 and AR-C124910XX plasma concentrations and IPA between Japanese and Non-Japanese Asian patients	Relationship of mean exposure of AZD6140/AR-C124910XX and IPA final extent at each assessment points.	PK/PD
To compare relationship of AZD6140 and AR-C124910XX plasma concentrations and IPA between Japanese patients and the study D5130C00008 (DISPERSE)	Relationship of mean exposure of AZD6140/AR-C124910XX and IPA final extent at each assessment points.	PK/PD
To investigate IPA of AZD6140 in Japanese patients by visual comparison with IPA from the study D5130C00008 (DISPERSE)	IPA final extent at each assessment points	PD
To assess the pharmacodynamic effects of two doses of AZD6140 (45 mg and 90 mg bid) in the presence of ASA compared to clopidogrel 75 mg qd plus ASA, in Japanese patients	IPA final extent at each assessment points	PD
To evaluate overall safety and tolerability (especially in Bleeding) of two doses of AZD6140 (45 mg and 90 mg bid) in Japanese and Non-Japanese Asian patients	(1) AEs, laboratory values, physical examination, 12-lead ECG and vital signs (2) Bleeding events (to be adjudicated using DISPERSE and PLATO definitions)	Safety
To evaluate overall safety and tolerability (especially in Bleeding) of two doses of AZD6140 (45 mg and 90 mg bid) in Japanese patients	(1) AEs, laboratory values, physical examination, 12-lead ECG, Holter ECG and vital signs (2) Bleeding events (to be adjudicated using DISPERSE and PLATO definitions)	Safety

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To compare the safety and tolerability of two doses of AZD6140 (45 mg and 90 mg bid) plus ASA with clopidogrel 75 mg qd plus ASA in Japanese and Non-Japanese Asian patients	(1) AEs, laboratory values, physical examination, 12-lead ECG and vital signs (2) Bleeding events (to be adjudicated using DISPERSE and PLATO definitions)	Safety

Study design

Randomised, double-blind, parallel group, Asian, multicenter trial, to assess efficacy of 2 doses of AZD6140 (45 mg bid and 90 mg bid) plus low dose ASA therapy on platelet aggregation

Target subject population and sample size

Male and female Japanese and Non-Japanese Asian patients with stable coronary artery disease.

The sample size was not based on formal statistical tests. As a measure of study precision, with 34 Japanese patients per group, the expected width of the 2-sided 95% confidence interval of the difference between 90 mg and 45 mg dose groups in IPA was approximately ±12%, assuming the SD for the final IPA of 25% based on DISPERSE.

In order to obtain PK and PD data in non-Japanese Asian patients and to make exploratory comparison between Japanese and non-Japanese Asian, 7 non-Japanese Asian patients per group were included. Based on DISPERSE, the difference between the higher dose (90 mg) and lower dose (45 mg) in final IPA at 12 hours post-dose at Week 4 was predicted to be at least 12%. With 7 non-Japanese Asian patients per group, P ($D_{NJP}>0$), where D_{NJP} was estimate of difference between 90 mg and 45 mg dose groups in IPA for non-Japanese Asian was more than 0.8. Therefore, 7 non-Japanese Asian patients per group was considered sufficient to obtain consistent result in terms of point estimates.

Assuming that there were approximately 10% premature discontinuations due to informed consent withdrawal and/or AE, 45 patients per group to be randomized in total.

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

AZD6140

AZD6140 was administered orally as tablets at 2 dose levels (45 mg bid and 90 mg bid). Batch numbers: 34-01 (45 mg bid) and KD518 (90 mg bid). Placebo to AZD6140 was also taken orally. Batch number: 10-000023AZ (45 mg bid) and KA205 (90 mg bid).

Clopidogrel

Clopidogrel (75 mg) as encapsulated tablets (clopidogrel capsule), taken orally od (Batch numbers: A09322). Placebo to match clopidogrel capsules, also taken orally od (Batch number: A08028).

Concomitant ASA

In addition to randomised study medication all patients were treated with concomitant ASA 75 to 100 mg daily for at least 2 weeks prior to Visit2 and during the treatment period according to local practice. ASA was open label and obtained locally.

Duration of treatment

This study consisted of a 2-week run-in period, 4-week treatment period and the follow-up examinations 4 weeks after completion of study medication.

Statistical methods

All Pharmacodynamics, Pharmacokinetics and safety data will be summarised descriptively by treatment group and region (Japan, Non-Japan).

Inhibition of Platelet Aggregation (final extent) at 2, 4, 8, 12 and 24 hours post-dose on Day 28 will be analysed separately based on ANOVA model including treatment group (AZD6140 45 mg, 90 mg and clopidogrel) and the difference between AZD6140 dose groups and its 2-sided 95% confidence interval will be estimated. In addition, the difference between each AZD6140 dose group and clopidogrel group and its 2-sided 95% confidence interval will be estimated.

Subject population

In total, 139 subjects (50, 43 and 46 subjects in AZD6140 45 mg bd, AZD6140 90 mg bd and Clopidogrel 75 mg od group, respectively) were randomised to treatment and received the investigational product. Most subjects completed the study and 2 Japanese patients discontinued the investigational product due to an AE during the 4 weeks treatment period.

The mean age was 63 years (minimum: 35 years, maximum: 80 years), and 124 (89.2%) were male and 15 (10.8%) were female. The proportion of male patients was higher than expected in the study but it was considered of no relevance to evaluate the study results.

Table S2 Demographic characteristics - Japanese and Non-Japanese Asian Patients

Demographic characteristics		AZD6140 45 mg bd (n=50)	AZD6140 90 mg bd (n=43)	Clopidogrel 75 mg od (n=46)	Total (n=139)
Age (years)	Mean	63	64	64	63
	SD	11	9	10	10
	Median	66	66	67	66
	Min	36	37	35	35
	Max	79	77	80	80
Sex n (%)	Male	46 (92.0)	40 (93.0)	38 (82.6)	124 (89.2)
	Female	4 (8.0)	3 (7.0)	8 (17.4)	15 (10.8)
Race n (%)	Asian	50 (100.0)	43 (100.0)	46 (100.0)	139 (100.0)
Ethnic group n (%)	Japanese	42 (84.0)	35 (81.4)	40 (87.0)	117 (84.2)
	Asian (other than Chinese and Japanese)	8 (16.0)	8 (18.6)	6 (13.0)	22 (15.8)
BMI (kg/m^2)	Mean	24.9	24.8	25.2	25.0
	SD	2.6	3.4	3.4	3.1
	Median	24.8	23.8	24.2	24.5
	Min	16.5	16.2	19.7	16.2
	Max	30.0	34.8	35.5	35.5

Data derived from Section 11.1, Table 11.1.3.1 and Table 11.1.4.1

In both of the overall population and Japanese sub-population, treatment groups were well balanced across analysis sets with respect to disposition, protocol deviations, demographic and baseline characteristics, concomitant medications and treatment compliance.

The overall demographic and baseline characteristics of the Japanese patients in this study were representative of Japanese patients with stable coronary artery disease populations of interest except for the higher proportion of male.

Summary of efficacy results

Summary of pharmacokinetic results

Exposures of AZD6140 and AR-C124910XX (C_{max}, AUC_{τ}) increased with dose increase from 45 to 90 mg bd in an approximately dose-proportional manner in Japanese patients. Exposures in Japanese patients showed not to be different from Non-Japanese Asian patients considering small number of Non-Japanese Asian patients, and if considering inter-patient

variability, plasma concentration-time curves in Non-Japanese Asian patients were overlapped with those in Japanese patients. It was not concluded that PK profile in Japanese differed meaningfully from Non-Japanese Asian patients.

Table S3 Derived AZD6140 and AR-C124910XX PK parameters in Japanese and Non-Japanese Asian patients on Visit 2 (Day 1) and Visit 5 (Day 28)

	Japanese patients				Non-Japanese Asian patients			
	Week 0 (Day 1)		Week 4 (Day 28)		Week 0 (Day 1)		Week 4 (Day 28)	
	N	Gmean (CV%)	N	Gmean (CV%)	N	Gmean (CV%)	N	Gmean (CV%)
45 mg bd								
AZD6140								
C_{max} (ng/mL)	38	283 (51)	38	422 (50)	8	220 (141)	8	341 (203)
t_{max} (h) [a)]	38	2.0 (0.9-8.0)	38	2.0 (1.9-4.0)	8	4.0 (1.0-4.0)	8	4.0 (2.0-4.0)
AUC_{τ} (ng·h/mL)	38	1640 (46)	38	3050 (55)	8	1550 (132)	8	2930 (229)
AR-C124910XX								
C_{max} (ng/mL)	38	62.8 (48)	38	135 (40)	8	45.2 (79)	8	101 (84)
t_{max} (h) [a)]	38	3.9 (1.9-8.1)	38	4.0 (1.9-11.9)	8	4.0 (1.0-8.0)	8	4.0 (2.0-8.0)
AUC_{τ} (ng·h/mL)	37	445 (39)	38	1180 (42)	8	336 (69)	8	954 (91)
90 mg bd								
AZD6140								
C_{max} (ng/mL)	33	612 (39)	33	931 (43)	7	766 (17)	7	1380 (24)
t_{max} (h) [a)]	33	2.0 (1.0-8.0)	33	2.0 (1.9-4.1)	7	2.0 (1.0-2.0)	7	4.0 (2.0-4.1)
AUC_{τ} (ng·h/mL)	31	3310 (36)	33	6080 (41)	7	4710 (19)	7	10900 (27)
AR-C124910XX								
C_{max} (ng/mL)	33	156 (45)	33	326 (36)	7	123 (37)	7	381 (51)
t_{max} (h) [a)]	33	3.9 (1.0-8.1)	33	2.1 (1.9-8.0)	7	2.0 (2.0-4.0)	7	2.0 (2.0-4.0)
AUC_{τ} (ng·h/mL)	31	1080 (30)	33	2720 (31)	7	906 (27)	7	3380 (41)

a) : median (range)

At steady state, on Day 28, C_{max} and AUC_{τ} of both AZD6140 and AR-C124910XX were 1.3 to 1.5-fold higher in Japanese patients than Western patients at the both doses.

Summary of pharmacodynamic results

AZD6140 90 mg bd group showed greater mean IPA (final extent) than AZD6140 45 mg bd group at every time point. Both AZD6140 45 mg and 90 mg bd groups showed greater mean

IPA (final extent) compared to Clopidogrel 75 mg od group. At Week 0, AZD6140 45 mg and 90 mg bd groups achieved IPA (final extent) level close to the level achieved at Week 4, where as in Clopidogrel 75 mg od group, the IPA (final extent) level at Week 0 was much lower than at Week 4.

The mean difference between AZD6140 90 mg and 45 mg bd group in IPA (final extent) at the end of dosing interval, ie, 12 hours post dose, on Week 4 was 9.97 (95% CI: 0.49, 19.45). At 12 hours post dose on Week 4, the mean difference between AZD6140 45 mg bd group and Clopidogrel 75 mg od group was 15.09 (95% CI: 5.81, 24.37). The mean difference between AZD6140 90 mg bd group and Clopidogrel 75 mg od group was 25.06 (95% CI: 15.47, 34.65).

Table S4 Efficacy of IPA (final extent) based on ANOVA model at week 4 - Japanese Patients [PD analysis set]

Protocol time	Difference	Estimate	95% CI	
			Lower	Upper
02:00	AZD6140 45 mg vs AZD6140 90 mg	8.53	0.90	16.16
	Clopidogrel 75 mg vs AZD6140 45 mg	25.57	18.09	33.04
	Clopidogrel 75 mg vs AZD6140 90 mg	34.10	26.38	41.82
04:00	AZD6140 45 mg vs AZD6140 90 mg	5.88	-1.95	13.71
	Clopidogrel 75 mg vs AZD6140 45 mg	23.59	15.92	31.26
	Clopidogrel 75 mg vs AZD6140 90 mg	29.47	21.55	37.39
08:00	AZD6140 45 mg vs AZD6140 90 mg	5.97	-2.23	14.16
	Clopidogrel 75 mg vs AZD6140 45 mg	20.13	12.10	28.16
	Clopidogrel 75 mg vs AZD6140 90 mg	26.10	17.80	34.39
12:00	AZD6140 45 mg vs AZD6140 90 mg	9.97	0.49	19.45
	Clopidogrel 75 mg vs AZD6140 45 mg	15.09	5.81	24.37
	Clopidogrel 75 mg vs AZD6140 90 mg	25.06	15.47	34.65
24:00	AZD6140 45 mg vs AZD6140 90 mg	12.93	3.21	22.66
	Clopidogrel 75 mg vs AZD6140 45 mg	8.17	-1.35	17.69
	Clopidogrel 75 mg vs AZD6140 90 mg	21.11	11.27	30.94

Data derived from Section 11.2, Table 11.2.3.6

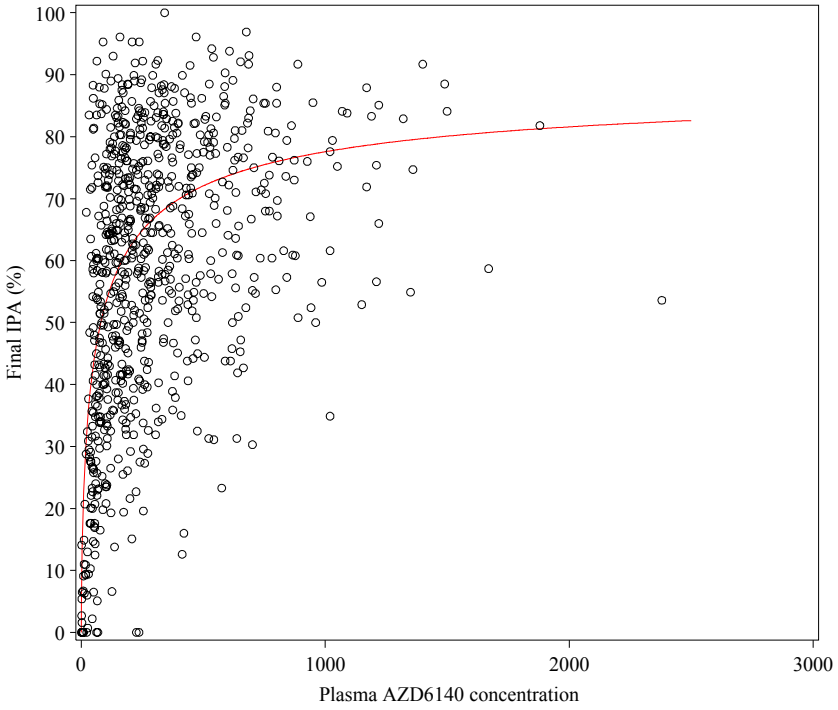
Overall, the mean IPA (final extent) in this study tended to be lower compared to DISPERSE, especially for AZD6140 90 mg bd group and Clopidogrel 75 mg od group, however, the differences in mean IPA (final extent) between AZD6140 90 mg bd group and Clopidogrel 75 mg od group were similar between this study and DISPERSE.

The mean IPA (final extent) in AZD6140 45 mg bd group showed consistently greater mean IPA (final extent) compared to Clopidogrel 75 mg od group in this study, while in DISPERSE, the mean IPA (final extent) in AZD6140 50 mg bd group (corresponding to 45 mg bd in this study) was closer to Clopidogrel 75 mg od group.

Summary of pharmacokinetic/pharmacodynamic relationships

IPA (final extent), IPA (final extent) AUEC, IPA_{max} (final extent) and IPA_{min} (final extent) increased with increasing plasma concentration, AUC_{τ}, C_{max} and C_{min}, respectively, of AZD6140 with indication of E_{max} model exposure-effect relationship.

Figure S1 Scatter plot of plasma concentration of AZD6140 versus IPA (final extent) (%) with prediction curve based on sigmoid Emax model-Japanese Patients [PK and PD analysis set]



Data derived from Section 11.2, Figure 11.2.3.8.1.2

When compared to DISPERSE result, the maximum effect on IPA (final extent) AUEC, IPA_{max} (final extent) and IPA_{min} (final extent) tended to be lower in this study.

Summary of safety results

No adverse events with fatal outcome were reported in this study. There were 3 SAEs reported in the AZD6140 treatment groups. One SAE (gastrointestinal haemorrhage) occurred during treatment period of AZD6140 45 mg bd group resulting in the discontinuation of it. Two patients discontinued the investigational product due to AEs, one in the AZD6140 45 mg bd group above mentioned and the other in the Clopidogrel 75 mg od group (urticaria).

In Japanese sub-population, similar trends in categories of adverse events were found as overall population. Comparing to DISPERSE, the proportion of patients experiencing any adverse events was same or even lower in this study.

The frequency of AEs and bleeding events tended to be higher in AZD6140 90 mg bd group compared to AZD6140 45 mg bd group and Clopidogrel 75 mg od group, however, majority of AEs were mild in intensity and majority of bleeding events were minimal bleeding by PLATO definition except for one gastrointestinal haemorrhage.

Table S5 Number (%) of patients who had at least 1 AE in any category - Japanese and Non-Japanese Asian Patients, Treatment and Follow-Up Period [Safety analysis set]

AE category	Number (%) of patients		
	AZD6140 45 mg bd (n=50)	AZD6140 90 mg bd (n=43)	Clopidogrel 75 mg od (n=46)
Any AE	28 (56.0)	32 (74.4)	22 (47.8)
Any AE with outcome = death	0	0	0
Any SAE (including events with outcome = death)	2 (4.0)	1 (2.3)	0
Any AE leading to discontinuation of IP	1 (2.0)	0	1 (2.2)
Any causally related AE	13 (26.0)	14 (32.6)	8 (17.4)
Any other significant AE	0	0	0
Not bleeding events	20 (40.0)	25 (58.1)	18 (39.1)
Bleeding events	13 (26.0)	17 (39.5)	10 (21.7)
Major bleeding events (DISPERSE definition)	1 (2.0)	0	0
Minor bleeding events (DISPERSE definition)	13 (26.0)	17 (39.5)	10 (21.7)
Major bleeding events (PLATO definition)	1 (2.0)	0	0
Minor bleeding events (PLATO definition)	0	0	0
Minimal bleeding events (PLATO definition)	13 (26.0)	17 (39.5)	10 (21.7)
Mild AE	27 (54.0)	32 (74.4)	22 (47.8)
Moderate AE	3 (6.0)	2 (4.7)	2 (4.3)
Severe AE	0	1 (2.3)	0

Note: Treatment and Follow-Up Period is defined as after first intake of investigational products
Data derived from Section 11.3, Table 11.3.2.1.4

In both the overall population and Japanese sub-population, the most common AE excluding bleeding events were nasopharyngitis and abdominal discomfort. The AEs were distributed among different SOCs and PTs with no specific PT predominating. The number of patients

reported dyspnea in this study was lower than that of DISPERSE study. In the AZD6140 90 mg bd group, 1 Japanese patient reported dyspnea and 2 Philippines patients reported dyspnea exertional.

There were no clinically important changes in haematology, clinical chemistry, urinalysis, vital, 12-lead ECG and Holter ECG for all treatment groups.