AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0837
Study Code	D1250C00042
Edition Number	1
Date	21 January 2010

Long-term treatment with the oral direct thrombin inhibitor AZD0837, compared to Vitamin-K antagonists, as stroke prevention in patients with non-valvular atrial fibrillation and one or more risk factors for stroke and systemic embolic events. A 5-year follow-up study

Study dates:

First patient enrolled: 25 October 2007
Last patient completed: 20 May 2009
Date of early study termination: 20 May 2009*
* Due to a limitation identified in long-term stability of the AZD0837 drug product, the study was prematurely closed with a maximum exposure of up to 22 months (including treatment duration in study D1250C00008).

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)

This was an international, multi-centre study carried out in 70 centres in Austria, Denmark, Hungary, Norway, Poland, Russia and Sweden.

Publications

For full references, see Clinical Study Report (CSR) Section 10 List of references.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate safety and tolerability of long-term treatment with AZD0837 compared to VKA in patients with atrial fibrillation (AF) and a moderate to high risk of stroke and systemic embolic events (SEE).	Adverse events, bleeding, laboratory safety values, physical examination, ECG and vital signs.	Safety
Secondary	**Secondary**	
To evaluate the pharmacokinetics of AZD0837, the intermediary metabolite (AR-H069927XX) and the active form (AR-H067637XX) with special regard to the variability.	Drug plasma concentration of AZD0837, AR-H069927XX and AR-H067637XX.	Pharmacokinetic
To evaluate the effect of AZD0837 on D-dimer levels compared to VKA in patients with AF and a moderate to high risk of stroke and SEE.	D-dimer levels	Pharmacodynamic
To evaluate the effect of AZD0837 on activated partial thromboplastin time (APTT) and ecarin clotting time (ECT) in patients with AF and a moderate to high risk of stroke and SEE.	APTT, ECT	Pharmacodynamic
To evaluate anticoagulation-related quality of life and satisfaction among patients given AZD0837 compared to patients given VKA agents.	Overall DASS score, negative impacts of anticoagulation and positive psychological impact score.	PRO*
To evaluate general treatment satisfaction with AZD0837 compared to VKA agents.	TSQM including Effectiveness, Side effects, Convenience and Global satisfaction.	PRO*

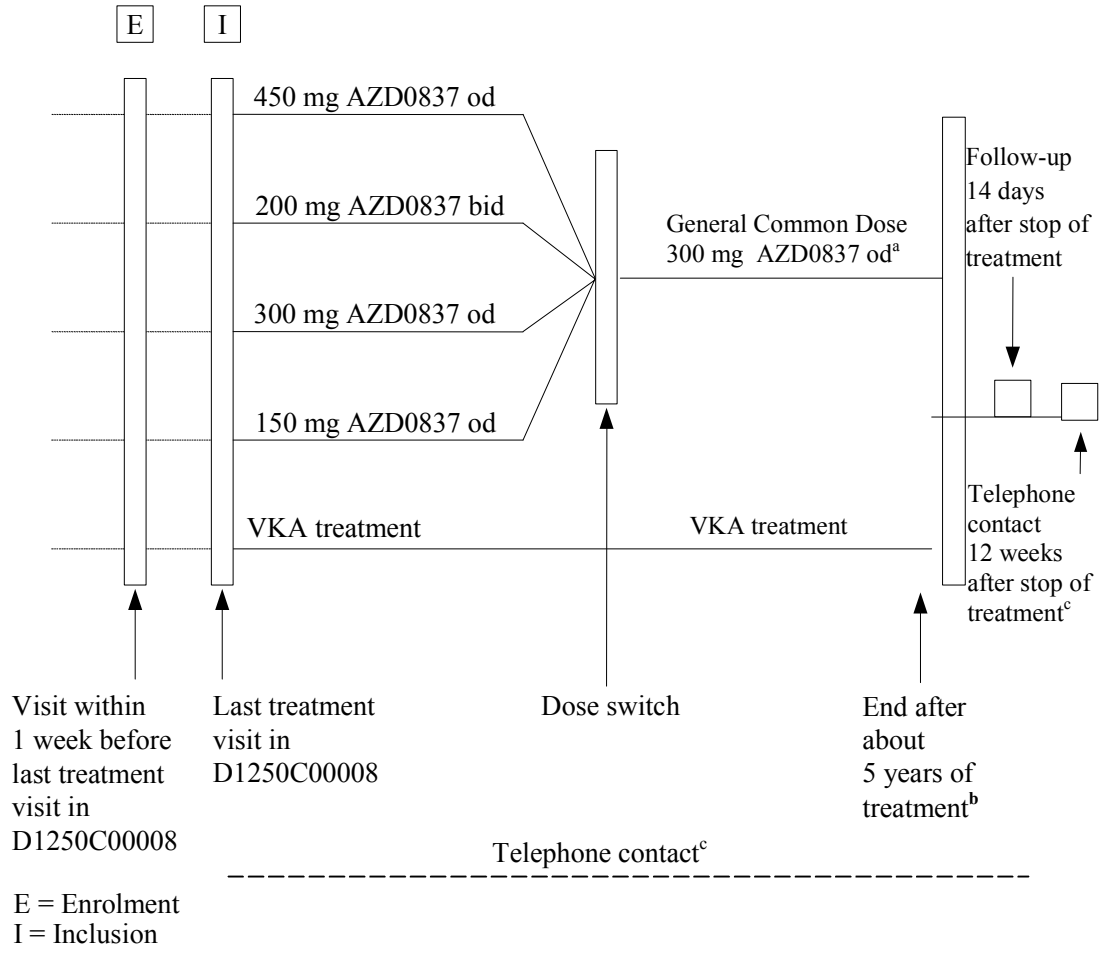
*PRO: Patient Reported Outcome

Study design

A multi-centre, randomised, parallel group study to evaluate safety and tolerability of treatment with AZD0837 in relation to treatment with Vitamin-K antagonist (VKA), aiming

for INR 2 to 3, as stroke prevention in patients with non-valvular atrial fibrillation (AF) and one or more risk factors for stroke and SEE. This study was a direct continuation of study D1250C00008. The study design is presented in Figure S1 below:

Figure S1 Flow Chart of Study Design



a Three patients switched to 450 mg od, 6 patients to 150 mg od, based on individual plasma concentrations.
b Due to a limitation identified in long-term stability of the drug product, the study was prematurely discontinued with a mean exposure of 515 days (including treatment duration in study D1250C00008).
c Telephone contact (TC) for all patients who prematurely discontinued study. AstraZeneca chose to prematurely terminate the study and all patients were considered prematurely discontinued.

The first part of the study was blinded and the AZD0837 patients were to continue on the same daily dose as administered in study D1250C00008 (ie, either 150 mg AZD0837 once daily [od], 300 mg AZD0837 od, 450 mg AZD0837 od, 200 mg AZD0837 twice daily [bd]). VKA patients were to continue on VKA treatment titrated to INR 2.0 to 3.0 with a target value of 2.5. The second part of this study was open and it started as soon as the results from study D1250C00008 had been analysed. A standard dose for AZD0837 treatment was selected, from here on referred to as the General Common Dose (GCD). 300 mg od was chosen, on which

most patients were estimated to be within the intended therapeutic drug plasma concentration interval. All AZD0837 patients were switched to GCD except for a few patients who were switched to 150 mg od or 450 mg od, based on their individual pharmacokinetic (PK) data. In conjunction with the dose switch a new, slightly modified extended release (ER) 150 mg tablet was used. To confirm that the bioavailability of the new ER formulation was the same as for the old, additional PK samplings were carried out in a patient cohort.

Target patient population and sample size

A maximum of 600 patients with paroxysmal, persistent or permanent non-valvular AF and at least one additional risk factor for stroke and SEE, and who had participated in study D1250C00008 for 3 to 9 months, could continue directly into study D1250C00042. However, due to a shortage in drug supply of AZD0837 and given the limited time interval for inclusion into study D1250C00042 as there was to be no wash out following study D1250C00008, fewer patients (in total 523) were included in study D1250C00042 (288 on AZD0837 and 235 on VKA). The patients continued on the same treatment regimen as in study D1250C00008. All patients had fulfilled the inclusion criteria in study D1250C00008 as well as completed the entire study treatment period without safety concerns regarding continued treatment, as assessed by the investigator.

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

AZD0837 ER besylate tablets 150 mg, 200 mg and matching placebos administered orally in four different doses; 450 mg od, 200 mg bd, 300 mg od and 150 mg od. Two ER besylate tablets 150 mg od were given after the dose switch as the GCD. In conjunction with the dose switch a new, slightly modified ER 150 mg tablet was used. The dosage form is presented as ER tablets which is an equivalent term to the European standard term Prolonged-Release (PR) tablets.

Fourteen batches of AZD0837 were used in this study (including placebo). Individual batch numbers and further information are included in the CSR.

Comparator: Open label oral VKA (warfarin, phenprocoumon, acenocoumarol) supplied by AstraZeneca and individually dosed, aiming for an INR of 2.0 to 3.0 with a target value of 2.5.

Duration of treatment

Study treatment was planned to continue for up to 5 years, but the study was stopped prematurely due to tablet shelf life stability problems. The mean exposure duration from 1st dose to last dose of intake of study drug was 515 days (including treatment duration in D1250C00008).

Statistical methods

The long-term safety and tolerability of AZD0837 in patients with AF was assessed with VKA as a reference. The baseline value was defined as the closest observation prior to the administration of the first dose of study drug. In most cases this was data from visit 2

(randomisation visit) in study D1250C00008. Hence, most presentations of data account for the period from start of study D1250C00008 to end of study D1250C00042.

Safety data and safety laboratory data were analysed by descriptive statistics. The latter was also depicted graphically, where appropriate.

Pharmacodynamic measurements and variables (D-dimer, APTT and ECT) were described with descriptive statistics and, where appropriate, depicted graphically over time by treatment.

PK measurements and variables were analysed by descriptive statistics and depicted graphically with box plots. Variability was evaluated using a mixed-effect model.

Patient reported outcome (PRO)[1] was not collected in study D1250C00008 and hence presented from start of study D1250C00042. Assessment of PRO was presented using descriptive statistics. Analysis of PRO was purely exploratory.

Patient population

Of the 949 patients who received treatment in study D1250C00008, 528 (55.6%) patients continued into this study (288 on AZD0837 and 235 on VKA) at 70 centres in 7 countries (see Table S2). The number of patients who could continue was restricted due to a limitation of drug supply of AZD0837. Five patients (4 in the AZD0837 group and 1 in the VKA group) discontinued before inclusion.

Following study inclusion, 126 patients (24.1%) discontinued the study prior to dose switch (see CSR Section 6.1 for further details), the majority as a result of early study closure in Hungary. Following the dose-switch, 397 (75.9%) patients discontinued the study, of which 374 (71.5%) patients as a result of early study closure initiated by AstraZeneca.

The randomised analysis set, safety analysis set and full analysis set were identical and included 523 patients.

Table S2 Patient disposition (D1250C00042)

	Number (%) of patients		
	AZD0837	**VKA**	**Total**
Patients enrolled			528
Patients who received treatment	288 (100)	235 (100)	523 (100)
Patients who discontinued study before dose switch	79 (27.4)	47 (20.0)	126 (24.1)
- Adverse Event	8 (2.8)	2 (0.9)	10 (1.9)
- Development of Study-Specific Discontinuation Criteria	2 (0.7)	1 (0.4)	3 (0.6)
- Voluntary Discontinuation by Subject	4 (1.4)	0 (0.0)	4 (0.8)

[1] Patient reported outcomes or PRO is an umbrella term referring to measurement of any aspect of a patient's health status that comes directly from the patient. It provides means for measuring treatment benefits by capturing how a patient feels or function in relation to his or her health or condition.

	Number (%) of patients		
	AZD0837	**VKA**	**Total**
- Severe Non-Compliance to Protocol	0 (0.0)	1 (0.4)	1 (0.2)
- AZ study closure	60 (20.8)	40 (17.0)	100 (19.1)
- Other	5 (1.7)	3 (1.3)	8 (1.5)
Patients who discontinued study after dose switch	209 (72.6)	188 (80.0)	397 (75.9)
- Adverse Event	10 (3.5)	5 (2.1)	15 (2.9)
- Development of Study-Specific Discontinuation Criteria	0 (0.0)	1 (0.4)	1 (0.2)
- Voluntary Discontinuation by Subject	1 (0.3)	2 (0.9)	3 (0.6)
- Severe Non-Compliance to Protocol	0 (0.0)	1 (0.4)	1 (0.2)
- Reason for discontinuation is missing	0 (0.0)	1 (0.4)	1 (0.2)
- AZ study closure	196 (68.1)	178 (75.7)	374 (71.5)
- Other	2 (0.7)	0 (0.0)	2 (0.4)

Bookmark: BeLONG_PAT_DISP2 Version: 14DEC2009 14:33 (knqp334)

The baseline characteristics of the study population indicated a moderate to high risk population, and resembled those of the target population in terms of current medical histories, presence of other risk factors for stroke/TIA and SEE in addition to AF, and concomitant medication usage. The AZD0837 and VKA group were quite well balanced with regard to demographic and patient characteristics. However, in the AZD0837 group there were a higher proportion of patients 75 years or over as well as a higher proportion of patients with previous stroke, TIA, SEE and venous thrombosis, while in the VKA group there were higher proportions of patients with diabetes mellitus and cardiac failure. The treatment compliance with the prescribed study drug was high. Overall frequency of protocol deviations was low. Due to the somewhat different patient characteristics, and also with a possible selection bias from study D1250C00008 in mind, interpretation of results should be made with caution. In addition, after the end of study treatment, the patients on AZD0837 were transferred to the local standard treatment while the VKA group could continue on the same regimen and thus without risk of interruption in anticoagulation.

Summary of efficacy results

Patient reported outcome (PRO) was assessed as an exploratory variable. Anticoagulation related quality of life and treatment satisfaction was explored and evaluated in AF patients using the Duke Anticoagulation Satisfaction Scale (DASS) and the Treatment Satisfaction Questionnaire for Medication (TSQM). Lower DASS scores were achieved in the AZD0837 group possibly indicating greater anticoagulation treatment satisfaction compared to the VKA group. Similar TSQM scores were achieved for both treatment groups.

Summary of pharmacokinetic results

For all dose groups, the plasma concentrations of AR-H067637XX appeared to be stable over time, ie, no obvious time-dependent changes. Following the dose switch to the GCD of 300 mg od, the expected dose-dependent changes in exposure were achieved. For the dose group receiving 300 mg, the exposure after dose switch appeared to be slightly lower for the new ER formulation compared to the old ER formulation, which was similar to the observation in the cohort of patients undertaking extra PK sampling.

The between patient variability was moderate. The estimate of within patient variability is uncertain given the available data of a single sampling time (2 to 3 hours post dose) at only two visits for the GCD.

Summary of pharmacodynamic results

Median D-dimer levels in the AZD0837 groups were generally below the upper limit of normal (ULN) of 130 ng/mL. Similar or slightly lower median levels were achieved for patients receiving VKA.

The mean APTT on treatment was prolonged compared to baseline for all dose levels. No patient in this study had an APTT >3xULN, the predefined safety limit for changing to open label AZD0837 150 mg od or discontinuation of the study drug. The mean ECT on treatment was prolonged for all AZD0837 groups compared to baseline with higher levels at increasing daily dose of AZD0837.

Summary of pharmacokinetic/pharmacodynamic relationships

APTT showed a lower correlation than the more sensitive ECT, with a close correlation, to the plasma concentration of AR-H067637XX.

Summary of safety results

288 patients were exposed to AZD0837 in this study and 235 received VKA during the treatment period. The mean exposure duration from 1st dose to last dose of intake for AZD0837 and VKA was 511 and 519 days, respectively, including treatment duration in study D1250C00008.

Overall, treatment was well tolerated, with a somewhat lower proportion of patients with any adverse event (AE) in the AZD0837 group compared to VKA (Table S3). There was a similar proportion of patients with SAE in both treatment groups. Compared to the VKA group, premature discontinuation of treatment with study drug due to AE (DAE) was higher in the AZD0837 group.

Table S3 Number (%) of patients with at least 1 new onset AE in any category on treatment (safety analysis set; D1250C00008 / D1250C00042)

Category[a]	AZD0837	VKA
No. of patients	288	235
Any AE	208 (72.2)	183 (77.9)
Any AE with outcome = death[b]	5 (1.7)	3 (1.3)
Any SAE (incl. AE with outcome = death)	73 (25.3)	61 (26.0)
Any AE leading to discont. of treatment	20 (6.9)	4 (1.7)
Any other significant AE[c]	0 (0.0)	0 (0.0)

Bookmark: BeLONG_FTAB_AE_SUMMARY Version: 29OCT2009 08:53 (knqp334)

[a] Patients with multiple events in one category are counted once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Three AEs with outcome = death starts on treatment, but patients dies during the follow up. These AEs are counted during treatment period.

[c] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as Other Significant AEs (OAEs)

The four most common AE in the AZD0837 group were diarrhoea (12.8% in the AZD0837 group compared to 8.1% in the VKA group) followed by nasopharyngitis (12.2% in the AZD0837 group compared to 12.8% in the VKA group), oedema peripheral (8.7% in the AZD0837 group compared to 8.5% in the VKA group) and dizziness (8.7% in the AZD0837 group compared to 7.2% in the VKA group). Flatulence (6.9% compared to 0.4%) was more common in the AZD0837 group compared to VKA.

Overall, few cerebrovascular thromboembolic events (stroke/TIA) and SEE were reported on treatment (1.7% of patients in the AZD0837 group compared to 1.3% of patients in the VKA group). During the 2 week follow-up period, at which time patients were to receive local standard treatment, the proportion of patients with these diagnoses were 1.4% in the AZD0837 group compared to 1.3% in the VKA group. One venous thrombosis event was reported in the AZD0837 group (a subclavian thrombosis following local haematoma). No myocardial infarctions were reported on treatment.

The proportion of patients with any bleeding event was lower in the AZD0837 group compared to VKA. There was 1 major bleeding event on treatment in patients randomised to AZD0837 compared to 9 major bleeding events on treatment in patients randomised to VKA.

For renal and urinary disorders, hepatobiliary disorders and cardiac related events no major differences were found in the AZD0837 group compared to VKA.

Thirteen patients died during the study up to and including the TC follow-up. In the AZD0837 treatment group 9 patients died: AE with onset on treatment led to death in 3 patients on treatment and to 2 deaths after stopping AZD0837 (5 patients in Table S3). In addition, another 4 patients died during the follow-up period, of which 2 were reported dead at TC follow-up. In the VKA group 4 patients died: AE with onset on treatment led to death in 2 patients on treatment and 1 death in the follow-up period after VKA study treatment (3 patients in Table S3). One patient in the VKA group was reported dead at TC follow-up. Note, at stop of study treatment patients on VKA continued on local VKA while the AZD0837 patients had a switch period where treatment with VKA was started.

S-creatinine increased in the AZD0837 group (a mean change from baseline of 5% to 10% was observed in this study). This observation is similar to results in previous studies. The mean value returned towards baseline by follow-up visit, approximately 2 weeks post-treatment. No consistent change in mean s-cystatin C was observed further indicating that the reversible increase in s-creatinine is not due to a reduced glomerular filtration rate.

For all liver function tests, the mean values were similar and only showed minor variations over time for both AZD0837 and VKA treatment groups. The proportion of patients with ALAT ≥3xULN were 9 of 288 (3.1%) for AZD0837 treated compared to 6 (7 if considering local laboratory results) of 235 (2.6%/3.0%) for VKA treated. Several of these patients

reported concurrent diagnoses known to be associated with increased liver enzyme tests. Two patients had combined ALAT ≥3x ULN and bilirubin ≥2xULN: 1 patient with pancreatic cancer after AZD0837 treatment and 1 patient onVKA treatment with cholestatic jaundice due to biliary stricture (the elevations were documented in local laboratory results only).

ECG, vital signs and physical examination did not show any pattern of an AZD0837 long-term drug related effect.