AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00013
Edition Number	1
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A single-centre, single-blind, randomised, placebo-controlled phase IIa study to investigate the effect of AZD1305 given as an intravenous infusion on left ventricular performance in patients with left ventricular dysfunction

Study dates: First subject enrolled: 20 August 2008
Last subject last visit: 20 July 2009

Phase of development: Therapeutic exploratory (IIa)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This was a single-centre study performed at the AstraZeneca R&D Clinical Pharmacology Unit Sahlgrenska Hospital, Gothenburg, Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To explore if AZD1305 compromises left ventricular performance in patients with left ventricular dysfunction.	Left ventricular ejection fraction (LVEF) – as measure for left ventricular systolic function E/A ratioa, E-wave deceleration time, and E/E´ ratiob – as measures for left ventricular diastolic function	PD
Secondary	**Secondary**	
To evaluate the tolerability and safety of AZD1305 given as an iv infusion to patients with left ventricular dysfunction	Adverse events, blood pressure, pulse, electrocardiogram, body temperature, physical examination and laboratory variables.	Safety
To evaluate the pharmacokinetics of AZD1305, given as an iv infusion, in patients with left ventricular dysfunction	AUC(0-t), AUC, maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), terminal half-life ($t_{½}$), volume of distribution at steady state (Vss) and total plasma clearance (CL)	PK
To exploratively evaluate the relationship between dose, plasma concentration and QTcF interval, QRS duration and, if possible, left ventricular performance	Plasma concentration of AZD1305 versus QTcF, QRS, Left ventricular ejection fraction (LVEF), E/A ratio, E-wave deceleration time, and E/E´ ratio	PK/PD
To collect and store DNA samples (from all randomised patients who give additional informed consent) for potential future exploratory research into genes which may influence drug response of AZD1305.	NA	genetic

[a] E/A ratio = E wave velocity divided by A wave velocity;
[b] E/E´ ratio = ratio of pulse wave Doppler mitral E velocity divided by tissue Doppler imaging E wave velocity,
Abbreviations: AUC = Area under the plasma concentration versus time curve from time zero to infinity, PD= pharmacodynamic, PK = pharmacokinetic

Study design

The study was a single-centre, single-blind, randomised, placebo-controlled study where AZD1305 or placebo was administered as a single-dose intravenous infusion. AZD1305 is a novel antiarrhythmic agent being developed for the treatment of atrial fibrillation. The study

evaluated 2 doses separated by a wash-out period of at least 24 days. Echocardiographic evaluations were performed by 1 person blinded to treatment.

Target subject population and sample size

The target population of the study consisted of patients with left ventricular systolic dysfunction with a LVEF of 30-45% on echocardiography. Patients with LVEF >45% could be included if he/she had a well documented diagnosis of cardiac failure/cardiomyopathy with a previous LVEF <45% and was judged to have a normal LVEF due to optimised medical treatment. The aim was to include at least 16 patients (12 on AZD1305 and 4 on placebo).

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

The investigational products used in the study were AZD1305 concentrate for solution for infusion (10 mg/mL, batch H 1958-01-01-04) and corresponding placebo (NaCl 9 mg/mL, batch H 0732-04-04-12).

The investigational product was given as an initial intravenous (iv) loading dose during 30 min followed by a maintenance iv dose during a maximum of 90 min. The infusion was stopped when all echocardiographic measurements had been carried out. The mean total dose of AZD1305 after dose 1 was 30 mg (range 29-31 mg) and after dose 2 was 77 mg (range 74 to 81 mg).

Duration of treatment

Single dose.

Statistical methods

All data were descriptively presented. Results for the echocardiographic variables were presented in tables with descriptive statistics and 95% confidence intervals and in figures with individual and mean curves over time. The results included outcomes before the infusion, during the infusion, and for the change during minus before infusion, for placebo and each dose of AZD1305. Results for plasma concentrations of AZD1305 and for ECG variables were also presented in figures with individual and mean curves over time. PK/PD analyses were performed exploratively.

Subject population

The study enrolled 33 patients of whom 16 were randomised. All randomised patients received 2 iv doses of either AZD1305 or placebo and all completed the study. The demographic and key baseline characteristics of the AZD1305 and placebo groups were appropriate for the purpose of the analyses in the study. All patients had a diagnosis of congestive heart failure and were in NYHA class I-II. In the whole study population, mean baseline LVEF was 49% (range 36-61).

Table S 2 Subjects population demographic and disposition (all randomised subjects, n=16)

Demographic characteristic		Subject/Treatment groups	
		AZD1305 (n=12)	Placebo (n=4)
Sex (n and % of subjects)	Male	12(100%)	3(75%)
	Female	0(0%)	1(25%)
Age (years)	Mean(SD)	62(4.9)	65(2.5)
	Range	51-69	62-68
Baseline characteristic			
Weight (kg)	Mean(SD)	88(7.4)	88(10)
BMI (kg/m^2)	Mean(SD)	29(3.7)	28(2.5)
SBP (mmHg)	Mean(SD)	135(19.3)	111(7.5)
DBP (mmHg)	Mean(SD)	73(10.7)	66(10.3)
Pulse (beats/min)	Mean(SD)	59(4.9)	54(3.2)
QTcF interval (ms)	Mean(SD)	405(20.3)	425(9.5)
LVEF (%)	Mean (SD)	48 (7)	53 (6)
NYHA class I / II	Class I n(%) / class II n(%)	8/4 (67%/33%)	3/1 (75%/25%)
Disposition			
N(%) of subject who	Completed study	12(100%)	4(100%)
	Discontinued treatment	12(100%)	4(100%)
N analysed for PK and PD		12	4
N analysed for safety		12	4

Summary of pharmacokinetic results

In patients with left ventricular systolic dysfunction, AZD1305 was rapidly and extensively distributed. The geometric mean CL was 34.4 and 34.8 L/h and the terminal t½ was 8.2 and 6.8 hr (estimated for dose 1 and 2, respectively).

Summary of pharmacodynamic results

For systolic function, neither clinically nor statistically significant changes in LVEF were detected after AZD1305 administration (p=0.12 and p= 0.34 for dose 1 and 2, respectively). This result is supported by results from the secondary variables systolic wave velocity, cardiac output and stroke volume. No statistically significant changes were observed for these variables after AZD1305 administration.

For diastolic function, no statistically significantly change in E/E´ ratio (p=0.98 and p= 0.17 for dose 1 and 2, respectively) and in E-wave deceleration time (p=0.45 and p= 0.65 for dose 1 and 2, respectively) were detected after AZD1305 administration. However, after AZD1305 administration, a statistically significant increase in transmitral E/A ratio was observed (an increase of 0.14, p=0.037 after dose 1 and an increase of 0.34, p= 0.01 after dose 2). Collective evaluation of the 3 variables, E/E´ ratio, E-wave deceleration time, and E/A ratio,

did not indicate a clinically significant change in diastolic left ventricular function after AZD1305 administration.

Summary of pharmacokinetic/pharmacodynamic relationships

As expected based on its mode of action, AZD1305 prolonged QTcF in a concentration-dependent manner. Moreover AZD1305 showed a concentration-dependent, small increase in QRS duration.

Results from exploratory analyses of PK/PD relationships for LVEF, E-wave deceleration time, E/E´ ratio, and E/A ratio were in line with results related to the primary objective (see "Summary of pharmacodynamic results").

Summary of safety results

In the study, AZD1305 was generally safe and well tolerated after single iv infusion up to total mean doses of 77 mg given during a mean infusion time of 1.6 h. No serious adverse events (SAEs) and no discontinuations due to adverse events (AEs) occurred in the study. The total number of AEs was low (5 during AZD1305 treatment and 1 during placebo treatment). No pattern of most common AEs was identified.

AZD1305 prolonged QT intervals as part of its mode of action. None of the patients responded with QTcF > 550 ms. One of 12 patients responded to AZD1305 administration with QTcF>500 ms. This was observed after both doses. In addition, AZD1305 administration was associated with a small mean increase in QRS duration (i.e., approximately 5-6 ms after dose 2). All QTcF and QRS prolongations were reversible.

A total of 7 episodes with asymptomatic, strictly monomorphic, ventricular tachycardia of maximum 15 beats were observed in 4 patients 1:57 – 18:37 h after start of infusion of AZD1305.