Drug substance(s):	AZD0837	**SYNOPSIS**	(For national authority use only)
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A Controlled, Randomised, Parallel, Multicentre Study to Assess Safety and Tolerability of the Oral Direct Thrombin Inhibitor AZD0837 in the Prevention of Stroke and other Thromboembolic Complications Associated with Atrial Fibrillation

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Study centre(s)

The study was performed in Denmark, Norway and Sweden at 20 sites.

Publications

None at the time of the finalisation of this report.

Study dates		**Phase of development**
First patient enrolled	9 September 2004	Therapeutic exploratory (II)
Last patient completed	4 August 2005	

Objectives

Primary:

To evaluate safety and tolerability of two different doses of AZD0837 in relation to warfarin during three months of treatment in atrial fibrillation patients with moderately increased risk of stroke.

Secondary:

To evaluate the pharmacokinetics of the active form of AZD0837 (AR-H067637XX) with special regard to variability in the patient population.

To evaluate the pharmacodynamics of AZD0837 in the patient population.

Study design

This was a controlled multicentre, randomised, parallel group study to evaluate safety and tolerability of AZD0837 in relation to warfarin during 3 months of treatment, in atrial fibrillation patients with moderately increased risk of stroke. AZD0837, 150 mg or 350 mg, was given twice daily in a blind fashion regarding doses and the warfarin group was given warfarin in an open fashion aiming for an international normalised ratio of 2.0-3.0.

Target patient population and sample size

The patient population included in the study was atrial fibrillation patients with moderately increased risk of stroke. In total 250 patients were randomised to treatment.

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

Oral immediate release AZD0837 tablets of 50 mg, formulation number [redacted], and matching placebo, formulation number [redacted], were used in the study. Warfarin (Waran®) 2.5 mg tablets for oral administration, formulation number [redacted], were used as comparator and were supplied in commercial bottles of 100 tablets.

Duration of treatment

Patients were to be treated for a maximum of 90 days.

Criteria for evaluation (main variables)

Efficacy/pharmacodynamic and pharmacokinetics

Activated partial thromboplastin time (APTT), Thrombin time (TCT), Endogenous thrombin potential (ETP), D-dimer and Pro-thrombin fragment I-II, explorative proteomic profiling in protein pattern were the main pharmacodynamic variables. Main variable for the pharmacokinetic part of the study was AUC of AR-H067637XX.

Safety

Adverse events including bleeding events with prespecified classification, electrocardiogram, vital signs defined as blood pressure and pulse rate, laboratory values and physical examination.

Statistical methods

No statistics hypotheses were pre-specified for the primary and secondary objectives of this study. This study was evaluated mainly using summary and descriptive statistics, presented in tables and graphical displays. Treatment effect on pharmacodynamic markers was exploratively evaluated using an analysis of variance approach, the relationship between pharmacodynamic markers and exposure was explored using both linear and nonparametric methods.

Patient population

The study patients had atrial fibrillation with at least one additional risk factor for stroke. They were predominately male and about one third was more than 75 years old. Co-medication was frequently used. Patients who discontinued study treatment generally switched to, alternatively remained on, warfarin treatment.

Table S1 Patient population and disposition

		AZD0837 150 mg	AZD0837 350 mg	Warfarin	Total
Population					
N randomised (N planned)		82 (75-90)	85 (75-90)	83 (75-90)	250 (225-270)
Demographic characteristics					
Sex (n and % of patients)	Male	64 (78%)	71 (84%)	60 (72%)	195 (78%)
	Female	18 (22%)	14 (16%)	23 (28%)	55 (22%)
Age (years)	Mean (SD)	71 (6.9)	71 (6.8)	71 (7.2)	
	Range	55 to 86	56 to 85	46 to 82	46 to 86
Race (n and % of patients)	Caucasian	82 (100%)	85 (100%)	83 (100%)	250 (100%)
Baseline characteristics					
Mean number of risk factors for stroke in addition to atrial fibrillation		1.8	2.1	1.9	1.9
Disposition					
N (%) of patients who	Completed	81 (99%)	78 (92%)	81 (98%)	240 (96%)
	discontinued	1 (1%)	7 (8%)	2 (2%)	10 (4%)
N analysed for safety[a]		82	85	82	249
N analysed for efficacy (Full analysis set)		82	85	83	250

a Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

Pharmacodynamic and pharmacokinetic results

The assays APTT, TCT and ETP showed a dose- and concentration-dependent response to AZD0837. For APTT, sampling at 2 hours after drug intake, ie, at the approximate time for peak values of the active metabolite AR-H067637XX, resulted in mean APTT values of 54 seconds and 63 seconds for AZD0837 150 mg bid and 350 mg bid, respectively (reference range 25 to 40s). The differences between mean values 2 hours after morning dose and before dose were approximately 7 seconds and 12 seconds for AZD0837 150 mg bid and 350 mg bid, respectively.

Comparisons with warfarin were made for EPT, D-dimer and prothrombin fragment 1+2. Mean ETP peak height values were similar for warfarin and AZD0837 350 mg groups at time points for AR-H067637XX trough. However, at other time points relative to drug intake, AZD0837 350 mg bid seems to have a more pronounced effect on ETP peak height compared to warfarin titrated to INR 2-3. AZD0837 150 mg bid had less effect on mean ETP peak height compared to warfarin.

Mean D-dimer and pro-thrombin fragment 1+2 values were generally low and stable in all treatment groups without any remarkable differences.

The inter-individual variability, in terms of relative standard deviation, was 26%, 35% and 27% for the oral clearance of AR-H067637XX, AR-H069927XX and AZD0837, respectively. The pharmacokinetics of AZD0837 were linear in the present analysis. However, AR-H067637XX, and AR-H069927XX showed dose-dependent pharmacokinetics with a less than dose proportional increase in AUC_{τ} at the high dose as compared to the low dose. Creatinine clearance was a predictive covariate for oral clearance for AR-H067637XX, AR-H069927XX and AZD0837. The estimated covariate effects predict an approximately two-fold difference in AUC_{τ} between an individual having the highest observed CrCL as compared to an individual having the lowest observed CrCL. There was no indication that any of the concomitantly administered drugs strongly influenced the oral clearance of AR-H067637XX, the most profound effect observed was a decrease of AR-H067637XX oral clearance of 19% (mean) when verapamil was co-administered with AZD0837. A statistically significant difference (for multiplicity unadjusted p-value <0.05) in AUC_{τ} of the active metabolite AR-H067637XX between MDR1 genotypes was observed.

Safety results

The tolerability of the lower dose of AZD0837, 150 mg bid, as judged by the treatment discontinuations, was comparable to that of warfarin and better than that of AZD0837 350 mg bid.

AZD0837 treatment groups had a reversible mean increase from baseline in S-creatinine values of approximately 10%. The increase had appeared at the first visit post randomisation and remained unchanged as long as the patients were on treatment. The mean value had returned to baseline on the follow-up visit. The shift from baseline appeared to be rather uniform with no particular outliers. There were no particular findings in urine lab variables or in AE reports within the system organ class Renal and urinary disorders in the study.

There was an uneven distribution of patients with serious adverse events (SAEs) within the SOC (system organ class) Cardiac disorders. Six (7.1%) cardiac related SAEs (all with different diagnoses) were reported in the AZD0837 350 mg bid treatment group, 1 (1.2%) in the AZD0837 150 mg bid group and none in the control (warfarin) group.

AEs within the SOC Gastrointestinal disorders were most common. A total of 33% of the patients in the AZD0837 groups reported AEs within the SOC Gastrointestinal disorders, as compared to 16% in the warfarin group. The most frequently reported events within this SOC was diarrhoea.

The number of patients reporting any AEs was similar in all treatment groups, but the number of events per patient was higher in the AZD0837 350 mg group. There were more patients with SAEs and discontinuations due to AEs in the AZD0837 350 mg group than in the other two treatment groups. One patient, randomised to AZD0837 350 mg bid, died during the study after drug stop. There were no apparent differences with regard to the very few major bleeding

events or clinically relevant minor bleeding events. Minimal bleeding events tended to be more frequent among patients treated with AZD0837 350 mg bid.

S-ALAT elevations >3x upper limit of normal were few and with no apparent differences between treatment groups. A total of 3 such events (1.8%) occurred among AZD0837 patients, all were transient. Elevations above lower cut-offs tended to be more common with AZD0837 350 mg than with the other treatments. There was no apparent difference between AZD0837 150 mg and warfarin in this regard.

There were no safety signals detected from vital signs, ECGs or physical examinations.

AEs, SAEs and Cardiac disorder SAEs seem to be more frequent among patients whose AUC_{τ} for either of AR-H067637XX, AR-H069927XX or AZD0837 was in the 4th quartile as compared to patients with AUC_{τ} in the 1st to 3rd quartiles. Bleeding event frequency seems to increase as AUC_{τ} for either of AR-H067637XX, AR-H069927XX or AZD0837 increases from the 2nd quartile to the 4th quartile.

Table S2 Number of patients who had at least one AE on study treatment in any category and total numbers of adverse events (Safety analysis set)

Category of adverse event	Number (%) of patients[a]		
	AZD0837 150mg (n=82)	AZD0837 350mg (n=85)	Warfarin (n=82)
Any AE	57 (69.5)	64 (75.3)	57 (69.5)
Any SAEs with outcome = death	0 (0.0)	1 (1.2)	0 (0.0)
Any SAE	5 (6.1)	13 (15.3)	4 (4.9)
Any AE leading to discontinuation of IP	4 (4.9)	11 (12.9)	1 (1.2)
Any AE leading to discontinuation from study	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to temporary discontinuation of IP	3 (3.7)	8 (9.4)	5 (6.1)
	Total number of adverse events[b]		
Adverse events	133	184	132
Serious adverse events	5	18	4
Other significant adverse events	0	0	0

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 Multiple events in the same category are counted only once in that category (i.e. multiple AEs within one patient and preferred term are counted only once). Patients with events in more than one category are counted once in each of those categories.

Table S3 Number (%) of patients with the most commonly reported adverse events (Safety analysis set)

Preferred term[b]	Number (%) of patients			
	AZD0837 150mg (n=82)	AZD0837 350mg (n=85)	Warfarin (n=82)	Total (n=249)
Patients with any AE[a]	57 (69.5)	64 (75.3)	57 (69.5)	178 (71.5)
Dizziness	9 (11.0)	12 (14.1)	6 (7.3)	27 (10.8)
Diarrhoea	10 (12.2)	11 (12.9)	5 (6.1)	26 (10.4)
Dyspnoea	4 (4.9)	6 (7.1)	7 (8.5)	17 (6.8)
Nasopharyngitis	6 (7.3)	5 (5.9)	6 (7.3)	17 (6.8)
Nausea	4 (4.9)	6 (7.1)	3 (3.7)	13 (5.2)
Flatulence	2 (2.4)	5 (5.9)	0 (0.0)	7 (2.8)
Epistaxis	1 (1.2)	5 (5.9)	3 (3.7)	9 (3.6)
Headache	3 (3.7)	4 (4.7)	4 (4.9)	11 (4.4)
Fatigue	2 (2.4)	4 (4.7)	4 (4.9)	10 (4.0)
Pruritus	4 (4.9)	1 (1.2)	0 (0.0)	5 (2.0)
Gastroenteritis	3 (3.7)	1 (1.2)	4 (4.9)	8 (3.2)
Arthralgia	1 (1.2)	1 (1.2)	4 (4.9)	6 (2.4)
Back pain	0 (0.0)	4 (4.7)	4 (4.9)	8 (3.2)
Bronchitis	4 (4.9)	0 (0.0)	3 (3.7)	7 (2.8)
Pneumonia	1 (1.2)	4 (4.7)	2 (2.4)	7 (2.8)
Rash	1 (1.2)	4 (4.7)	2 (2.4)	7 (2.8)
Depression	0 (0.0)	4 (4.7)	1 (1.2)	5 (2.0)
Rectal haemorrhage	0 (0.0)	4 (4.7)	0 (0.0)	4 (1.6)

a All preferred terms

b Preferred terms with a frequency of ≥4% in at least one treatment group (Sorted by decreasing order of frequency as summarised over all treatment groups).

Conclusions

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- [redacted]

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