AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00019
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A Randomised, Placebo-controlled, Double-blind, Parallel-group, Multicentre, Phase IIa Study to Explore the Relationship between QT_{cF} Interval at First Dose (Loading Dose) and at Steady State after Treatment with AZD1305 Extended-release Tablets or Placebo when given to Patients with Documented AF

Study dates: First healthy volunteer/patient enrolled: 12 March 2008
Last healthy volunteer/patient completed: 28 August 2008

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)

The study was a multicentre study in which 15 centres randomised patients ie, 4 centres in Denmark, 4 centres in Norway, 3 centres in Poland, 2 centres in Slovakia, and 2 centres in Sweden.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to explore the relationship between QT_{cF} at first dose (loading dose) and QT_{cF} at steady state after treatment with AZD1305, in order to identify outliers with regards to QT_{cF} response when given to patients with documented AF but presently in stable SR for at least 2 h and a maximum of 90 days.

The secondary objectives of the study were to:

- investigate the safety and tolerability of AZD1305 compared to placebo
- evaluate the Pharmacokinetics (PK) of AZD1305 with special regard to:

  evaluation of the influence of concomitant medication and demographic variables on the PK variables of AZD1305

  assessment of the relationship between exposure of AZD1305 and QT_{cF}
- evaluate the use of trans telephonic monitoring (TTM) measured as patient compliance, number of unscheduled recordings and correlation between symptoms and rhythm
- collect blood samples for future DNA analysis in the optional genetic research part of the study

Study design

The study was a randomised, placebo-controlled, double-blind, parallel-group, multicentre, phase IIa study. AZD1305 or placebo was administered with a first single oral loading dose followed by 9 days of maintenance treatment where IP were administered twice daily (at day 4 the patients were discharged, out-of hospital phase)

Target healthy volunteer population and sample size

The study included patients with documented AF but in stable SR for at least 2 h and a maximum of 90 days. The aim was to include 80 patients and 94 patients were enrolled of which 65 patients were randomised.

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

The details of investigational products are given in Table S 1.

Table S 1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD1305	Extended release tablet, 125 mg	AstraZeneca R&D Mölndal	H 1893-01-01	H 1893-01-01-01
AZD1305 placebo	Tablet	AstraZeneca R&D Mölndal	H 1894-01-01	H 1984-01-01-01

AZD1305 were given as extended release (ER) tablets designed to release 80% of AZD1305 within 10 hours.

Duration of treatment

The patients were randomised to one of the following treatment groups:

A. AZD1305 loading dose 250 mg + 125 mg evening dose on Study Day 1, maintenance dose 125 mg twice daily from Study Day 2 to 10.

B. AZD1305 loading dose 500 mg + placebo evening dose on Study Day 1, maintenance dose 125 mg twice daily from Study Day 2 to 10.

C. Placebo corresponding to AZD1305 loading dose + evening dose on Study Day 1, maintenance dose twice daily from Study Day 2 to 10.

Criteria for evaluation - pharmacodynamics (main variables)

ECG variables, Trans telephonic monitoring (TTM) measured as patient compliance, number of unscheduled recordings and correlation between symptoms and rhythm.

Criteria for evaluation - pharmacokinetics (main variables)

Population PK model parameter estimates derived from plasma concentrations of AZD1305.

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

The pharmacodynamic and PK analyses was based on a per protocol (PP) analysis set using an as-treated approach (ie, actual exposure). The PP analysis set includes all data in the full analysis set which can be assumed to be unaffected by major protocol deviations. The full

analysis set includes all data from all randomised subjects with available data after randomisation.

Safety analyses was based on an as-treated approach (i.e. actual exposure) on the safety analysis set consisting of all subjects who received at least one/any dose of IP, and for whom any post-dose data were available.

Subject population

65 patients were randomised of which 43 received AZD1305. There were no important imbalances between the placebo group and AZD1305 group.

Table S 2 Patient population demographic and disposition (all randomised subjects)

Demographic characteristic		**subjects/treatment group**	
		AZD1305 (n=43)	**Placebo (n=22)**
Sex (n and % of subjects)	Male	25(58%)	14(64%)
	Female	18(42%)	8(36%)
Age (years)	Mean(SD)	64(10.1)	64(8.6)
	Range	30-78	44-79
Baseline characteristic			
Weight (kg)	Mean(SD)	84(17.2)	86(11.8)
BMI (kg/m^2)	Mean(SD)	28(4.3)	29(4.6)
SBP (mmHg)	Mean(SD)	130(18.1)	138(17.7)
DBP (mmHg)	Mean(SD)	78(11)	78(8.6)
Pulse (bpm)	Mean(SD)	59(8.3)	59(8)
QT_{cF} interval (ms)	Mean(SD)	408(25.6)	407(26.1)
Disposition			
N(%) of subject who	Completed study	43(100%)	22(100%)
	Discontinued treatment	9(21%)	6(27%)
N analysed for PK and PD		43	22
N analysed for safety		34	16

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Summary of pharmacokinetic results

The pharmacokinetics of AZD1305 was described by an 1-compartment model. Apparent clearance of AZD1305 was estimated to 76.3 L/h and the interindividual variability was 43% (CV). At steady state following 125 mg of AZD1305 bd, the typical patient was predicted to have a C_{max} of approximately 0.4 µmol/L that was reached around 3.5 hours post dosing and a C_{min} of 0.2 µmol/L according to the model. The model predicted that most patients reached steady state within 48 hours. The covariate analysis showed that body weight and coronary artery disease influenced the PK of AZD1305. The oral clearance increased and the absorption rate constant decreased with increasing body weight and patients with coronary artery disease had a lower absorption rate than patients without.

Summary of pharmacodynamic results

Most patients with a maximum observed QT_{cF} <500 ms during 6 h after the first dose also had a maximum observed QT_{cF} <500 ms during the following 2-10 treatment days. There were 3 patients in group B who discontinued treatment at day 1 (after receiving the loading dose) due to QT_{cF} >550 ms. Additionally, there were 2 patients with a QT_{cF} >500 ms during days 2-10 in group B (1 patient had a QT_{cF} value of 504 ms on day 2 and the other patient had a QT_{cF} value of 517 ms on day 4 but all other measurements after day 1 were <457 ms). Both patients continued the treatment. The data indicate that in the majority of patients, the QT_{cF} at steady state could be predicted by the initial (0-6 h) QT_{cF} response after a first (loading) dose.

The compliance with the TTM procedure was very high (>97%) for the study population and there was a clear correlation between AF and symptoms with a majority of patients in AF reporting symptoms at their TTM recording. Four (4) patients reported 8 unscheduled recordings. All but one recording was associated with AF.

Summary of pharmacokinetic/pharmacodynamic relationships

The relationship between QT_{cF} and the plasma concentration of AZD1305 was described by a sigmoidal E_{max} model with effect compartment with a non-linear disappearance, which is accounting for a small delay between plasma concentration and QT_{cF} measurements. The delay between C_{max} (maximum plasma concentration) and maximum QT_{cF} was predicted in a typical patient to be 1.5 hours following a 125 mg dose of AZD1305.

The E_{max} ie, the maximum change in QT_{cF} caused by AZD1305 at an infinite concentration in the typical patient, was estimated to 141 ms (CV 32%), corresponding to a 35% increase from the estimated baseline of 408 ms (CV 4.2%).

Summary of safety results

AZD1305 was generally safe and well tolerated in AF patients receiving a first loading dose of 250 mg, followed by repeated dosing of 125 mg twice daily up to 9 days (including the out-of-hospital period, day 4 to 10).

Most AEs were of mild intensity and of a kind commonly observed in AF patients participating in clinical studies. Generally, the most commonly reported AEs were gastrointestinal disorders, general disorders, cardiac disorders and nervous system disorders. Gastrointestinal disorders were somewhat more frequent on AZD1305, and occurred on loading dose as well as maintenance dose, but the specific condition was widely distributed over the SOC. Also nervous system disorders, more specifically headache and dizziness, were reported more frequently on AZD1305, especially on loading dose.

As expected from the mode of action of AZD1305, QT prolongations were observed on AZD1305 but not on placebo. The peak in mean QT_{cF} occurred during 4-10 h after the first dose of AZD1305 in both dose groups, and was around 430 to 440 ms in treatment group A (loading dose 250 mg) and around 480 ms in treatment group B (loading dose 500 mg).

Following administration of a single 500 mg loading dose, 3 patients discontinued treatment due to QT_{cF} >550 ms according to pre-specified stopping criteria.