AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2927
Study Code	D4120C00002
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A Multi-Centre, Double-Blind, Randomised, Placebo-Controlled Phase II Study to Assess the Effects on Atrial and Ventricular Refractoriness of an Intravenous Infusion of AZD2927 in Patients Undergoing an Invasive Electrophysiological Procedure

Study dates: First patient enrolled: 26 September 2011
Last subject last visit: 4 January 2012

Phase of development: Therapeutic exploratory (II)

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

Study centres

This was a multi-centre study conducted at 7 centres: 2 in Norway and 5 in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary objective		
To evaluate the effects of AZD2927, compared to baseline, on the left atrial effective refractory period (LAERP), in patients undergoing an invasive electrophysiological (EP) procedure	EP variable: LAERP	Pharmacodynamic
Secondary objectives		
To evaluate the effects of AZD2927, compared to baseline, on the ventricular effective refractory period (VERP), paced QT interval, and other EP and electrocardiographic variables in patients undergoing an invasive EP procedure	EP variables: VERP, PA interval; AH interval; HV interval; atrio-ventricular effective refractory period (AVERP) Electrocardiographic (ECG): PR (PQ) interval QRS duration paced QT interval RR interval	Pharmacodynamic
To investigate the safety and tolerability of AZD2927	Adverse events (AEs), ECG (including HR), BP, physical examination, weight, and laboratory variables	Safety
To describe the pharmacokinetics (PK) of AZD2927	Plasma concentration of AZD2927 including observed C_{max} and the time to C_{max} (t_{max})	Pharmacokinetic
To describe the AZD2927 PK/PD relationship for LAERP, VERP and paced QT interval	Population PK/PD variables, eg, E_{max}, EC_{50} or slope depending upon shape of the model	Pharmacokinetic/ Pharmacodynamic

BP blood pressure; C_{max} maximum plasma (peak) drug concentration; EC_{50} concentration giving 50% of the drug-induced effect (response); HR heart rate; t_{max} time to reach maximum plasma concentration.

Study design

This was a multi-centre, double-blind, randomised, parallel-group, placebo-controlled study conducted at 7 centres in Norway and Sweden. It comprised 1 dose group (and an

optional 2nd dose group) where AZD2927 or placebo was administered as an intravenous (iv) infusion. An internal safety review committee at AstraZeneca conducted an interim analysis after the 1st dose group (when data from 12 evaluable patients on AZD2927) was available. The SRC and the AZD2927 project team decided that the study should be stopped after the 1st dose group.

Target subject population and sample size

Males or postmenopausal females aged 20 to 80 years with history of paroxysmal atrial flutter scheduled for ablation that had received adequate anticoagulation or antithrombotic treatment and had sinus rhythm at randomisation were eligible for enrolment.

It was planned to randomise 24 patients in order to have 18 evaluable patients.

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

The investigational product (IP) used in the study was AZD2927 solution for infusion (0.5 mg/mL, batch 11-002109AZ) and matching placebo (batch 11-001630AZ), supplied in glass vials containing 100 mL. The IP was administered as a 15-minute iv loading infusion at the rate of 120 mL/hour (60 mg/hour), followed by a maintenance infusion for a maximum of 45 minutes at a rate of 45 mL/h (23 mg/hour).

AZD2927 and matching placebo were manufactured and supplied by AstraZeneca.

Duration of treatment

Single dose; the infusion was stopped after electrophysiological measurements had been completed or after a maximum of 60 minutes after start of infusion.

Statistical methods

The primary analysis of the primary pharmacodynamic (PD) variable of left atrial effective refractory period (LAERP), using the per-protocol (PP) approach, was based on a paired t-test of the mean difference from baseline, for patients randomised to AZD2927. It was reported using 95% confidence intervals and p-values were calculated using Student's t distribution.

The secondary PD variables of ventricular effective refractory period (VERP) and paced QT interval were analysed similarly as for LAERP. Other secondary PD variables, pharmacokinetic (PK) variables, and safety were summarised using descriptive statistics, and figures as applicable.

Subject population

The first patient was enrolled in the study on 26 September 2011 and the last patient last visit date was 4 January 2012. The study had enrolled 20 patients. The study randomised 18 patients and 12 of those patients received AZD2927. All the patients who received treatment completed the study. There were 2 important protocol deviations in 2 patients in the placebo group; these 2 patients did not fulfil eligibility criteria. In 1 patient in the AZD2927 group,

the IP administration did not comply with the method that was defined in the protocol, and this patient was excluded from the PP analysis set. The mean age of the patients was lower in the AZD2927 group (57.9 years [SD: 7.7 years]) compared to the patients in the placebo group (63.8 years [SD: 8.3 years]). The number of males was higher than females in the study. This is/was not unexpected given the low number of patients in the study. All the patients were Caucasian. All patients had a good cardiac output; and as expected in this study, most of the patients had a history of hypertension and the atria were slightly enlarged. Eight patients had experienced atrial flutter in the past and 10 patients had current atrial flutter. Three patients had experienced atrial fibrillation (AF) in the past and 3 patients had current AF. Majority of patients had a longer than expected time since last episode of atrial flutter and AF; none of the AZD2927 patients had a documented episode within the last 30 days prior to randomisation. There was not much difference in the demographic and baseline characteristics between the treatment groups.

Summary of pharmacokinetic results

The plasma concentrations obtained were as expected based on the single ascending dose (SAD) study. The mean AZD2927 plasma levels rapidly increased in a linear fashion from the start of the infusion until 15 min and then remained relatively constant during the maintenance infusion (with only a small increase at the 2nd assessment of LAERP). The mean (range) plasma concentration at the time of the 2nd LAERP measurements was 1.150 μmol/L (0.709-1.900).

Summary of pharmacodynamic results

The primary analysis of the primary PD variable (LAERP) and secondary PD variables (VERP and paced QT interval), based on the PP approach, is summarised in Table S2.

Table S2 Mean (SD) of PD variables (msec) before IP infusion, last assessment during IP infusion, and difference (Last - Before) by treatment (PP analysis set)

PD Variable	Treatment	Before IP infusion (N=17)		After last assessment of IP infusion (N=17)		Difference between time points[a]		
		n	Mean (SD)	n	Mean (SD)	Difference (SD)	95% CI	p-value
LAERP	AZD2927	11	245.9 (24.5)	11	248.6 (22.7)	2.7 (10.1)	(-4.1, 9.5)	0.3911
	Placebo	6	241.0 (34.1)	6	249.2 (24.2)	8.2 (31.4)	(-24.8, 41.2)	0.5525
VERP	AZD2927	11	224.5 (23.8)	11	223.6 (17.5)	-0.9 (9.4)	(-7.3, 5.4)	0.7560
	Placebo	6	218.3 (21.4)	6	220.0 (21.0)	1.7 (7.5)	(-6.2, 9.6)	0.6109
Paced QT interval	AZD2927	11	355.7 (32.3)	11	354.7 (31.0)	-1.0 (9.1)	(-7.1, 5.1)	0.7346
	Placebo	6	390.0 (29.5)	6	396.3 (31.2)	6.3 (8.4)	(-2.5, 15.1)	0.1236

[a] obtained from paired t-test

CI: confidence interval; IP investigational product; PD pharmacodynamic; PP per protocol ; LAERP left atrial effective refractory period; QT ECG interval measured from the onset of the QRS complex to the end of the T-wave; SD standard deviation; VERP ventricular effective refractory period.

The mean change from baseline in LAERP for the AZD2927 group was 2.7 msec (95% CI -4.1 to 9.5, p-value 0.3911). The corresponding mean change in LAERP for the placebo group was 8.2 msec (95% CI -24.8 to 41.2, p-value 0.5525). There was no statistically significant difference in either treatment group in change from baseline to last assessment for LAERP, VERP, and paced QT interval. Results from the intent to treat approach were supportive of the results of the primary analysis. Shortening on AVERP was observed for the AZD2927 group; otherwise, no systematic changes were detected for any of the other EP or ECG variables.

Summary of pharmacokinetic/pharmacodynamic relationships

The PK/PD relationship between exposure of AZD2927 and LAERP resulted in an estimated LAERP change from baseline of 2.8 msec (95% CI -7.9, 13.5) at a plasma concentration of 1.5 μmol/L. The corresponding results for paced QT resulted in an estimated change from baseline of -3.7 msec (95% CI -11.0, 3.6). Due to poor resolution of the data, it was not found meaningful to fit an exposure-response model for VERP.

Summary of safety results

Of the 18 randomised and treated patients, 12 patients were exposed to AZD2927 and 6 patients were exposed to placebo. The patients received the IP according to protocol and the planned exposure was achieved. There were very few AEs during the study. No AEs with fatal outcome or any serious AEs were reported in this study. One patient in the placebo group had premature discontinuation of IP due to an episode of AF. No patient had any AE that was reported to be severe in intensity. No AE seen in the study was assessed by the investigator as being causally related to study treatment. No relevant changes in haematology, clinical chemistry, vital signs, or ECG variables were observed.