AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3191C00009
Edition Number	1
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A Double-Blind, Randomised, Placebo-Controlled, Multicentre, Dose-Escalating Study of AZD1305 Given Intravenously for Cardioversion of Atrial Fibrillation

Study dates:

First subject enrolled: 25 May 2009
Last subject last visit: 4 December 2009
Date of study termination: 20 November 2009 (fulfilment of study stopping criterion)

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)

The study was a multicentre study in which 33 centres enrolled patients in 8 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Study objectives and outcome variables are presented in Table S 1. Due to discontinuation of the clinical programmes of AZD1305, the planned statistical analyses have been changed for outcome variables as indicated in Table S 1.

Table S 1 Primary and secondary objectives and outcome variables

Objective			Outcome variables
Priority	**Type**	**Description**	
Primary	Safety	To evaluate the dose-response relationship for QT effects of AZD1305	QTcF interval
Primary	Efficacy	To demonstrate a dose-response relationship for AZD1305 given intravenously for conversion of AF to SR, and a statistically significant pair-wise difference for at least one of the dose levels of AZD1305 versus placebo	Heart rhythm (which primarily was evaluated as the proportion of patients that have converted from AF to SR within 90 min from start of infusion. Conversion of AF has occurred if SR is maintained for at least 1 min)
Secondary	Safety	To investigate the safety and tolerability of different doses of AZD1305 compared to placebo in this patient population	Significant arrhythmias as determined by an Adjudication Committee, AEs, ECG variables and physical examination, vital signs and laboratory variables
Secondary	Efficacy	To compare the proportion of patients with early relapse between different doses of AZD1305 versus placebo.	Heart rhythm
Secondary	Efficacy	To compare the proportion of patients remaining in SR up to 24 h and up to 13-18 days between different doses of AZD1305 versus placebo.	Heart rhythm
Secondary	Pharmacokinetic/ Pharmacodynamic	To study the relationship between systemic exposure and response, with special regards to conversion of AF to SR and the effect on the QTcF interval.	Systemic exposure[a] Heart rhythm QTcF interval

Objective			Outcome variables
Priority	**Type**	**Description**	
Secondary	Pharmacokinetic	To evaluate the predictability of AZD1305 pharmacokinetics including influence of co-variables	Population PK variables[a], Dose[a], Demographic variables[a], Concomitant diseases[a], Concomitant medication[a]
Secondary	Safety/ Efficacy	To study the importance of co-variables, with respect to efficacy and safety of AZD1305	Heart rhythm, QTcF interval[a], Co-variables (Duration of current AF episode, Demographic variables[a], Concomitant diseases[a], Concomitant medication[a], Baseline potassium[a], Atrial dimension[a])
Secondary	Safety	To evaluate the proportion of patients, who could be discharged within 6 h (QTcF ≤500 ms) after start of infusion	QTcF interval
Exploratory	Pharmacogenetic[b]	To collect and store DNA samples for potential future exploratory genetic research related to • PK, efficacy, safety and tolerability responses to AZD1305 • Susceptibility to and prognosis of cardiovascular disease.	NA[b]

NA Not applicable, PK Pharmacokinetics
[a] Due to discontinuation of the clinical programmes of AZD1305, the statistical analyses regarding this variable was changed.
[b] Not part of the Clinical Study Report.

Study design

The study was a double-blind, randomised, placebo-controlled, multicentre, dose-escalating study of AZD1305 given intravenously (during a maximum of 30 min) for cardioversion of atrial fibrillation (AF). The dose-escalation comprised 4 dose groups, and a 5th optional dose group. The optional 5th dose group was never conducted since a pre-defined study stopping criterion was fulfilled in the 4th dose group. The dose in dose groups 2, 3 and 4 were recommended by a Data Safety Monitoring Board (DSMB) and were initiated after decision of a Steering Committee. The DSMB made their recommendation after review of unblinded safety, pharmacokinetic, pharmacodynamic and efficacy data from previous dose group(s). Recommendations for any modification regarding the conduct of the study, or early stopping of the study for safety reasons were made by the DSMB and approved by the SC.

An Adjudication Committee analysed the 12-lead Holter reports from each randomised patient and classified occurrence of significant arrhythmias (other than AF or atrial flutter) and pauses. The Committee also adjudicated all pauses and all wide QRS complex tachycardias.

The study included 3 visits: an enrolment visit, the study day (2 days) when the infusion of the investigational product was given, and a follow-up visit (13 to 18 days after the study day). At the visit when the investigational product was given, the patient stayed in the hospital for at least 24 h after start of the infusion. If the patient had not converted from AF to SR within 90 min after start of infusion of the investigational product at the study day, a direct current (DC) cardioversion was performed 91 to 180 min after start of infusion.

Target subject population and sample size

The target population consisted of male or postmenopausal female patients (age 20 to 80 years) with clinical indication for cardioversion of AF and current episode of AF lasting between 3 h and 3 months at randomisation. The patients had to be on effective anticoagulation according to national or international guidelines. Approximately 212 patients were planned to receive AZD1305 (approximately 159 patients) or placebo (approximately 53 patients): dose group 1 AZD1305 (24 patients) and placebo (8 patients), in dose groups 2, 3 and 4 AZD1305 (45 patients) and placebo (15 patients).

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

The investigational product used in the study was AZD1305 concentrate for solution for infusion (20 mg/mL, batch 09-001537AZ) and corresponding placebo (batch 09-001540AZ). The concentrate was diluted in vials of 100 mL of sodium chloride for infusion (9 mg/mL, batches 09-001510AZ and 09-000955AZ) according to dilution and dosing instruction. The total dose (dose rate) of AZD1305 after 30 min infusion was 25 mg (50 mg/h), 50 mg (101 mg/h), 65 mg (130 mg/h) and 90 mg (180 mg/h) in dose groups 1, 2, 3 and 4, respectively.

The investigational product was administered as an iv infusion, with an infusion rate of 120 mL/h, and the patients received 1 single infusion of AZD1305 or placebo.

Duration of treatment

Single dose (The infusion had to be stopped 1 min after successful conversion from AF to sinus rhythm [SR], or after a maximum of 30 min after start of infusion.)

Statistical methods

The primary outcome measure was the proportion of patients converted from AF to SR within 90 min from start of infusion. A logistic regression model was used to address the hypothesis of a significant dose-response relationship, with dose rate (mg/h) as a continuous covariate. Time patterns for the cumulative conversion rate, by treatment group, were illustrated with Kaplan-Meier curves. The proportions converted, with 95% confidence intervals, were estimated within, and also for the differences between, treatment groups. The primary safety variable was QTcF. The dose-response relationship was estimated with an Emax model, with dose rate (mg/h) as explanatory variable. QTcF was summarized with descriptive statistics, including mean levels (with 95% confidence intervals) within, and for differences between,

treatment groups. QTcF was also assessed in terms of proportions of patients exceeding predefined cut-off levels.

Subject population

The study enrolled 228 patients (at 33 centres in 8 countries) and of the 171 patients randomised 170 patients completed the study. All randomised patients received investigational product (ie, AZD1305 or placebo).

The population in this study was representative of the population with clinical indication for cardioversion of AF. Demographic and baseline characteristics such as gender, age (age groups) and duration of current AF episode were similar across the treatment groups. The mean duration of the current AF episode in the study population was 43 days.

Table S 2 Subjects population demographic and disposition (all randomised subjects, n=171)

Demographic characteristic		Subjects/Treatment groups				
		AZD1305 group 1 (n=26)	AZD1305 Group 2 (n=45)	AZD1305 Group 3 (n=45)	AZD1305 Group 4 (n=12)	Placebo (n=43)
Sex (n and % of subjects)	Male	17(65%)	28(62%)	31(69%)	8(67%)	25(58%)
	Female	9(35%)	17(38%)	14(31%)	4(33%)	18(42%)
Age (years)	Mean(SD)	65(9)	65(7.3)	64(9.9)	66(6.7)	66(9.2)
	Range	47-80	48-78	33-79	54-75	41-79
Baseline characteristic						
QTcF interval (ms)	Mean(SD)	400(21.8)	400(27.7)	398(25.2)	410(32)	399(25.4)
AF duration (days)	Mean(range)	44(3-91)	41(1-91)	39(2-90)	47(2-89)	44(1-83)
Disposition						
N(%) of subject who	Withdrawn study	1(1%)	0	0	0	0
	Completed study	25(96%)	45(100%)	45(100%)	12(100%)	43(100%)
N analysed for ITT		26	45	45	12	43
N analysed for safety		26	45	45	12	43
N analysed for PP		24	43	45	11	42

demog2 17MAY10

Summary of efficacy results

There was a statistically significant relationship ($p<0.001$) between dose rate of AZD1305 (mg/h) and the probability for drug induced conversion from AF to SR.

The proportion of patients treated with AZD1305 that converted from AF to SR within 90 min after start of infusion was 8%, 18%, 38% and 50% in dose groups 1 (50 mg/h), 2 (101 mg/h), 3 (130 mg/h), 4 (180 mg/h), respectively, and the majority of the patients converted between 10 min to 1 h after start of infusion, see Figure S 1. None of the patients treated with placebo converted from AF to SR. Three patients converted from AF to SR after more than 90 min

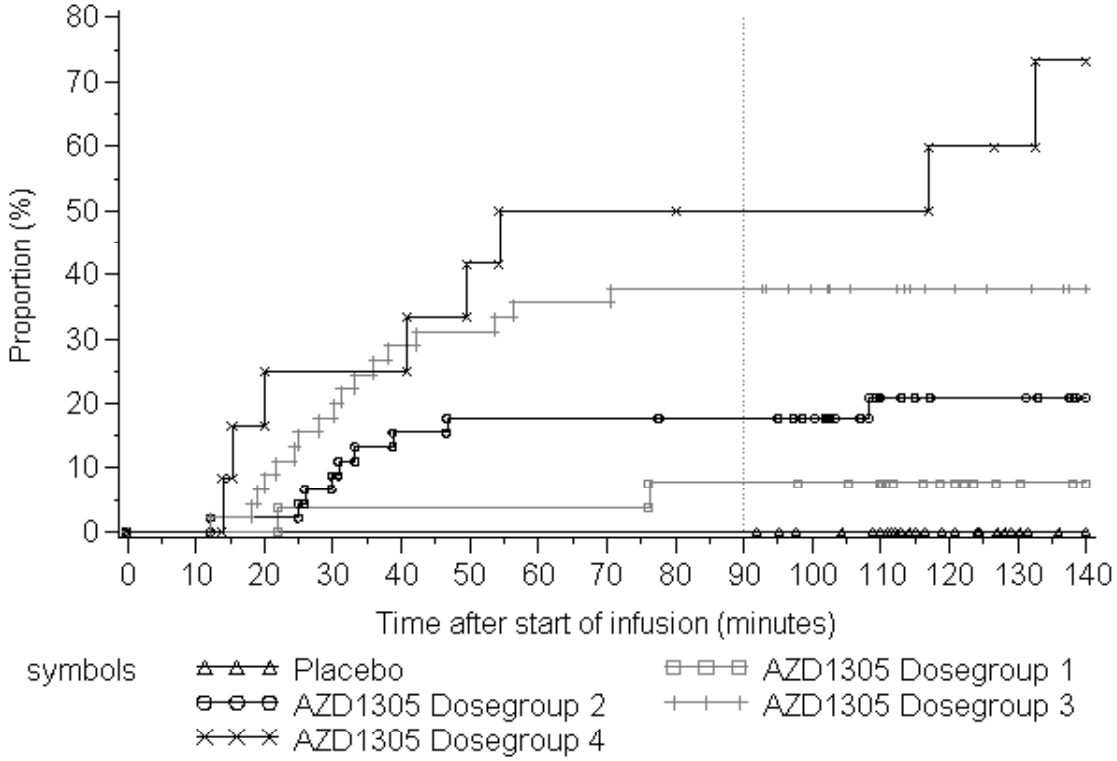
after start of infusion. The differences between AZD1305 and placebo were statistically significant for all dose groups, except for the lowest. The general trend observed across duration of current AF episode subgroups was that it is easier to convert a patient with a shorter current AF episode duration.

Thirty patients out of the 171 patients undergoing an attempt of pharmacological or DC cardioversion, were not possible to convert from AF to SR.

There were 5 patients who had early relapse (within 5 min) from SR to AF. There was no difference between AZD1305 and placebo regarding early relapse: among patients cardioverted with AZD1305, 1 patient (3%) relapsed and after DC, 4 patients (4%) relapsed.

Among all the 141 patients who were converted from AF to SR, by either AZD1305 or DC, 136 patients (96%) remained in SR at 24 h and 91 patients (65%) remained in SR 13 to 18 days after conversion, without any differences between the treatment groups.

Figure S 1 **Proportion of patients (Kaplan Meier) converted from AF to SR from start of infusion by treatment and dose. ITT Population**



Summary of pharmacokinetic results

The pharmacokinetics of AZD1305 was predictable based on the mean maximal plasma concentrations being proportional to the dose given. The mean plasma concentrations at stop

of infusion was 0.5 µmol/L, 1.2 µmol/L, 1.3 µmol/L and 1.7 µmol/L in dose groups 1, 2, 3 and 4, respectively. However, large variability in plasma concentrations between patients was observed.

Summary of pharmacokinetic/pharmacodynamic relationships

QTcF increased with increasing plasma concentration of AZD1305 in the dose range investigated and appeared to reach a plateau at high plasma concentrations, with the exception of a few patients with more pronounced QT prolongations (7 patients had a maximal QTcF >550 ms).

Summary of safety results

The were no deaths or discontinuations of the investigational product due to an adverse event (AE) during the study. During the study, 2 cases of severe ventricular arrhythmia (TdP+TdP-like and TdP) were reported. One of these 2 ventricular arrhythmias occurred during dose group 4 and fulfilled a pre-defined study stopping criterion. The most commonly reported AEs were of cardiovascular origin, which is to be expected in the studied population. In general, AEs were of a kind commonly observed in a patient population with AF undergoing cardioversion. During the day when the iv infusion was administered, 7% of the patients in the AZD1305 dose groups and 2% of the patients in the placebo group reported at least one AE. During follow-up, 29% of the patients in the AZD1305 groups and 26% of the patients in the placebo group reported at least one AE. There were 13 serious AEs reported in 10 patients during active treatment and during follow-up, and there was no difference between AZD1305 dose groups and the total placebo group.

Table S 3 summarises the adjudication of pauses and wide QRS complex tachycardias.

Table S 3 Number of patients with pauses and wide QRS tachycardias, including supraventricular origin (safety analysis set)

Variable	Treatment groups				
	AZD1305 Group 1 (n=26)	AZD1305 Group 2 (n=45)	AZD1305 Group 3 (n=45)	AZD1305 Group 4 (n=12)	Placebo (n=43)
RR intervals 3-5 s	0	0	0	0	1
Ventricular pauses >5 s	0	1	0	0	0
Wide QRS complex Tachycardias	4	15	16	2	7
SVT with aberration/bundle brach block	1	8	7	1	7
Monomorphic VT	3	7	8	0	1
Polymorphic VT	1	1	4	1	0
Torsade de Pointes	0	0	1	1	0
Torsade de Pointes Like	0	0	1	0	0

As expected from the mode of action of AZD1305, a dose-dependent increase in mean QTcF was observed. No AZD1305 related observations in QRS and PR variables could be found. QTcF increased with increasing dose rate of AZD1305 (mg/h) and appeared to reach a plateau at the higher end of the dose rates investigated, with the exception of a few patients with more pronounced QT prolongations (7 patients had a maximal QTcF >550 ms). In all the AZD1305 dose groups, the level of the mean of QTcF at 24 h after start of infusion was elevated compared to the pre-dose level.

In the study, the highest QTcF observed in an individual patient was 633 ms occurring at 4 h after start of infusion of AZD1305 (dose group 3). Up to 24 h after start of infusion, 27 (21%) patients responded to AZD1305 with a maximal QTcF >500 ms, 7 (6%) patients had QTcF >550 ms, and 3 patients were observed with a QTcF >600 ms. In the majority of the AZD1305 patients (111 out of 127) the observed individual maximal QTcF occurred within 4 h after start of infusion. Of all patients treated with AZD1305, 95% of the patients had QTcF ≤500 ms 6 h after start of infusion.

There were no unexpected observations or differences between the treatment groups with respect to safety laboratory variables, vital signs and physical examination. There were no indications of any haemodynamic effects of AZD1305.