AstraZeneca

Drug product:		**SYNOPSIS**	
Drug substance(s):	AZD6140		
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A Double-blind, Double-dummy, Parallel Group Randomised Dose Confirmation and Feasibility Study of AZD6140 + Acetyl Salicylic Acid (ASA) Compared with Clopidogrel + ASA in Patients with Non-ST Segment Elevation Acute Coronary Syndromes - DISPERSE2-TIMI 33

International co-ordinating investigator

Redacted

Study centres

This study was conducted in 153 investigational sites (132 of which enrolled patients) in 14 countries: Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Norway, Poland, Slovakia, South Africa, Spain, United Kingdom and USA.

Publications

None at the time of writing this report.

Study dates

First patient enrolled 03 October 2004

Last patient completed 03 June 2005

Phase of development

Therapeutic exploratory (II)

Objectives and associated variables

Objectives	Variables
Primary objective	**Primary variable**
To assess the safety and tolerability of different doses of AZD6140 in the presence of acetyl salicylic acid (ASA), compared with clopidogrel plus ASA, in patients with non-ST segment elevation ACS	ICAC-adjudicated total bleeding events (excluding minimal) observed within the first 4 weeks of treatment (Day 29).
	Secondary variables
	ICAC-adjudicated total bleeding events (excluding minimal) at Weeks 8 and 12, plus overall bleeding rate using total patient exposure.
	Each individual ICAC-adjudicated bleeding category (excluding minimal), separately.
	Discontinuations due to ICAC-adjudicated bleeding events.
	ICAC-adjudicated bleeding (excluding minimal) associated with coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) vs ICAC-adjudicated bleeding (excluding minimal) not associated with CABG or PCI.
	Number of transfusions, categorised as 1 unit, 2-3 units or ≥4 units associated with ICAC-adjudicated bleeding events.
Secondary objectives	**Secondary variables**
To assess the PD effects of AZD6140 in the presence of ASA compared to clopidogrel plus ASA (in clopidogrel-naïve patients).	IPA_{max}, IPA_{min}, $TIPA_{max}$, $AUEC_{0-12}$ and $AUEC_{0-24}$ for IPA time courses at Weeks 4, 8 and 12 for both final and maximal extent of ADP-induced platelet aggregation.
To compare the platelet aggregation response to AZD6140 on Day 1 in clopidogrel-naïve patients and clopidogrel pre-treated patients.	Final and maximal extent ADP-induced platelet aggregation response over time.
To evaluate the PK of AZD6140 and metabolite AR-C124910XX by evaluation of AZD6140 and metabolite plasma concentrations.	**Clopidogrel-naïve sub-study patients:** C_{max}, C_{min}, C_{av}, t_{max} and AUC_{τ} for AZD6140/AR-C124910XX (Day 1, and Weeks 4, 8 and 12) and AZD6140 steady state CL/F (Weeks 4, 8 and 12).
	Clopidogrel pre-treated sub-study patients: C_{max}, C_{min}, t_{max} and AUC_{τ} for AZD6140 and AR-C124910XX on Day 1.
	All patients: Parameter estimates of population mean PK parameters, covariate effects on population mean PK parameters, inter-subject variability in PK parameters and residual error variability obtained from the population PK modelling analysis.
To evaluate the relationship between AZD6140 PK and platelet aggregation inhibition.	Plots of platelet aggregation inhibition vs AZD6140 and AR-C124910XX concentrations for clopidogrel-naïve sub-study patients; parameter estimates of the relationship between IPA and AZD6140 and AR-C124910XX concentrations.
To evaluate the relationship between AZD6140 and AR-C124910XX exposures and the occurrence of major and minor bleeding.	Plots of major and minor bleeding events vs exposures (concentrations or derived PK parameters) of AZD6140 and AR-C124910XX.
	Parameter estimates of the relationship between the bleeding events and the exposures.
To compare the safety and tolerability of AZD6140 plus ASA with clopidogrel plus ASA	Evaluation of AEs including investigator-assessed bleeding AEs and safety laboratory analyses.
To assess the safety and tolerability of the AZD6140 loading dose	Evaluation of AEs including investigator-assessed bleeding AEs.

Objectives	Variables
To evaluate the effect of AZD6140 on inflammatory markers (CRP, CD40L, MPO, IL-6) and compare changes to those with clopidogrel.	Within-patient change in inflammatory markers from Day 1 to Day 2-4 and Day 29.
Tertiary objectives	**Tertiary variables**
To observe individual and composite incidence of MI (including silent MI), death, stroke and severe recurrent ischaemia; to test operational procedures for endpoint reporting to aid further development of the Phase III programme.	Individual and composite incidence of MI (including silent MI), death, stroke and severe recurrent ischaemia.
To observe the incidence of recurrent ischaemia with AZD6140 plus ASA and clopidogrel plus ASA using total duration of ischaemia.	Total duration of ischaemia defined as ≥1.0 mm ST depression or elevation, measured during continuous Holter monitoring for 4 to 7 days following randomisation.
To measure the HCRU associated with clinical endpoints (MI, death, stroke and severe recurrent ischaemia) and compare between treatment groups.	Hospitalisation data collected if the patient experienced MI, stroke, severe recurrent ischaemia or died.
To measure HCRU associated with major bleeding events and compare between treatment groups.	Hospitalisation data collected if the patient experienced major bleeding.
To explore the use of work productivity measurements and work/activity limitations to describe differences in clinical outcome and work status between treatment groups.	Work Characteristics Questionnaires (WCQ1 and WCQ2), the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH) and the Work Limitations Questionnaire (WLQ).

Bleeding events (excluding minimal bleeds) used in the primary analyses were those as reviewed by an Independent Clinical event Adjudication Committee (ICAC)
CD40L = CD40 ligand; CRP = C-Reactive Protein; HCRU = Health care resource utilisation; IL-6 = interleukin-6; MI = myocardial infarction; MPO = myeloperoxidase;

Study design

A double-blind, double-dummy, parallel group, randomised, multicentre study comparing the safety and tolerability of 2 doses of AZD6140 with clopidogrel (all in combination with ASA) in patients with non-ST segment elevation ACS.

Target patient population and sample size

The target population was patients with documented evidence of non-ST segment elevation ACS in the previous 48 h. It was planned to randomise 990 patients (330 to each treatment arm) into the study, such that approximately 900 patients would complete at least 4 weeks' treatment. No formal sample size calculation was performed since the study was considered exploratory in nature.

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

AZD6140 90 mg bd and 180 mg bd, administered as 90 mg tablets (batch numbers: P6971 to P6978). Placebo to AZD6140 90 mg tablets (batch numbers: P6958, P7006). Half of all patients on each AZD6140 arm also received a loading dose of 270 mg AZD6140. Patients

receiving no loading dose took their standard first dose plus additional placebo tablets to maintain blinding. All patients also received ASA 75-100 mg od with their study drug.

Clopidogrel 75 mg od, administered as encapsulated tablets (capsules) (batch numbers: P7025, P7026). Placebo to clopidogrel capsules (batch number: P7007). All patients allocated to clopidogrel received a 300 mg clopidogrel loading dose, unless the patient was already on a maintenance dose or had received an open-label loading dose of clopidogrel as part of their local clinical care prior to randomisation. An additional 300 mg clopidogrel could be given with the first dose, or within 48 h post-first dose, for patients proceeding to PCI within 48 h after randomisation. All patients also received ASA 75-100 mg od with their study drug.

Blinding was ensured by the provision of 2 tablets bd plus one capsule od for all patients, using a double-dummy design.

Duration of treatment

Either 4, 8 or 12 weeks. All patients were randomised to at least 4 weeks' treatment with some patients continuing to either 8 or 12 weeks' treatment duration. It was planned that 50% patients would be randomised to 12 weeks' treatment, and 25% each to 8 weeks' and 4 weeks' treatment.

Statistical methods

The analysis of the primary variable was exploratory and based on the safety analysis set. Differences between treatment groups in the % of patients reporting at least one centrally adjudicated bleeding event (excluding minimal bleeds) at Week 4 (Day 29) were assessed using Cochran's statistic with Mantel-Haenszel weights, adjusting for the effects of country. The primary analysis investigated the total bleeding event rate within each group regardless of loading doses and other design considerations. The estimates of the treatment group differences and corresponding 95% 2-sided confidence intervals (CI) were used to interpret the assessment of total bleeding events; the CIs were interpreted descriptively and were not adjusted for multiplicity.

Patient population

In total, 1018 patients were enrolled into the study, 990 were randomised and 984 (99%) patients received at least one dose of study drug. Of the patients who received study drug, 190 (19%) withdrew prematurely and 794 (81%) patients completed all visits required by the study protocol. Of the 984 patients who received study drug, 719 (73%) were clopidogrel-naïve and 265 (27%) were clopidogrel pre-treated. A total of 250 (25%) patients were randomised to receive study drug for 4 weeks, 243 (25%) for 8 weeks and 491 (50%) for 12 weeks.

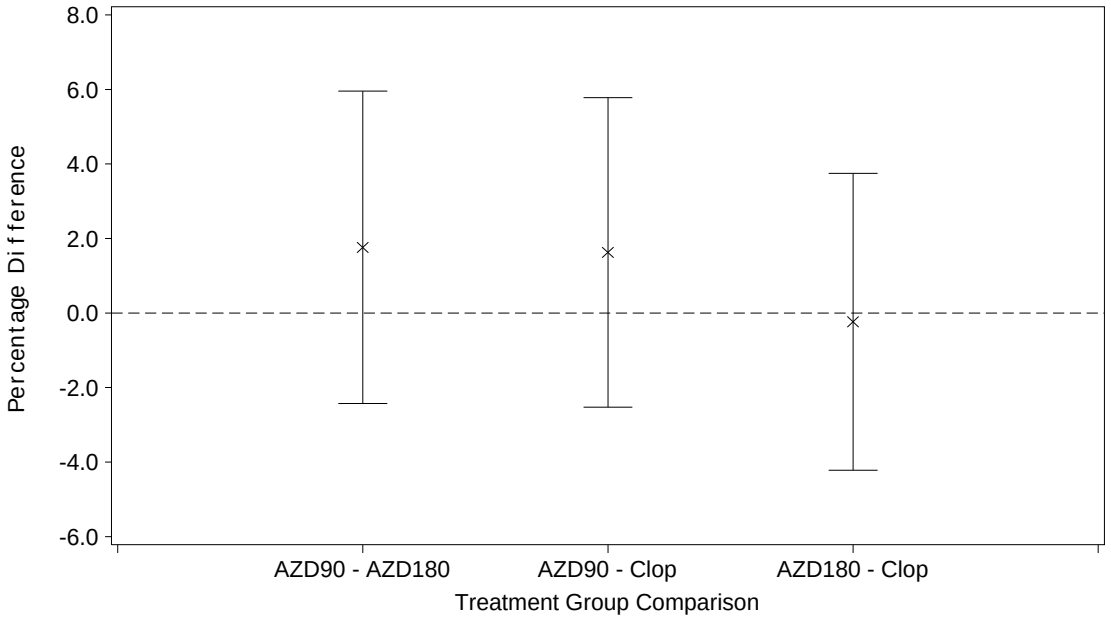
Overall, the treatment groups were similar for disposition, demographics, baseline characteristics, index events, treatment compliance, concomitant medications, diagnostic angiography and revascularisation procedures and were representative of the target population of patients with non-ST segment elevation ACS.

There were more males (64%) than females (36%) in the study, and the highest proportion of patients was Caucasian (94%). The mean age was 63 y (range 30 to 93 y), and the mean weight was 82 kg (range 40 to 150 kg) with body mass index 29 kg/m^2 (range 16 to 61 kg/m^2). The majority of patients' index events were assessed to be non-Q-wave myocardial infarction (59%) or unstable angina pectoris (38%), and the mean time between the start of the index event and first dose was 27.6 h.

Results - Primary objective (ICAC-adjudicated bleeding events)

The ICAC-adjudicated total bleeding event rate (defined as major fatal/life-threatening, major other and minor bleeding events) at Week 4 in the safety analysis set was observed to be similar for the AZD6140 90 mg bd (9.6%), 180 mg bd (7.7%) and clopidogrel 75 mg od (8.0%) groups; however the 95% CIs suggest increases in total bleeding event rate of up to 5.8% in the AZD6140 groups over clopidogrel cannot be ruled out. Treatment group comparisons are presented in Figure S1. The results of the per-protocol analysis supported these findings.

Figure S1 Plot of the percentage difference and 95% confidence intervals between treatment groups in ICAC-adjudicated total bleeding event rate at Week 4 – safety analysis set



The majority of the ICAC-adjudicated total bleeding events were observed during the first 14 days post-first dose of study drug for all treatment groups. The cumulative total bleeding event rate appeared higher for the AZD6140 90 mg bd group over the first 6 weeks than the other 2 groups, but this difference was not maintained over the remainder of the study.

The ICAC-adjudicated bleeding event rates for major fatal/life threatening and major other bleeding events at Week 4 were observed to be similar for all groups. An apparent

dose-related trend towards an increase in minor bleeds was observed: AZD6140 90 mg bd 9 (2.7%), AZD6140 180 mg bd 12 (3.7%) and clopidogrel 75 mg 4 (1.2%) patients. A similar trend was observed for the overall study. Increased reporting of epistaxis in the two AZD6140 groups may account for the apparent increase in minor bleeding events.

Permanent discontinuations from study drug due to ICAC-adjudicated total bleeding events at Week 4 were observed to be similar for the AZD6140 90 mg bd 6 (1.8%), AZD6140 180 mg bd 4 (1.2%) and clopidogrel 75 mg od 3 (0.9%) treatment groups. The majority of bleeds leading to patients discontinuing from the study were major and most occurred within the first 14 days post-first dose of study drug.

ICAC-adjudicated bleeding events associated with PCI or CABG at Week 4 were observed to be similar for the AZD6140 90 mg bd 18 (5.4%), AZD6140 180 mg bd 12 (3.7%) and clopidogrel 75 mg od 19 (5.8%) treatment groups. The majority of events associated with PCI and CABG were major fatal/life-threatening and major other, for all treatment groups, and no trends were observed in the preferred terms reported. Bleeding events not related to CABG or PCI occurred more frequently in the two AZD6140 groups (AZD6140 90 mg bd 14 [4.2%]; AZD6140 180 mg bd 14 [4.3%] than in the clopidogrel 75 mg od group 7 [2.1%]).

There were no apparent differences between the treatment groups in transfusions of haemoglobin products received by patients with ICAC-adjudicated bleeding events.

Efficacy and pharmacodynamic results

(a) ADP-induced platelet aggregation

At Week 4 (steady state), AZD6140 180 mg bd produced greater inhibition of ADP-induced platelet aggregation than clopidogrel 75 mg od: higher mean IPA_{max}, IPA_{12}, $IPAAUEC_{0-12}$ (final extent) were observed for 180 mg bd compared to clopidogrel 75 mg od (IPA_{max} 97% vs 73%, IPA_{12} 90% vs 55%, and $IPAAUEC_{0-12}$ 1150%.h vs 688%.h, respectively). AZD6140 90 mg bd produced an intermediate effect (IPA_{max} 88%, IPA_{12} 77%, and $IPAAUEC_{0-12}$ 928%.h). Similar results were seen at Weeks 8 and 12, although the numbers of patients with available data at these 2 visits were smaller than Week 4.

On Day 1, for AZD6140 90 mg, 180 mg and 270 mg the final extent mean IPA_{max} (81%, 86% and 89%), IPA_{12} (63%, 70% and 79%), and $IPAAUEC_{0-12}$ (708, 787 and 922%.h), was higher than for clopidogrel 300 mg od (IPA_{max} 44%, IPA_{12} 28%, and $IPAAUEC_{0-12}$ 267%.h).

For both clopidogrel-naïve and clopidogrel pre-treated patients on Day 1, all AZD6140 groups had lower mean ADP-induced platelet aggregation than clopidogrel 300 mg (eg, clopidogrel pre-treated: AZD6140 90 mg group 10% to 12% over 12 h; the clopidogrel 300 mg group was higher 27% to 36%). In addition, lower levels of ADP-induced platelet aggregation for a given AZD6140 dose were seen in clopidogrel pre-treated patients than clopidogrel-naïve patients (ie, AZD6140 90 mg had the same aggregation in clopidogrel pre-treated patients [10% to 12% over 12 h] as 270 mg in clopidogrel-naïve patients [9% to 12%]), indicating that AZD6140 confers an additional antiplatelet effect onto clopidogrel pre-treatment.

(b) Inflammatory markers

There were no apparent differences between the treatment groups. CD40L and MPO values changed little during the study. CRP increased in all groups from time of Visit 1 pre-dose to Visit 1 discharge, but had decreased to below Visit 1 pre-dose levels by Week 4 (eg, AZD6140 90 mg pre-dose 18.81 at pre-dose, 31.17 at discharge and 9.48 mg/L at Week 4, respectively). IL-6 decreased in the AZD6140 90 mg bd, AZD6140 180 mg bd and clopidogrel 75 mg groups from Visit 1 (11.7, 12.1 and 9.4 ng/L, respectively) to Week 4 (4.0, 4.1, 3.8 ng/L, respectively).

(c) ICAC-adjudicated clinical endpoints

The majority of clinical endpoints were reported during the first 4 weeks of the study. Overall, there were no clear differences between the treatment groups; however a trend was observed indicating a decrease in MI endpoint events with the AZD6140 groups (clopidogrel 75 mg od 14 [4.3%]; AZD6140 90 mg bd 9 [2.7%] and AZD6140 180 mg bd 7 [2.1%] patients for the overall study). The same trend was observed at Week 4.

(d) Holter monitoring

In total, 24% patients experienced episodes of ischaemia ≥1.0 mm ST depression or elevation on Holter monitoring; there were no apparent differences between the treatment groups. Of those patients who had episodes of ischaemia, the mean total durations were similar across the treatment groups (114 to 122 min).

(e) HCRU and work productivity

There were no meaningful differences between the treatment groups in total length of hospital stay following clinical endpoints.

Following the 12-week treatment period (regardless of the actual length of study drug administration) the majority of patients (65% to 78%) returned to their main job and were working an average of 37 to 40 h per week. The planned retirement age for patients was on average 61 to 63 y, similar to that seen at the time of the index event. There were no major differences between the treatment groups.

Pharmacokinetic results

At Week 4 (steady state), AZD6140 showed a more than dose proportional increase in geometric mean AUC_{τ} (12333 vs 4146 ng.h/mL for 180 mg bd and 90 mg bd, respectively), and an approximately dose proportional increase in geometric mean C_{max} (1339 vs 685 ng/mL for180 mg bd and 90 mg bd, respectively). On Day 1, there was no consistent trend for the geometric mean C_{max} of AZD6140 between clopidogrel-naïve and clopidogrel pre-treated patients across the three doses (455 vs 614 ng/mL for 90 mg, 812 vs 1064 ng/mL for 180 mg, and 1939 vs 1686 ng/mL for 270 mg, respectively). However, the geometric mean C_{max} for AR C124910XX was comparable between the two groups (138 vs 124 ng/mL for 90 mg, 250 vs 235 ng/mL for 180 mg, and 412 vs 347 ng/mL for 270 mg, respectively). The geometric

mean ratios of C_{max} and AUC_{τ} of AR C124910XX over AZD6140 at the steady state visit Week 4 were similar for both the AZD6140 90 mg bd and 180 mg bd doses (C_{max} ratio 0.31 and 0.29 for 90 mg bd and 180 mg bd, respectively, and AUC_{τ} ratio 0.40 and 0.33 for 90 mg bd and 180 mg bd, respectively).

Population PK of AZD6140

The estimated population typical apparent clearance of AZD6140 (CL/F) for a patient weighing 80 kg and without dihydropyridine usage was 14.7 L/h; an extreme body weight or dihydropyridine usage may cause up to 14% change of the typical CL/F. The estimated apparent volume of distribution of the central compartment for AZD6140 (V_2/F) for a patient weighing 80 kg and without a history of congestive heart failure (CHF) was 115 L; an extreme body weight or a history of CHF may cause up to 32% change of the typical V2/F. Relative AZD6140 bioavailability (F_1) increased slightly with dose. The F_1 for the 90 mg and 270 mg doses was estimated to be 88% and 112% of the 180 mg dose, respectively. Age also had an effect on relative bioavailability, with predicted F_1 values for patients aged 40 and 85 y at 74% and 118% of the F_1 for a typical patient aged 65 y. Estimated inter-subject variability for PK parameters was high (>50%CV).

PK/PD

The relationship between IPA and AZD6140 exposure was described using a sigmoid E_{max} model. The estimated population typical AZD6140 concentration necessary to achieve 50% of the maximal IPA (EC_{50}) was 9.1 and 33.1 ng/mL for clopidogrel pre-treated and naïve patients. Age, co-administration of nitrates and sulfonamides were identified to cause several-fold change of the EC_{50}. However, the precision of the EC_{50}, as well as the parameter estimates of the covariate effect on the EC_{50}, was poor and any extrapolation should be done with caution.

There was no meaningful dependence of the probabilities of bleeding characteristics (incidence rate, frequency and severity of bleeding events; total or stratified by the category of bleeding events) on AZD6140 or AR-C124910XX exposure (AUC and C_{max}).

Safety and tolerability results

The overall occurrences of adverse events in any category are presented in Table S1.

During the treatment period 2232 AEs were reported by 700 (71%) of the 984 patients in the safety analysis set. The number of patients reporting any AE was similar for each treatment group, however the total number of AEs in each group was greater in each of the AZD6140 groups than the clopidogrel 75 mg group.

In total, 17 patients died during the study (10 during the treatment period and 7 in follow-up). None of these events with fatal outcome were assessed by the investigator to be causally related to study treatment. During the treatment period 6 patients in the AZD6140 90 mg bd group, 3 patients in the AZD6140 180 mg bd group and 1 patient in the clopidogrel 75 mg group died. During the follow-up period 1 patient died in the AZD6140 90 mg bd group and 3 patients died in each of the AZD6140 180 mg bd and clopidogrel 75 mg groups.

During the treatment period, 146 (15%) patients experienced non-fatal SAEs. Overall, there were fewer patients experiencing non-fatal SAEs in the AZD6140 90 mg bd group (41 [12%]) compared to the AZD6140 180 mg bd (54 [17%]) and clopidogrel 75 mg od (51 [16%]) groups, which were similar. As expected in this patient population, the most common non-fatal SAEs were cardiac disorders, with 18 (5%), 25 (8%) and 20 (6%) patients in the AZD6140 90 mg bd, AZD6140 180 mg bd and clopidogrel 75 mg groups, respectively.

Sixty-three (6%) patients permanently discontinued study drug during the treatment period due to adverse events (DAEs) with 21 (6%), 23 (7%) and 19 (6%) in the AZD6140 90 mg bd, AZD6140 180 mg bd and clopidogrel 75 mg groups, respectively. Other significant adverse events (OAEs) were identified for 35 (4%) patients with 15 (4%) patients and 19 (6%) patients in the AZD6140 90 mg bd and AZD6140 180 mg bd groups, respectively and 1 (0%) patient in the clopidogrel 75 mg group. The most frequently experienced OAEs were anaemia, renal failure and gout (including gouty arthritis and hyperuricaemia).

Patients reporting bleeding-related AEs in all categories other than minimal was similar in each treatment group. The number of patients experiencing minimal bleeds was greater for the AZD6140 90 mg bd and 180 mg bd groups than the clopidogrel 75 mg group.

Table S1 Number (%) patients with an adverse event any category in the treatment period - safety analysis set

Adverse Event[a]	AZD6140 90 mg bd (n= 334)	AZD6140 180 mg bd (n= 323)	Clopidogrel 75 mg od (n= 327)	Total (n=984)
Number of Patients:				
Deaths	6 (2%)	3 (1%)	1 (0%)	10 (1%)
SAE other than deaths	41 (12%)	54 (17%)	51 (16%)	146 (15%)
Discontinued Study Drug due to AE	21 (6%)	23 (7%)	19 (6%)	63 (6%)
Other Significant AE[b]	15 (4%)	19 (6%)	1 (0%)	35 (4%)
Major fatal/life-threatening bleeding AE	4 (1%)	3 (1%)	3 (1%)	10 (1%)
Major other bleeding AE	15 (4%)	13 (4%)	15 (5%)	43 (4%)
Minor bleeding AE	16 (5%)	17 (5%)	10 (3%)	43 (4%)
Minimal bleeding AE	89 (27%)	100 (31%)	70 (21%)	259 (26%)
Any AE	233 (70%)	244 (76%)	223 (68%)	700 (71%)
Total Number of AEs	803	840	589	2232

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

b Patients with OAEs were identified during an unblinded review.

Treatment period - from first administration of study drug to 48 h after the last administration, or until the transition-loading dose is taken in the follow-up period of the study.

The number of patients experiencing non-bleeding AEs in SOCs for gastrointestinal disorders, respiratory, thoracic and mediastinal disorders, psychiatric and vascular disorders was greater in each of the AZD6140 groups compared to the clopidogrel 75 mg group. In the AZD6140 90 mg bd and 180 mg bd groups the number of patients experiencing *nausea* was 22 (7%) and 21 (7%), greater than clopidogrel 75 mg with 11 (3%) patients. There was also increased

reporting of *vomiting* in each of the AZD6140 groups. In the AZD6140 180 mg bd group, *diarrhoea* was reported by 24 (7%) patients; approximately double that seen in each of the AZD6140 90 mg bd and clopidogrel 75 mg groups. The number of patients who experienced the sensation of shortness of breath in terms associated with dyspnoea in the AZD6140 90 mg bd and 180 mg bd groups, was 35 (10%) and 51 (16%), respectively and greater than clopidogrel 75 mg with 21 (6%) patients.

There were no remarkable changes in haematology and clinical chemistry values during the study apart from a modest increase in mean serum uric acid in the AZD6140 groups.

There were no apparent differences between treatment groups in physical examination findings, vital signs data or cardiopulmonary assessments at baseline. There were no apparent differences between the treatment groups in transfusions of haemoglobin products received and procedures and operations during the study.

Conclusions

- Redacted

Date of the report

12 October 2005