Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00009
Edition Number	1
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A phase I, single-centre, randomised, open, three-way crossover study to evaluate the effect of ketoconazole and verapamil, respectively, on the pharmacokinetics of AZD1305 after repeated oral administration of ketoconazole and verapamil and single oral dosing of AZD1305 to young healthy male volunteers

Study dates:	First healthy volunteer enrolled: 3 July 2008 Last healthy volunteer completed: 3 November 2008
Phase of development:	Clinical pharmacology (I)

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

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Study centre(s)

The study was a single centre-study and was conducted at PAREXEL International GmbH, Germany.

Publications

None at the time of writing this report.

Objectives

The primary objectives of the study were:

- To evaluate the effect of ketoconazole on the pharmacokinetics (PK) of AZD1305 by assessment of PK variables of AZD1305.
- To evaluate the effect of verapamil on the PK of AZD1305 by assessment of PK variables of AZD1305.

The secondary objectives of the study were:

- To evaluate the effect of AZD1305 on the PK of verapamil by assessment of PK variables of R- and S-verapamil and norverapamil.
- To evaluate the effect of ketoconazole on the pharmacodynamics (PD) of AZD1305 by assessment of digital electrocardiogram (dECG) variables.
- To evaluate the effect of verapamil on the PD of AZD1305 and vice versa by assessment of dECG variables.
- To evaluate the safety and tolerability of AZD1305 in combination with ketoconazole and verapamil, respectively, by assessment of adverse events (AEs), ECG, blood pressure (BP), pulse, weight, physical examination and laboratory variables.
- To collect and store DNA samples (from all randomised subjects who give additional informed consent) for potential future exploratory research into genes which may influence drug response of AZD1305.

Study design

AZD1305 is a novel antiarrhythmic agent and potential indications include rapid conversion of AF to sinus rhythm and maintenance of sinus rhythm after conversion of AF.

The study was a phase I, single-centre, randomised, open, three-way crossover study to evaluate drug-drug interactions of a strong (ketoconazole) or a moderate (verapamil) CYP3A4 inhibitor in steady-state and a single dose of AZD1305.

Target healthy volunteer population and sample size

The target population consisted of healthy male volunteers aged 20 to 45 years. The aim was to randomise 27 healthy volunteers.

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

The investigational products used in the study were 2 tablets of ketoconazole 200 mg (total 400 mg) once daily (Fungoral® oral tablet 200 mg, batch number H 1272-01-01-05), 1 tablet of verapamil hydrochloride 240 mg once daily (Isoptin® Retard oral extended release [ER] tablet 240 mg, batch number H 1768-01-01-04), and 1 tablet of AZD1305 125 mg (oral ER tablet 125 mg, batch number H 1893-01-01-01).

Duration of treatment

The study included 3 treatment periods with 7 to 21 days of washout between the periods:

- Ketoconazole 400 mg once daily for 5 days in combination with a single dose of AZD1305 125 mg on day 3
- Verapamil 240 mg once daily for 7 days in combination with AZD1305 125 mg on day 5
- A single dose of AZD1305 125 mg

Criteria for evaluation - pharmacokinetics (main variables)

Primary: AUC and C_{max} of AZD1305.

Secondary: AUC_{τ} and C_{max} of R- and S-verapamil and norverapamil.

Criteria for evaluation - pharmacodynamics (main variables)

Variables from dECG were RR, PQ (PR), QRS, QT and QTcF.

Criteria for evaluation - safety (main variables)

AEs, ECG, BP, pulse, weight, physical examination and laboratory variables.

Statistical methods

All data were descriptively presented.

For the primary objectives and the secondary PK objective, the log-transformed variables AUC and C_{max} were analysed using an analysis of variance model with fixed effect for treatment and a random effect for subjects.

No clinically relevant effect on the PK of AZD1305 after co-administration with ketoconazole 400 mg, or with verapamil 240 mg ER, were to be concluded if the 2-sided 90% CIs for the

within-subject ratio of both AUC and C_{max} were within 0.8 and 1.25 (the no effect boundaries).

No clinically relevant effects on the PK of verapamil after co-administration with AZD1305 were to be concluded if the 2-sided 90% CIs for the within-subject ratio of both AUCτ and C_{max} were within 0.8 and 1.25 (the no effect boundaries) for R- and S-verapamil and norverapamil.

Subject population

The study randomised 28 male healthy volunteers, 27 of these received investigational product (5 discontinued treatment) and 22 completed the study. All volunteers were Caucasians, except for 1 who was of Mixed race.

Table S 1 Subject population demographic and disposition (safety population) .

Demographic characteristic		**subjects (n=27)**
Age (years)	Mean(SD)	34(7.5)
	Range	21- 45
Baseline characteristic		
Weight (kg)	Mean(SD)	81(9.8)
BMI (kg/m^2)	Mean(SD)	25(2.4)
SBP (mmHg)	Mean(SD)	115(7.4)
DBP (mmHg)	Mean(SD)	69(8.1)
Pulse (bpm)	Mean(SD)	57(8)
QTcF interval (ms)	Mean(SD)	391(14.7)
Disposition		
N(%) of subject who	Received treatment	27(96%)
	Discontinued treatment	5(18%)
	Completed study	22(79%)
N analysed for PK and PD		25
N analysed for safety		27

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Summary of pharmacokinetic results

Co-administration of a single dose of AZD1305 and ketoconazole in steady-state resulted in significantly altered plasma levels of AZD1305. The ratio (with versus without ketoconazole) of the geometric means of AUC and C_{max} of AZD1305 were 7.66 (90% confidence interval [CI] 6.65 to 8.84) and 4.79 (90% CI 4.18 to 5.48).

Co-administration of a single dose of AZD1305 and verapamil in steady-state resulted in significantly altered plasma levels of AZD1305. The ratio (with versus without verapamil) of the geometric means of AUC and C_{max} of AZD1305 were 2.18 (90% CI 1.89 to 2.50) and 2.01 (90% CI 1.76 to 2.29).

The AUCs of S-verapamil, R-verapamil and norverapamil were not altered by co-administration with AZD1305 as the ratios (with versus without AZD1305) of the geometric means were within the pre-defined no effect boundaries of 0.8 to 1.25. The ratios (with versus without AZD1305) of the geometric means for C_{max} of S-verapamil was 1.16 (90% CI 1.01 to 1.34), for R-verapamil 1.16 (90% CI 1.01 to 1.33) and for norverapamil 1.16 (90% CI 1.01 to 1.33), with the upper limit of the CIs slightly above the no effect boundary of 1.25.

Summary of pharmacodynamic results

Co-administration of a single dose of AZD1305 and ketoconazole in steady-state increased the mean QTcF by 106 ms as maximal change at 12 h post dose. The mean individual maximal QTcF was 487 ms (highest individual maximal QTcF was 607 ms) and the increase of mean individual maximal QTcF for the combination of AZD1305 and ketoconazole was 73 ms compared to AZD1305 alone.

Co-administration of a single dose of AZD1305 and verapamil in steady-state increased the mean QTcF by 48 ms as maximal change at 6 h post dose with similar values at 4, 8 and 12 h. The mean individual maximal QTcF was 437 ms (highest individual maximal QTcF was 504 ms) and the increase of mean individual maximal QTcF for the combination of AZD1305 and verapamil was 27 ms compared to AZD1305 alone.

A single dose of AZD1305 increased the mean QTcF by 28 ms as maximal change at 12 h post dose. The mean individual maximal QTcF was 407 ms (highest individual maximal QTcF was 450 ms).

Summary of safety results

A single dose of AZD1305 125 mg was generally safe and well tolerated. There were no deaths, other serious AEs or other significant AEs in the study. Four healthy volunteers discontinued treatment due to AEs (2 due to ECG QT prolongation of which 1 was protocol mandated due to development of a specific QT-prolongation discontinuation criterion). The AEs tended to be more frequent when ketoconazole and AZD1305 were co-administereded as compared to when verapamil and AZD1305 were co-administered, or AZD1305 alone. All AEs were of a kind most commonly observed in clinical studies with healthy volunteers.

AZD1305 prolonged QT intervals as part of its mode of action. A maximal QTcF >500 ms was observed in the analysis of the dECGs in 9 of the 23 subjects who received ketoconazole and a single dose of AZD1305 and 1 of these subjects also had a maximal QTcF >500 ms when verapamil and a single dose of AZD1305 were co-administered. There were no QTcF values >500 ms on AZD1305 alone in the analysis of the dECGs. All QT prolongations were reversible and were not associated with any signs of proarrhythmia.