Drug substance(s):	AZD0837	**SYNOPSIS**	
Study code:	D1250C00008		
Date:	16 June 2009		

A Controlled, Randomized, Parallel, Multicentre Study to Assess Safety and Tolerability of the Oral Direct Thrombin Inhibitor AZD0837, given as an Extended-release Formulation, in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation

Study centre(s)

In total, 95 centres in 9 countries (Austria, Denmark, Hungary, Ireland, Norway, Poland; Russia, Sweden, United Kingdom) recruited patients into this study.

Publications

The oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with atrial fibrillation: A phase II randomised dose-guiding, safety and tolerability study, Lip GY, et al (2009) J Am Coll Cardiol 2009;53 (10, suppl 1):A430.

Study dates		**Phase of development**
First patient enrolled	20 February 2007	Therapeutic exploratory (II)
Last patient completed	5 June 2008	

Objectives

Primary:
To provide dose-guiding information through evaluation of safety and tolerability of four dosing regimens of AZD0837 in relation to Vitamin-K antagonist (VKA) treatment in atrial fibrillation (AF) patients with moderate to high risk of stroke.

Secondary:

1. To evaluate the pharmacokinetics (PK) of the active form of AZD0837 (AR-H067637XX) with special regard to:

   - Evaluation of the influence of concomitant medications on the PK variables of AR-H067637XX in plasma with special regards to estimated systemic exposure
   - Assessment of the relationship between systemic plasma exposure of AR-H067637XX and clinical events (AEs)

2. To evaluate the pharmacodynamic (PD) properties of AZD0837 in the patient population.

3. To evaluate the influence of a genetic variant (C3435T) of the ABCB1 (previously termed MDR1) gene, coding for the drug transporter P-glycoprotein (P-gp), on PK parameters of AZD0837 and/or its metabolites. To collect and store DNA, for future retrospective research into genes that may influence therapeutic response of AZD0837 and VKA. Appropriate informed consent was obtained before genetic blood sampling.

Study design

A multi-centre, randomised, parallel-group study to evaluate safety and tolerability of AZD0837 in relation to VKA (aiming for an INR of 2.0 to 3.0) during treatment in AF patients with moderate to high risk of stroke. Patients were to be randomised into 5 parallel groups; 4 groups receiving different doses of an oral ER formulation of AZD0837 once daily or twice daily in a double-blind fashion, and 1 group receiving open label VKA. The VKA treatment group was twice the size of each of the AZD0837 treatment groups. The study was stratified with respect to VKA naïve patients.

Target patient population and sample size

Approximately 600 to 900 patients with paroxysmal, persistent or permanent nonvalvular AF and at least one additional risk factor for stroke were to be randomised in this study. The study was stratified with respect to VKA naïve patients aiming for 50 patients (at least 20) in each AZD0837 dose arm, and 100 patients (at least 40) in the open label VKA arm.

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 once daily, 200 mg twice daily, 300 mg once daily and 150 mg once daily. The dosage form is presented as ER tablets which is an equivalent term to the European standard term Prolonged-Release (PR) tablets.

Comparator, dosage and mode of administration

Locally available oral VKA, individually dosed, aiming for an INR of 2.0-3.0.

Duration of treatment

The study drug was to be given for at least 3 months but not longer than 9 months.

Criteria for evaluation (main variables)

- **Safety**
  - **Primary outcome variable:**
    - Adverse events (AE), including bleedings
    - electrocardiogram
    - vital signs (blood pressure and pulse)
    - laboratory values
    - physical examination
- **Efficacy**
  - **Secondary outcome variables/Pharmcodynamic:**
    - D-dimers
    - activated partial thromboplastin time (APTT)
    - endogenous thrombin potential (ETP)
    - ecarin clotting time (ECT)
    - thrombin coagulation time (TCT)
    - plasma protein pattern
- **Pharmacokinetic**
  - Plasma concentration of AZD0837 (prodrug)
  - Plasma concentration of AR-H069927XX (intermediate metabolite)
  - Plasma concentration of AR-H067637XX

Statistical methods

Safety data are presented descriptively. Visit 2 (randomisation visit) was regarded as baseline for safety laboratory assessment, physical examination, ECG, BP and pulse.

The PK and PD variables are presented as mean values and mean changes from baseline with 95% confidence intervals.

Patient population

In total 1083 patients at 95 centres in 9 countries were enrolled in the study and 955 patients were randomised (636 to AZD0837 and 319 to VKA) (see Table S 1). Six patients (5 patients randomised to AZD0837 and 1 patient randomised to VKA) did not receive any dose of the investigational product (IP). 818 patients completed IP treatment and 884 completed the study. There was an imbalance between the treatment groups in the proportion of randomised

patients that completed treatment: 80% to 85% of the patients in the AZD0837 treatment groups compared to 92% of the patients in the VKA treatment group. 523 patients transferred to the long-term follow up study and did therefore not attend the follow up visit in this study. Given the study design of the long-term study aiming for an 1:1 ratio of VKA and AZD0837 treated patients, 74% of the patients in the VKA treatment group in this study and ca 45% of the patients in each AZD0837 treatment group were transferred. The follow up telephone contact 24 weeks after permanent stop of IP provided vital status information on 78 patients from the VKA treatment group and 324 patients from the AZD0837 treatment group.

All patients received the correct treatment according to randomisation and therefore analysing according to the as-treated and as-randomised approach is equivalent. The safety analysis set and full analysis set were identical and included 949 patients. The population pharmacokinetics models provided exposure estimations for 630 patients in the study. 514 of the AZD0837 treated patients included in the population pharmacokinetics model had genotype data.

Table S 1 Patient disposition

	Number of patients (%)					
	AZD0837 150mg	**AZD0837 300 mg od**	**AZD0837 450 mg od**	**AZD0837 200 mg bd**	**VKA INR 2-3**	**Total**
Patients enrolled						1083
Patients randomised	166 (100%)	152 (100%)	157 (100%)	161 (100%)	319 (100%)	955 (100%)
Patients who were not randomised:						128
Patients who received treatment	164 (98.8%)	151 (99.3%)	156 (99.4%)	160 (99.4%)	318 (99.7%)	949 (99.4%)
Patients who did not receive treatment	2 (1.2%)	1 (0.7%)	1 (0.6%)	1 (0.6%)	1 (0.3%)	6 (0.6%)
Patients who completed treatment	140 (84.3%)	129 (84.9%)	128 (81.5%)	128 (79.5%)	293 (91.8%)	818 (85.7%)
Patients who discontinued treatment[a]	24 (14.5%)	22 (14.5%)	28 (17.8%)	32 (19.9%)	25 (7.8%)	131 (13.7%)
Patients who completed study	153 (92.2%)	139 (91.4%)	137 (87.3%)	151 (93.8%)	304 (95.3%)	884 (92.6%)
Patients who discontinued study	13 (7.8%)	13 (8.6%)	20 (12.7%)	10 (6.2%)	15 (4.7%)	71 (7.4%)
Patients continuing in long-term extension study[b]	75 (45.2%)	71 (46.7%)	72 (45.9%)	70 (43.5%)	235 (73.7%)	523 (54.8%)
Follow-up 1 week after visit 14	73 (44.0%)	70 (46.1%)	62 (39.5%)	80 (49.7%)	68 (21.3%)	353 (37.0%)
Follow-up 4 weeks after visit 14	77 (46.4%)	68 (44.7%)	64 (40.8%)	81 (50.3%)	68 (21.3%)	358 (37.5%)
Patients who fulfilled at least one Follow-up visit	78 (47.0%)	70 (46.1%)	67 (42.7%)	84 (52.2%)	69 (21.6%)	368 (38.5%)

Bookmark: pat_disp Version: 25MAR2009 08:37 (mdblo)

[a] Count of discontinuations with main reason of AE in this table is to be distinguished from count of discontinuation due to AE (DAE) presented in the safety section

[b] Study D1250C00042

In line with the inclusion criteria all patients had AF with at least one additional risk factor for stroke. In all treatment groups approximately 70% met the criteria for high risk of stroke. The most common additional risk factor was hypertension requiring anti-hypertensive treatment. The proportion of VKA naïve patients in the 5 treatment groups was 27% to 30%. The mean age was about 69 years, one third of patients were female. All patients but one were Caucasian. The VKA treatment group and the combined group of all AZD0837 treatment groups were well balanced with regard to demographic and patient characteristics. Between the four AZD0837 treatment groups there were some minor differences in demographic and patient characteristics.

Almost all patients randomised to AZD0837 treatment showed a good compliance in the range of 90% to 110% of the prescribed doses. No patient was dose-adjusted to 150 mg open AZD0837 treatment according to the protocol criterion of APTT>3ULN. In the VKA treatment group, INR within the target of 2.0 to 3.0 was achieved for 50% of the patients at week 4 and then for 58% to 68% during weeks 6 to 36. If the INR was outside the target interval, it was more frequently below 2.0 than above 3.0. Concomitant medication was well balanced between the treatment groups. Almost all patients received concomitant cardiovascular medication.

Efficacy and pharmacokinetic results

In VKA-naïve patients D-dimer, used as an explorative surrogate variable for thrombogenesis, decreased after start of treatment in all treatment groups; a rapid onset of the D-dimer reductive effect was seen within 2 to 4 weeks in all treatment groups. In the AZD0837 300 mg od, 450 mg od, and 200 mg bd treatment groups similar changes in fibrin D-dimer levels as in VKA were seen; less suppression was observed in the 150 mg AZD0837 od treatment group. In VKA pre-treated patients, D-dimer levels started low and remained low in all treatment groups.

Other pharmacodynamic markers (APTT, TCT, ECT, ETP) consistently showed a dose-related anticoagulant effect of AZD0837. Evaluation of the relationship between PD markers and the plasma concentration of AR-H067637XX revealed moderate to high correlations. ECT was most sensitive, ie a higher correlation was observed, and the response was less variable than for other PD markers.

The analysis of protein pattern showed a clear effect of VKA treatment with a reduction of coagulation factors like prothrombin as well as factors from the classical pathway of the complement system and increased levels of apolipoproteins. No significant change after AZD0837 treatment was seen when using exactly the same analysis system and an equal number of subjects.

The inter-individual variability in oral clearance (CL/F), which determines the average steady-state plasma concentration (C_{ss}) of AR-H067637XX, was found to be moderate (33%). The pharmacokinetics of AR-H067637XX were stable over the study period. Dosing with food or fasting did not appear to have a significant influence on the pharmacokinetics. Patient demographic factors had no or minor influence on the pharmacokinetics of AR-H067637XX.

Age and renal function were statistically significant yet weak predictors of CL/F. The only comedication found to have significant influence on CL/F of AR-H067637XX was verapamil, which decreased CL/F by 25% (corresponding to a 33% increase in C_{ss} of AR-H067637XX)

Pharmacogenetic analysis of P-glycoprotein gene polymorphism in population PK modelling did not support any influence of ABCB1 (C3435T) genotype on oral clearance (CL/F) of AR-H067637XX.

Safety results

631 patients were exposed to AZD0837 in this study and 318 received VKA during the randomized treatment period.

Overall, treatments were well tolerated, with a similar proportion of patients with any AE in each treatment group (see Table S 2). There was a lower proportion of patients with SAEs in the AZD0837 150 mg od and AZD0837 300 mg od and VKA groups than in the other 2 treatment groups. Compared to the VKA treatment group, the frequency of DAEs was higher in all AZD0837 treatment groups and increases with dose. 3 patients died during treatment (1 on AZD0837 150 mg od and 2 on VKA), and 3 patients during the follow up period lasting from stop of IP to visit 16 (all 3 previously treated with AZD0837). At the TC follow up 24 weeks after permanent stop of IP information on vital status was collected for 78 patients from the VKA treatment group and 324 from the AZD0837 treatment groups, eight patients were reported dead, all previously treated with AZD0837 but at the time of the TC treated according to local practice (ie either ASA, VKA or no medication). Based on additional information obtained after database lock no systematic pattern of cause of death, IP treatment duration, time of death from start or stop of IP treatment was identified in the patients reported dead at the TC follow up.

Table S 2 Number (%) of patients who had at least 1 AE in any category with onset during treatment (safety analysis set)

AE Category	Number (%) of patients				
	AZD0837 150 mg od (n=164)	AZD0837 300 mg od (n=151)	AZD0837 450 mg od (n=156)	AZD0837 200 mg bd (n=160)	VKA INR 2-3 (n=318)
Any AE	96 (58.5)	88 (58.3)	92 (59.0)	92 (57.5)	197 (61.9)
Any AE with outcome=death	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Any SAE (incl. AE with outcome=death)	11 (6.7)	17 (11.3)	25 (16.0)	23 (14.4)	38 (11.9)
Any AE leading to discontinuation of IP	11 (6.7)	11 (7.3)	16 (10.3)	20 (12.5)	5 (1.6)
Any other significant AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Bookmark: ae_summary Version: 27JAN2009 07:54 (mdblo)
Mean duration of exposure (days): 150mg od=141, 300mg od=144, 450mg od=145, 200mg bd=138. VKA=160
[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

The proportion of patients with any bleeding event was lower in the AZD0837 150 mg od, 300 mg od and 200 mg bd dose groups than in the VKA group; whilst it was similar to the

VKA group in the AZD0837 450 mg od group. For the AZD0837 300 mg od treatment group only minimal bleeding events were reported; in the other treatment groups few major bleeding events or clinically relevant minor bleeding events were reported with no apparent differences between the treatment groups.

The most commonly reported adverse event in AZD0837 patients was diarrhoea (11% in AZD0837 groups and 5% in VKA) followed by flatulence (6% in AZD0837 groups and 0.3% in VKA). No AZD0837 dose-dependency was seen for diarrhoea or flatulence.

As in previous studies, s-creatinine increased in the AZD0837 treatment groups (a mean change from baseline by 8%, 10%, 11% and 11% was observed in the dose groups of 150mg od, 300mg od, 450mg od, and 200mg bd AZD0837, respectively). The increase was noted at the 1st visit after randomisation (after about 2 weeks of treatment) upon which s-creatinine remained unchanged throughout the AZD0837 treatment. The mean value had returned towards baseline by 1 week post-treatment for the patients who stopped AZD0837 treatment and attended the follow-up visit. More marked increases in s-creatinine observed in individual patients were explained by their concurrent medical condition and not considered related to AZD0837. S-cystatin C was stable over time and there were no findings in urine laboratory variables indicating a possible AZD0837 related effect on renal function.

No pattern of changes in liver function test possibly related to drug treatment was observed, neither in mean nor in individual values. One patient receiving AZD0837 200 mg bd had a transient asymptomatic combination of s-ALAT≥3xULN and bilirubin≥2xULN (7.2xULN in ALAT and 2.5xULN in bilirubin). This patient, who also had an increase in ALP and γ-GT, had findings of calculous cholecystitis on ultrasound one month after the peak in liver tests. A relationship to AZD0837 treatment cannot be excluded from a temporal viewpoint.

EKG, vital signs and physical examination did not show any pattern of an AZD0837 related effect in this study.