AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00005
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A Multi-centre, Double-blind, Randomised, Placebo-controlled, Single-dose, Phase II Study to Assess the Effects on Atrial and Ventricular Refractoriness and Haemodynamics of an Intravenous Infusion of AZD1305 in Patients Undergoing an Invasive Electrophysiological Procedure

Study dates: First patient enrolled: 23 January 2008
Last patient completed: 19 June 2008

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 13 centres randomised patients i.e., 3 centres in Denmark, 3 centres in Finland, 3 centres in Norway, and 4 centres in Sweden.

Date of early study termination: 11 July 2008

The date for End of Trial was 11 July 2008. When 3 patients had been randomised into the optional 4th dose group, 1 patient had reached a QTend of 720 ms (QT_{cF} 689 ms) during sinus rhythm. At the same time, the blinded data from the complete dose group 3 became available and indicated that the effects on PD variables and safety/tolerability were well enough established. Therefore, further inclusion of patients into dose group 4 was stopped.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to evaluate the effects of AZD1305, compared to placebo, on the left atrial effective refractory period (LAERP), in patients undergoing an invasive electrophysiological procedure.

The secondary objectives of the study were to:

- evaluate the effects of AZD1305, compared to placebo, on the right atrial effective refractory period (RAERP) in patients undergoing an invasive electrophysiological procedure
- evaluate the effects of AZD1305, compared to placebo, on the ventricular effective refractory period (VERP) and other electrophysiological and electrocardiographic variables in patients undergoing an invasive electrophysiological procedure
- investigate the effects of AZD1305, compared to placebo, on haemodynamic variables in patients undergoing an invasive electrophysiological procedure
- study the pharmacokinetic (PK)-pharmacodynamic relationship between plasma concentration of AZD1305 and $QT/QT_{cF,}$ and if data is sufficient LAERP, RAERP and VERP
- investigate the safety and tolerability of AZD1305 compared to placebo in this patient population
- describe the PK of AZD1305 in this patient population
- collect and store DNA samples for potential future exploratory genetic research related to PD and PK responses to AZD1305. (Not reported in the Clinical Study Report)

Study design

The study was a multi-centre, double-blind, randomised, parallel-group, placebo-controlled study where AZD1305 or placebo was administered as a single-dose intravenous infusion. The study included 4 dose groups in a dose escalating manner.

Target population and sample size

The target population consisted of patients with atrial flutter who had undergone a succesfull catheter ablation with cryoablation or radiofrequency ablation. After an amendment, patients had to have ventricular rate of <100 beats/minute at enrolment. Per dose group, the aim was to include 16 patients of whom 12 were to be randomised to AZD1305 and 4 to 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 (10mg/mL, 3 batches i.e., H 1958-01-01-01 to -03) and corresponding placebo (2 batches i.e., H 1959-01-01-01 and -02).

The investigational product was given iv as an initial 15 min loading infusion followed by a maintenance infusion for a maximum of 60 min. The infusion was stopped when all the electrophysiological measurements had been carried out. Within each dose group, the total dose and the estimated plasma concentration of AZD1305 achieved per patient ranged between the intervals shown in Table S 1.

Table S 1 Dosing and estimated concentrations (mean and range) at time of LAERP measurement (PK and PD analysis set)

	AZD1305				
Dose group	**1**	**2**	**3[a]**	**4**	**Placebo**
	n=(11)	**n=(12)**	**n=(13)**	**n=(2)**	**n=(12)**
Aimed Δ LAERP (ms)	20	40	60	60	0
Infusion time (min)[b]	51	48	46	55	49
Mean (range)	(40-67)	(34-61)	(30-65)	(52-57)	(23-59)
Total dose AZD1305 (mg)	22.6	65.3	150.9	266.8	0
Mean (range)	(19-27.8)	(51.2-77.6)	(89.5-203.5)	(257.6-275.9)	
Actual dose at LAERP (mg)	17.3	53	127.7	241.1	0
Mean (range)	(12.5-21.3)	(37.5-63.9)	(89.5-166.9)	(221-261.3)	
Aimed Cp at LAERP[c]	0.2	0.6	1	1.25	0
Estimated Cp at LAERP (µmol/L)	0.14	0.51	1.14	2.28	0
Mean (range)	(0.08-0.2)	(0.36-0.68)	(0.47-2.11)	(2.2-2.36)	

a In dose group 3 two patients received a dose of AZD1305 with an infusion rate of 85/36 ml/h instead of 110/49.5 ml/h (loading infusion rate/maintenance infusion rate)
b time for loading infusion plus time for maintenance infusion
c at time of LAERP measurement. LAERP = Left atrial effective refractory period.

Duration of treatment

Single dose.

Criteria for evaluation - pharmacokinetics (main variables)

Population PK model parameter estimates derived from plasma concentrations of AZD1305

Criteria for evaluation - pharmacodynamics (main variables)

Electrophysiological: LAERP (primary variable), RAERP, VERP, intra-atrial conduction (PA), intra-nodal conduction (AH), Infra-nodal conduction (HV), Wenchebach point (Wb), atrio-ventricular effective refractory period (AVERP). Electrocardiographic: RR, P wave duration, PR, QRS, QT, QT_{cF}, QT_{top}, QT_{end} - $QT_{top.}$ Haemodynamic: Right atrial (RA) pressure, pulmonary artery pressure and the pulmonary capillary wedge pressure (PCWP)

Criteria for evaluation - pharmacokinetic-pharmacodynamic relationship (main variables)

AZD1305 plasma concentrations, QT /QT_{cF} and, LAERP, RAERP and VERP

Criteria for evaluation - safety (main variables)

Adverse events (AEs), electrocardiogram (ECG) (including heart rate [HR]), blood pressure (BP), physical examination and laboratory variables

Statistical methods

All data were descriptively presented. For PD variables, mean changes (after minus before infusion) with 95% confidence intervals were calculated, both within treatment groups and for between treatment group differences. Concentration- and dose-effect relationships were estimated with linear and non-linear regression analyses.

Subject population

The study randomised 55 patients and 50 of those patients received investigational product. There were no important imbalances between the placebo groups and AZD1305 dose group 1 to 3. Dose group 4 (n=2) was too small to allow comparisons with the other groups.

Table S 2 Demographic, baseline characteristics (full analysis set) and disposition

Demographic characteristic	Statistic	Placebo (n=12)	Dose group 1[a] (n=11)	Dose group 2[a] (n=12)	Dose group 3[a] (n=13)	Dose group 4[a] (n=2)
Age (years)	Mean (SD)	62 (6)	60 (14)	62 (6)	60 (8)	50 (23)
	Range	51 to 73	32 to 72	50 to 73	40 to 70	34 to 66
Sex (n and %)	Male	12 (100%)	9 (82%)	10 (83%)	11 (85%)	2 (100%)
	Female	0 (0%)	2 (18%)	2 (17%)	2 (15%)	0 (0%)
Baseline characteristic						
Weight (kg)	Mean (SD)	90 (15)	85 (12)	84 (15)	86 (13)	73 (16)
BMI (kg/m2)	Mean (SD)	28 (6)	27 (3)	27 (4)	27 (4)	24 (0)
SBP (mmHg)	Mean (SD)	150 (22)	139 (13)	139 (14)	148 (17)	144 (1)
DBP (mmHg)	Mean (SD)	86 (12)	82 (13)	81 (8)	88 (11)	84 (17)
Pulse (bpm)	Mean (SD)	68 (19)	71 (15)	76 (30)	71 (18)	64 (5)
QTcF (ms)	Mean (SD)	409 (24)	389 (23)	412 (32)	399 (27)	377 (26)
Disposition (n)						

Demographic characteristic	Statistic	Placebo (n=12)	Dose group 1[a] (n=11)	Dose group 2[a] (n=12)	Dose group 3[a] (n=13)	Dose group 4[a] (n=2)
Randomised		12	13	14	14	2
Treated with IP		12	11	12	13	2
Completed treatment		12	11	12	13	2
Analysed for PK and PD		12	11	12	13	2
Analysed for safety		12	11	12	13	2

a One dose group represents a group of patients who had received AZD1305 within a range. For each dose group, the total doses of AZD1305 administered and the plasma concentrations obtained, are provided in Table S 1.

Summary of pharmacokinetic results

The pharmacokinetics of AZD1305 was described by a 3-compartment model. The population mean clearance of AZD1305 was 34 L/h and the variability between patients was 28% (CV). The half-lives of the 3 declining phases were 0.17, 4.5, and 27 hours, consecutively.

Summary of pharmacokinetic/pharmacodynamic relationships

In patients undergoing an invasive electrophysiological procedure, evaluation of the effects of AZD1305 on LAERP showed that in a concentration range of 0.1 - 2.3 µmol/L (derived from iv infusion of actual doses up to 261 mg (see Table S 1)):

- AZD1305 concentration- and dose-dependently increased LAERP ($p<0.001$).
- among the dose groups, the highest difference in mean LAERP from placebo was 64 ms ($p<0.001$, dose group 3)

Moreover, it was shown that AZD1305 concentration- and dose-dependently increased RAERP ($p<0.001$), VERP ($p<0.001$), and QT interval. ($p<0.001$). In dose group 3, AZD1305 increased the mean values of LAERP by 55 ms, RAERP by 84 ms, and VERP by 59 ms. AZD1305 dose-dependently increased QRS width under paced conditions, several markers of cardiac conduction time, and did not change intracardiac pressures.

The PK/PD relationship between plasma concentrations of AZD1305 and QT_{cF}, LAERP, RAERP and VERP could be accurately described by E_{max} models.

Summary of safety results

In single, iv doses up to total doses of 276 mg (see Table S 1), AZD1305 was generally safe and well tolerated.

The AEs most commonly reported were of cardiovascular origin. During the active treatment period, 7 (18%) patients who were treated with AZD1305 experienced 8 AEs and 1 (8%) patient who was treated with placebo experienced 1 AE. SAEs, regarded as vagal reactions (reported as vagal reactions/hypotension/ bradycardia), were reported in 3 patients with a relatively long duration of heart rates >100 beats/min. These reactions occurred in 2 patients

treated with AZD1305 and in 1 patient treated with placebo. Causality towards the invasive electrophysiological procedure is most likely. All AEs were of a kind commonly observed in a patient population with atrial flutter undergoing an invasive electrophysiological procedure.

AZD1305 prolonged QT intervals as part of its mode of action in a concentration and dose dependent manner. In 4 of the 38 patients treated with AZD1305, QT_{cF} >550 ms was observed in 10 protocol-defined ECGs during any time of the study. All QT prolongations were reversible and not associated with any signs of proarrhythmia.

There was a small but statistically significant dose-dependent increase of the pulmonary wedge pressure (PCWP). Because also a transient, slight decrease in mean systolic blood pressure was observed in the dose groups, a transient, slight, effect of increased PCWP on the haemodynamics could not be excluded.