AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00010
Edition Number	1
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A phase I, randomised, open, single-centre, three-period crossover study to evaluate the effect of AZD1305 on the pharmacokinetics of digoxin after repeated oral administration of AZD1305 and digoxin to young healthy male volunteers

Study dates: First healthy volunteer enrolled: 18 August 2008
Last healthy volunteer completed: 18 November 2008

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

The study was a single centre-study and was conducted at the AstraZeneca R&D Clinical Pharmacology Unit at the Sahlgrenska University Hospital in Göteborg, Sweden.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was:

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

The secondary objectives of the study were:

- To evaluate the effect of digoxin on the PK of AZD1305 by assessment of PK variables of AZD1305
- To evaluate the effect of AZD1305 on pharmacodynamics of digoxin and vice versa by assessment of digital electrocardiogram (dECG) variables
- To evaluate the safety and tolerability of AZD1305 in combination with digoxin by assessment of adverse events (AEs) occurring during the study, blood pressure (BP), pulse, laboratory variables, body temperature, physical examination, ophthalmological variables, ECG and body weight
- To collect and store DNA samples (from all randomised subjects who gave additional informed consent) for potential future exploratory research into genes that 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, 3-period crossover study to evaluate PK properties of digoxin (a substrate for the transporter protein P-glycoprotein [P-gp]) after co-administration with AZD1305 (a weak inhibitor of P-gp as indicated by in vitro data).

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 18 healthy volunteers.

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

The investigational products used in the study were digoxin 0.25 mg once daily (tablet 0.25 mg, batch number H 1557-02-01-01) and AZD1305 125 mg (oral extended release [ER] tablet 125 mg, batch number H 1893-02-01-02).

Duration of treatment

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

- AZD1305 125 mg twice daily for 6 days
- AZD1305 125 mg twice daily in combination with digoxin 0.25 mg once daily for for 6 days (on the 1st treatment day digoxin was given 0.5 mg in the morning and 0.25 mg in the evening)
- Digoxin 0.25 mg once daily for 6 days (on the 1st treatment day digoxin was given 0.5 mg in the morning and 0.25 mg in the evening).

Criteria for evaluation - pharmacokinetics (main variables)

Primary: AUC_{τ} and C_{max} for digoxin.

Secondary: AUC_{τ}, and C_{max} for AZD1305.

Criteria for evaluation - pharmacodynamics (main variables)

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

Criteria for evaluation - safety (main variables)

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

Statistical methods

All data were descriptively presented.

For the primary objective and the secondary PK objective, the log-transformed variables AUC_{τ} 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 digoxin after co-administration with AZD1305 125 mg ER was to be concluded if the 2-sided 90% CIs for the within-subject ratio of both AUC_{τ} and C_{max} were within 0.8 and 1.25 (the no effect boundaries).

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

Subject population

The study randomised 18 male healthy volunteers, of which all received investigational product, and 17 completed the study. All volunteers were Caucasians.

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

Demographic characteristic		**subjects (n=18)**
Age (years)	Mean(SD)	25(4.5)
	Range	22-39
Baseline characteristic		
Weight (kg)	Mean(SD)	80(8.5)
BMI (kg/m^2)	Mean(SD)	24(2.2)
SBP (mmHg)	Mean(SD)	127(11.5)
DBP (mmHg)	Mean(SD)	71(9.5)
Pulse (bpm)	Mean(SD)	60(9.5)
QTcF interval (ms)	Mean(SD)	388(16.7)
Disposition		
N(%) of subject who	Received treatment	18(100%
	Discontinued treatment	1(6%)
	Completed study	17(94%)
N analysed for PK and PD		14
N analysed for safety		18

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Summary of pharmacokinetic results

Co-administration of digoxin and AZD1305 in steady-state resulted in similar plasma levels of digoxin compared to digoxin alone. The ratio (with versus without AZD1305) of the geometric means of AUC_{τ} and C_{max} of digoxin were 1.16 (90% confidence interval [CI] 1.11 to 1.21) and 1.20 (90% CI 1.04 to 1.40).

Co-administration of digoxin and AZD1305 in steady-state resulted in similar plasma levels of AZD1305 compared to AZD1305 alone. The ratio (with versus without digoxin) of the geometric means of AUC_{τ} and C_{max} of AZD1305 were 1.10 (90% CI 1.00 to 1.21) and 1.10 (90% CI 1.00 to 1.20).

Summary of pharmacodynamic results

Treatment with AZD1305 alone: The mean QTcF increased from before start of treatment to steady-state (day 6) with approximately 25 ms and was stable over time as measured on day 6.

The mean of individual maximal QTcF was 407 ms (highest individual maximal QTcF was 440 ms).

Co-administration of AZD1305 and digoxin: The mean QTcF increased from before start of treatment to steady-state (day 6) with approximately 25 ms and was stable over time as measured on day 6. The mean of individual maximal QTcF was 410 ms (highest individual maximal QTcF was 459 ms). No difference was seen for the mean of individual maximal QTcF relative to treatment with AZD1305 alone (mean difference between treatments was 1 ms).

Treatment with digoxin alone: The mean QTcF decreased from before start of treatment to steady-state (day 6) with approximately 20 ms and was stable over time as measured on day 6. The mean of individual maximal QTcF was 364 ms (highest individual maximal QTcF was 382 ms) and the increase of mean of individual maximal QTcF for the combination of digoxin and AZD1305 was 44 ms compared to digoxin alone.

Summary of safety results

AZD1305 was generally safe and well tolerated when administered alone and when co-administered with digoxin 0.25 mg once daily. There were no deaths, other serious AEs, other significant AEs or discontinuations of the investigational product due to AEs in the study. The frequency of AEs was similar following all 3 treatments and all AEs were of a kind commonly observed in clinical studies with healthy volunteers.

There were no clinically relevant changes in the ophthalmologic variables between pre-entry and follow-up as judged by the ophthalmologist.

AZD1305 prolonged QT intervals as part of its mode of action. There was no individual maximal QTcF >500 ms observed in the dECGs analysis after treatment with AZD1305 alone, digoxin alone or when AZD1305 and digoxin were co-administered. All QT prolongations were reversible and were not associated with any signs of proarrhythmia.