Drug substance(s):	AZD7009	**SYNOPSIS**	
Study code:	D1461C00006		
Date:	12 December 2007		

A double-blind, randomized, placebo-controlled, parallel-group, multicentre, Phase II study to assess the efficacy of AZD7009 (AR-H065522XX) given intravenously (infusion for 15 or 30 minutes) to patients for conversion of atrial fibrillation

Study centre(s)

This study was conducted in Denmark (4 centres), Finland (2 centres), Germany (5 centres), Hungary (5 centres), the Netherlands (3 centres), Norway (3 centres), Poland (9 centres) and Sweden (3 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	7 September 2005	Therapeutic exploratory (II)
Last patient completed	31 March 2006	

Objectives

The primary objective was to study the efficacy of intravenous (iv) AZD7009 in all treatment groups, versus placebo, in conversion of atrial fibrillation (AF).

The primary outcome variable for the evaluation of this objective was:

- the proportion of patients that had converted from AF within 90 min from start of infusion. Conversion had occurred if sinus rhythm (SR) (and/or atrioventricular (AV) junctional rhythm) was maintained for at least 2 min

A secondary outcome variable evaluating the primary objective was:

- the time to conversion from AF from start of infusion up to 90 min

The secondary objectives and variables of this study were:

- To study the efficacy of AZD7009, versus placebo, in facilitating direct current (DC) cardioversion from AF in patients who do not convert on AZD7009 or placebo by assessment of:
  - the proportion of patients converted by DC cardioversion
- To study the efficacy of AZD7009, versus placebo, in maintaining DC cardioverted patients in SR in patients who do not convert on AZD7009 or placebo, by assessment of:
  - the proportion of patients with relapse of AF within 2 min after DC cardioversion (immediate relapse of AF [IRAF])
- To study the dosing regimen/efficacy response by assessment of:
  - the proportion of patients that have converted from AF within 90 min from start of infusion
  - the time to conversion from AF from start of infusion up to 90 min
- To study QT dynamics before and after conversion from AF by assessment of:
  - changes in interval data over time in continuous digital electrocardiograms (ECGs)
- To study the importance of AF duration, demographic variables, atrial size, concomitant diseases and concurrent medication, with respect to success of conversion by assessment of:
  - the proportion of patients that have converted from AF within 90 min from start of infusion
- To study the duration of rhythm control by assessment of:
  - the proportion of patients in SR at 60 min, 90 min, 3 h and 24 h after start of infusion
- To evaluate safety and tolerability of AZD7009 by assessment of:

  - significant arrhythmias as determined by an Adjudication Committee, adverse events (AEs), ECG variables and physical examination, vital signs and laboratory variables

- To characterize the pharmacokinetics (PK) of AZD7009 after iv administration in the AF population using population PK methodology

- To study the PK-pharmacodynamic (PD) relationship between plasma concentration and QT/QT_c interval

- To study the PK-PD relationship between exposure to AZD7009 and proportion of patients that have converted from AF within 90 min.

Study design

This was a double-blind, randomized, placebo-controlled, multicentre study with 5 parallel treatment groups where 167 patients with AF and a clinical indication for cardioversion received AZD7009 (124 patients) or placebo (43 patients) as an iv infusion for up to 15 min (AZD7009 3.25 mg/min, AZD7009 4.40 mg/min or placebo) or 30 min (AZD7009 3.25 mg/min or placebo).

Target patient population and sample size

The target patient population was male and female (post-menopausal or surgically sterile) patients aged between 18 and 80 years with current AF and a clinical indication for cardioversion.

It was estimated that approximately 160 patients were needed to be randomized to achieve 152 evaluable patients. With 38 evaluable patients in treatment groups with AZD7009 and 19 in treatment groups with placebo, the power of the hypothesis test of no difference in conversion rate is 77% (the sample size calculation was based on the comparison of treatment AZD7009 3.25 mg/min for 15 min versus its time-matched placebo).

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

AZD7009 (AR-H065522XX) for maximally 15 min (3.25 mg/min or 4.40 mg/min) or 30 min (3.25 mg/min), or time-matched placebo. The investigational product was administered intravenously with an infusion rate of 72 mL/h (1.2 mL/min). Batch numbers were: AZD7009 with dose rate 3.25 mg/min (2.71 mg/mL solution for infusion, H 1781-01-01-02), AZD7009 with dose rate 4.40 mg/min (3.67 mg/mL solution for infusion, H 1782-01-01-01) and placebo (solution for infusion, H 1627-01-02-01). The investigational product was supplied in 100 mL glass vials containing 65 mL solution.

Duration of treatment

A single iv infusion was administered for maximally 15 or 30 min. If the patient converted to SR (and/or AV junctional rhythm) during the infusion, and still were in SR 2 min after conversion, the infusion was prematurely stopped.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary outcome variable: The proportion of patients that had converted from AF within 90 min from start of infusion. Conversion had occurred if SR (and/or AV junctional rhythm) was maintained for at least 2 min.
- Secondary outcome variables:
  - The time to conversion from AF from start of infusion up to 90 min
  - The proportion of patients converted by DC cardioversion
  - The proportion of patients with relapse of AF within 2 min after DC cardioversion (IRAF)
  - The proportion of patients in SR at 60 min, 90 min, 3 h and 24 h after start of infusion
  - Population PK model parameter estimates derived from plasma concentrations of AZD7009.

Safety

Secondary outcome variables:

- Assessment of significant arrhythmias as determined by an Adjudication Committee, AEs, ECG variables, physical examination, vital signs and laboratory variables
- Changes in interval data over time in continuous digital ECGs
- Change in QT/QT_c with plasma concentration, as described by population PK-PD parameter estimates

Statistical methods

The primary variable was evaluated using Fisher's exact test. There were no corrections for multiplicity. The primary analyses were based on the per protocol (PP) population. All efficacy variables were also analyzed using the intention to treat (ITT) population.

Patient population

In total 206 patients were enrolled, out of whom 168 patients were randomized to treatment (125 to the AZD7009 and 43 to the placebo). The investigational product was administered to 167 patients, and for 18 of these the infusion was prematurely discontinued, all of them in accordance with the clinical study protocol (16 due to SR obtained [for 1 of these also for bradycardia] and 2 due to other heart rhythm obtained). The number of discontinuations due to SR obtained were predominant in the AZD7009 30 min 3.25 mg/min treatment group (14 out of 16). There were no premature discontinuations in the placebo groups.

There were no apparent differences between treatment groups in demographic characteristics at enrolment. In all treatment groups, the mean age was around 60 years, approximately 2/3 of patients were male and all patients were of Caucasian origin. There were no important differences between treatment groups with respect to AF history and duration of current AF episode.

The patient population and disposition are presented in Table S1.

Table S1 Patient population and disposition

		AZD7009 15 min 3.25 mg/min	AZD7009 15 min 4.40 mg/min	AZD7009 30 min 3.25 mg/min	Placebo 15 min	Placebo 30 min	Total
Population							
N randomized (N planned)		45 (40)	37 (40)	43 (40)	21 (20)	22 (20)	168 (160)
Demographic characteristics[a]							
Age (years)	Mean (SD)	63 (9)	64 (10)	63 (12)	62 (9)	57 (9)	62 (10)
	Range	42-78	47-81	20-77	42-75	45-72	20-81
Sex n (% of patients)	Male	31 (70)	25 (68)	31 (72)	15 (71)	19 (86)	121 (72)
	Female	13 (30)	12 (32)	12 (28)	6 (29)	3 (14)	46 (28)
Race n (%)	Caucasian	44 (100)	37 (100)	43 (100)	21 (100)	22 (100)	167 (100)
Baseline characteristics							
AF history, duration in years	Mean (SD)	2.4 (4.8)	2.5 (6.1)	1.7 (3.5)	1.7 (3.1)	2.5 (3.9)	2.2 (4.5)
	Range	0.0-21.0	0.0-35.0	0.0-18.0	0.0-11.0	0.0-15.0	0-35.0
Current AF episode, duration in days	Mean (SD)	45.5 (25.5)	49.5 (25.4)	45.9 (25.7)	40.3 (22.4)	55.1 (24.7)	47.1 (25.1)
	Range	4.0-90.0	0.8-88.0	6.0-90.0	3.0-80.0	9.0-92.0	0.8-92.0
Disposition							
N (%) of patients who	Completed	44 (98)	36 (97)	43 (100)	21 (100)	22 (100)	166 (99)

	AZD7009 15 min 3.25 mg/min	AZD7009 15 min 4.40 mg/min	AZD7009 30 min 3.25 mg/min	Placebo 15 min	Placebo 30 min	Total
Discontinued	1 (2)	1 (3)				2 (1)
N analyzed for safety[b]	44	37	43	21	22	167
N analyzed for efficacy (ITT)	44	37	43	21	22	167
N analyzed for efficacy (PP)	39	36	42	20	22	159

[a] Demographic characteristics are based on the safety population (for definition of safety population, see table footnote b).

[b] Number of patients who received any dose of study treatment and had at least 1 data point after dosing.

ITT=Intention to treat, N=number, PP=Per protocol, SD=Standard deviation

Efficacy and pharmacokinetic results

The efficacy results showed that treatment with AZD7009, compared to placebo, was effective in converting patients from AF to SR. The most effective regimen was infusion of AZD7009 for 30 min at a dose rate of 3.25 mg/min, with a conversion rate of 50% (21/42) within 90 min after start of infusion. The mean time to conversion was 24.3 min in the AZD7009 30/3.25 treatment group. Irrespective of dose regimen, all patients who converted on AZD7009 were still in SR 24 h after infusion. There were no conversions in the placebo groups occurring before DC cardioversion.

AZD7009 did not demonstrate facilitation of DC cardioversion when initiated 90 to 120 min after start of infusion according to protocol. There were few patients who had IRAF within 2 min after DC cardioversion. There were no significant diffences between the AZD7009 dose groups or versus time-matched placebo.

Demographic variables, including concomitant diseases and medication, were analyzed with relation to pharmacological conversion to SR within 90 min after start of infusion. The estimated treatment effect of AZD7009 30/3.25, compared to the other dose groups of AZD7009, after adjusting for covariates, was similar to the unadjusted analysis. Small left atrial size or no use of calcium channel-blocking agent were significantly more common among patients converted to SR. History of thromboembolism (TE) was significantly more common among patients converted to SR. Use of ACE-inhibitors or small right atrial size were more common among patients converted to SR.

The pharmacokinetics of AZD7009 were described by 3-compartment model and PK parameter estimates were consistent with previous studies. None of the demographic and laboratory variables evaluated was found to have clinically significant impact on the pharmacokinetics of AZD7009.

Safety results

AZD7009 was found to be safe and tolerable in this study. The number and type of AEs were anticipated considering the target population, disease under study and procedures. Six cases of AEs reported as hypotension were reported and all of them had received AZD7009, but

none of them was serious. There were more patients with AEs possibly related to a flu-like inflammatory reaction or fever in the AZD7009 groups compared to placebo, but there were no events resembling the cases seen with the oral formulation. Two of the cases (*sensation of warmth* and *fever*) were judged to be causally related to study drug but none of them had any documented increase in CRP, WBC or body temperature. There were few findings of increased body temperature and high increase in CRP and none of them were suspected to be related to AZD7009. .AEs related to bradycardia were evenly distributed between the treatment groups and was judged to be mainly related to the conversion per se.

In 2 patients, the study drug was stopped prematurely due to an AE. In one case the patient (AZD7009 15/4.40) had a run of 7 beats of wide QRS tachycardia 12 min after start of infusion and the other (AZD7009 30/3.25) had a similar run of 7 beats after 13 min from start of infusion. These actions were according to instructions regarding stopping of infusion. Both these cases were adjudicated by the Adjudication Committee to have supraventricular origin with an aberrant ventricular conduction.

There was 1 fatal AE in the study occuring on day 5 (AZD7009 15/4.40). The cause of death was a ruptured aortic aneurysm which was diagnosed after autopsy and judged to be without any relation to study drug. Arrhythmias that were adjudicated were not seen in higher frequency in the AZD7009 groups, except for short runs of supraventricular wide QRS tachycardias with abberant ventricular conduction. This could be expected with a drug like AZD7009. Monomorphic and polymorphic VTs were evenly distributed across the treatment groups and there was 1 polymorphic VT that was adjudicated to be TdP-like according to predefined criteria. This patient had 2 runs of 7 beats each with polymorphic appearance 69 min after start of infusion (AZD7009 30/3.25) in the setting of significant QT prolongation. The patient had no symptoms and the arrhythmia was not noted by the patient or by the investigator, but was discovered at the analysis of the Holter recording.

AZD7009 prolonged the QT_{cF} intervals by an average 15 to 20%. Around 90% of the patients showed QT_{cF} intervals that had returned to values below 480 ms 4 h after start of infusion.

Findings in laboratory variables, vital signs and physical examination were anticipated and did not raise any safety concerns.

Adverse events by category on treatment and during follow-up are presented in Table S2 and Table S3, respectively. The most common adverse events on treatment and during follow-up are presented in Table S4 and Table S5, respectively.

Table S2 Number (%) of patients with at least 1 AE in any category on treatment (safety population)

AE category	AZD7009 15min 3.25mg/min n=44	AZD7009 15min 4.40mg/min n=37	AZD7009 30min 3.25mg/min n=43	Placebo 15min n=21	Placebo 30min n=22
All AEs	6 (14)	5 (14)	9 (21)	6 (29)	1 (5)
All SAEs (including events with	0 (0)	2 (5)	2 (5)	1 (5)	0 (0)

AE category	AZD7009 15min 3.25mg/min n=44	AZD7009 15min 4.40mg/min n=37	AZD7009 30min 3.25mg/min n=43	Placebo 15min n=21	Placebo 30min n=22
outcome = death)					
All AEs with outcome = death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All AEs leading to discontinuation of treatment	0 (0)	1 (3)	1 (2)	0 (0)	0 (0)

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.

Table S3 Number (%) of patients with at least 1 AE in any category during follow-up period (safety population)

AE category	AZD7009 15min 3.25mg/min n=44	AZD7009 15min 4.40mg/min n=37	AZD7009 30min 3.25mg/min n=43	Placebo 15min n=21	Placebo 30min n=22
All AEs	11 (25)	10 (27)	13 (30)	8 (38)	5 (23)
All SAEs (including events with outcome = death)	2 (5)	4 (11)	7 (16)	2 (10)	2 (9)
All AEs with outcome = death	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
All AEs leading to discontinuation of treatment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Table S4 Number (%) of patients with the most commonly reported[a] AEs on treatment, sorted by decreasing order of frequency as summarized over all treatment groups (safety population)

System Organ Class Preferred Term	AZD7009 15min 3.25mg/min n=44	AZD7009 15min 4.40mg/min n=37	AZD7009 30min 3.25mg/min n=43	Placebo 15min n=21	Placebo 30min n=22
Cardiac disorders	**0 (0)**	**4 (11)**	**6 (14)**	**3 (14)**	**0 (0)**
Angina pectoris	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Atrial fibrillation	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Atrial tachycardia	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Bradycardia	0 (0)	2 (5)	3 (7)	1 (5)	0 (0)
Bundle branch block right	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Nodal rhythm	0 (0)	1 (3)	1 (2)	0 (0)	0 (0)
Sick sinus syndrome	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Sinus tachycardia	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Supraventricular extrasystoles	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Ventricular arrhythmia	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Ventricular tachycardia	0 (0)	1 (3)	1 (2)	0 (0)	0 (0)
Vascular disorders	**2 (5)**	**1 (3)**	**3 (7)**	**1 (5)**	**0 (0)**
Hypertension	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Hypotension	2 (5)	1 (3)	3 (7)	0 (0)	0 (0)

[a] Events with a total frequency of ≥4% across all treatment groups are included in this table. Patients with multiple events in the same SOC or PT are counted only once in that SOC or PT. Patients with events in more than 1 SOC or PT are counted once in each of those SOC or PT. PT within SOC are presented in alphabetical order. SOC=System organ class, PT=Preferred term

Table S5 Number (%) of patients with the most commonly reported[a] AEs during follow-up, sorted by decreasing order of frequency as summarized over all treatment groups (safety population)

System Organ Class Preferred Term	AZD7009 15min 3.25mg/min n=44	AZD7009 15min 4.40mg/min n=37	AZD7009 30min 3.25mg/min n=43	Placebo 15min n=21	Placebo 30min n=22
Cardiac disorders	**3 (7)**	**6 (16)**	**8 (19)**	**6 (29)**	**3 (14)**
Angina pectoris	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Arrhythmia	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Atrial fibrillation	2 (5)	4 (11)	2 (5)	2 (10)	3 (14)
Atrial flutter	0 (0)	0 (0)	1 (2)	0 (0)	1 (5)
Atrial tachycardia	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Bradycardia	0 (0)	2 (5)	2 (5)	2 (10)	0 (0)
Cardiac failure	0 (0)	1 (3)	1 (2)	0 (0)	0 (0)
Nodal rhythm	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Sick sinus syndrome	0 (0)	1 (3)	0 (0)	0 (0)	1 (5)
Sinus bradycardia	1 (2)	0 (0)	0 (0)	1 (5)	1 (5)
Sinus tachycardia	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Supraventricular extrasystoles	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Ventricular fibrillation	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Vascular disorders	**2 (5)**	**0 (0)**	**3 (7)**	**1 (5)**	**0 (0)**
Haematoma	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Hypertension	1 (2)	0 (0)	0 (0)	1 (5)	0 (0)
Hypotension	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)
General disorders and administration site conditions	**0 (0)**	**2 (5)**	**3 (7)**	**1 (5)**	**0 (0)**
Discomfort	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Pitting oedema	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Pyrexia	0 (0)	1 (3)	1 (2)	1 (5)	0 (0)
Infections and infestations	**3 (7)**	**0 (0)**	**2 (5)**	**1 (5)**	**0 (0)**
Herpes simplex	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Laryngitis	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Nasopharyngitis	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Pneumonia	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Respiratory tract infection	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Investigations	**2 (5)**	**2 (5)**	**2 (5)**	**0 (0)**	**0 (0)**
Blood glucose increased	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Blood urine present	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
C-reactive protein increased	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Electrocardiogram qt corrected interval prolonged	0 (0)	1 (3)	2 (5)	0 (0)	0 (0)

System Organ Class Preferred Term	AZD7009 15min 3.25mg/min n=44	AZD7009 15min 4.40mg/min n=37	AZD7009 30min 3.25mg/min n=43	Placebo 15min n=21	Placebo 30min n=22
Haemoglobin decreased	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)

[a] Events with a total frequency of ≥4% across all treatment groups are included in this table.
Patients with multiple events in the same SOC or PT are counted only once in that SOC or PT. Patients with events in more than 1 SOC or PT are counted once in each of those SOC or PT. PT within SOC are presented in alphabetical order. SOC=System organ class, PT=Preferred term