AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00021
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An Open-label Study to Assess the Effect of AZD5672 at Steady-state on the Pharmacokinetics of Digoxin Following Single Dose Administration in Healthy Volunteers

Study dates: First healthy volunteer/patient enrolled: 04 July 2008
Last healthy volunteer/patient completed: 23 December 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

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Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to examine the effect of AZD5672 (dosed to steady-state) on the pharmacokinetics of digoxin (single dose administration).

The secondary objectives of the study were:

1. To examine the effect of digoxin on the steady-state pharmacokinetics of AZD5672

2. To assess the effect of AZD5672 on the safety and tolerability of a single dose of 0.5 mg digoxin.

The exploratory objectives of the study were:

1. To explore the effect on urine pharmacokinetics when digoxin and AZD5672 were co-administered

2. To explore whether the variability in systemic AZD5672 exposures can be explained by genetic variation.

Study design

The study was designed as a 2-period, open-label, single centre study to investigate the pharmacokinetic effect of co-administrating single dose digoxin (0.5 mg) with AZD5672 at steady-state (50 and 150 mg doses) in healthy male and female subjects aged 18 to 50 years.

Target healthy volunteer population and sample size

Twenty-four healthy men or women of non-childbearing potential were recruited in 2 groups of 12 subjects.

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

Drug: AZD5672
Formulation: Tablets for oral use
Strength: 50 mg
Daily dose: Group A: 50 mg
Group B: 150 mg
Batch number: 08-012857AZ

Drug: Digoxin
Formulation: Tablets for oral use
Strength: 0.25 mg
Daily dose: 0.5 mg
Batch numbers are not required for non-investigational product/test drug

On Day 12, digoxin and AZD5672 were co-administered.

Duration of treatment

The study consisted of 2 periods, Period I lasted for 6 days and Period II for 17 days. In Period I, subjects received a single dose of digoxin 0.5 mg. Period II commenced at least 7 days after the day of digoxin dosing in Period I. In Period II, subjects received AZD5672 50 mg (Group A) or 150 mg (Group B) once-a-day for 13 days and a single dose of digoxin 0.5 mg on Day 12.

Criteria for evaluation - pharmacokinetics (main variables)

Primary:

For digoxin in plasma: C_{max}, AUC[a], $AUC_{(0-72)}$ and t_{max}

Secondary:

For digoxin in plasma: $t_{1/2}$, CL/F, V_z/F

For AZD5672 in plasma: $C_{max,ss}$, $t_{max,ss}$, AUC_{ss}[a], CL/F

Exploratory:

For digoxin in urine: $CL_{R(0-48)}$, $Ae_{(0-48)}$ and $Fe_{(0-48)}$

For AZD5672 in urine: $CL_{R(0-24)}$, $Ae_{(0-24)}$, and $Fe_{(0-24)}$

a) Depending on the actual data, other AUC parameters, eg, partial AUCs, could be derived if AUC could not reliably derived in all subjects. For digoxin, $AUC_{(0-72)}$ was derived because AUC was calculable only in 7 subjects.

Criteria for evaluation - safety (main variables)

Vital signs, clinical chemistry, haematology, urinalysis, standard ECG, telemetry, weight and AEs.

Criteria for evaluation - pharmacogenetics (main variables)

The purpose of the pharmacogenetic research was to generate data for use in future retrospective analyses in relation to AZD5672. Future analyses could explore pharmacogenetic factors which could help to explain some of the variability associated with pharmacokinetic parameters and/or observed safety profiles.

Statistical methods

To address the primary objective, a point estimate and 90% confidence interval for the ratio of AUC and C_{max} (with AZD5672 : without AZD5672) were presented for each dosing group of AZD5672. This was obtained by an analysis of the log-transformed AUC and C_{max} for digoxin using a paired t-test (comparing digoxin + AZD5672 and digoxin alone). The 90% confidence intervals limits of (0.67, 1.5) were used to interpret any evidence of any drug-drug interactions.

The influence of digoxin on steady-state PK of AZD5672 was evaluated in a similar fashion by analysis of the AUC_{ss} and $C_{ss,max}$ ratios of AZD5672 + digoxin versus AZD5672 alone, separately for each treatment group (AZD5672 50 mg and AZD5672 150 mg).

Time to peak concentration, t_{max} for digoxin (digoxin + AZD5672 versus digoxin alone) and $t_{max\ ss}$ for AZD5672 (AZD5672 + digoxin versus AZD5672 alone) data were compared using non-parametric methods.

Subject population

In total, 6 female and 18 male healthy volunteers between the age of 23 and 50 years were enrolled into the study; all of them received treatment and completed the study as per protocol. All volunteers were healthy based on the Screening Examination, complied with the inclusion criteria and none met any exclusion criteria. The 24 subjects were all included in the Safety and in the PK analysis set. No major protocol deviations were recorded.

Summary of pharmacokinetic results

Digoxin

The results of the statistical analysis of the primary endpoints of the study are summarised in Table S1 for Group A and in Table S2 for Group B.

Table S1 **Geometric mean, geometric mean ratio and 90% CIs for ratio of digoxin alone (Period I) to digoxin with steady-state AZD5672 50 mg (Period II) in Group A (PK analysis set)**

Pharmacokinetic parameter	Digoxin		Digoxin + AZD5672 50 mg		Point estimate of geomean ratio of digoxin + AZD5672 to digoxin	90%CI of geomean ratio of digoxin + AZD5672 to digoxin
	n	Geomean	n	Geomean		
Digoxin						
C_{max} (ng/mL)	12	2.87	12	2.88	1.00	0.83, 1.21
$AUC_{(0-72)}$ (ng·h/mL)	12	19.73	12	19.55	0.99	0.92, 1.07

'Digoxin' represents Day 1 (Period I), 'digoxin + AZD5672 50 mg' represents Day 12 (Period II)
C_{max}= maximum plasma concentration; $AUC_{(0-72)}$= area under the plasma concentration-time curve from time point 0 to 72 hours post-dose; CI= confidence interval; geomean= geometric mean; n= number of observations.

Table S2 **Geometric mean, geometric mean ratio and 90% CIs for ratio of digoxin alone (Period I) to digoxin with steady-state AZD5672 150 mg (Period II) in Group B (PK analysis set)**

Pharmacokinetic parameter	Digoxin		Digoxin + AZD5672 150 mg		Point estimate of geomean ratio of digoxin + AZD5672 to digoxin	90%CI of geomean ratio of digoxin + AZD5672 to digoxin
	n	Geomean	n	Geomean		
Digoxin						
C_{max} (ng/mL)	12	2.58	12	4.70	1.82	1.38, 2.39
$AUC_{(0-72)}$ (ng·h/mL)	12	19.85	12	26.35	1.33	1.12, 1.57

'Digoxin' represents Day 1 (Period I), 'digoxin + AZD5672 150 mg' represents Day 12 (Period II)
C_{max}= maximum plasma concentration; $AUC_{(0-72)}$= area under the plasma concentration-time curve from time point 0 to 72 hours post-dose; CI= confidence interval; geomean= geometric mean; n= number of observations.

The PK of digoxin was affected by AZD5672 150 mg (Group B), but not by AZD5672 50 mg (Group A), both given at steady-state. In Group B, exposure to digoxin in terms of $AUC_{(0-72)}$ increased by about 1.3-fold (90% CI: 1.12; 1.57), whereas geometric mean C_{max} of digoxin increased by about 1.8-fold with a corresponding 90% CI (1.38; 2.39) that was clearly above the pre-defined interval of (0.67; 1.5).

There were no significant differences between digoxin t_{max} after administration of digoxin alone and in combination with AZD5672 50 mg (90% CI: –0.250 hours; 0.125 hours) or 150 mg (90% CI: –0.375 hours; 0.125 hours).

AZD5672

The results of the statistical analysis of the secondary endpoints of the study regarding AZD5672 are summarised in Table S3 for Group A and in Table S4 for Group B.

Table S3 Geometric mean, geometric mean ratio and 90% CIs for ratio of AZD5672 50 mg alone or with digoxin (Period II) in Group A (PK analysis set)

Pharmacokinetic parameter	AZD5672 50 mg		AZD5672 50 mg + digoxin		Point estimate of geomean ratio of AZD5672 + digoxin to AZD5672	90%CI of geomean ratio of AZD5672 + digoxin to AZD5672
	n	Geomean	n	Geomean		
AZD5672 50 mg						
$C_{ss\ max}$ (nM)	12	49.06	12	36.17	0.74	0.48, 1.14
AUC_{ss} (nM·h)	12	330.37	12	276.47	0.84	0.64, 1.09

'AZD5672 50 mg' represents Day 10 (Period II), 'AZD5672 50 mg + digoxin' represents Day 12 (Period II)
C_{max}= maximum plasma concentration; AUC_{ss}= area under the plasma concentration-time curve at steady-state; CI= confidence interval; geomean= geometric mean; n= number of observations.

Table S4 Geometric mean, geometric mean ratio and 90% CIs for ratio of AZD5672 150 mg alone or with digoxin (Period II) in Group B (PK analysis set)

Pharmacokinetic parameter	AZD5672 150 mg		AZD5672 150 mg + digoxin		Point estimate of geomean ratio of AZD5672 + digoxin to AZD5672	90%CI of geomean ratio of AZD5672 + digoxin to AZD5672
	n	Geomean	n	Geomean		
AZD5672 50 mg						
$C_{ss\ max}$ (nM)	12	299.08	12	341.67	1.14	0.96, 1.36
AUC_{ss} (nM·h)	12	1906.84	12	2029.56	1.06	0.97, 1.17

'AZD5672 150 mg' represents Day 10 (Period II), 'AZD5672 150 mg + digoxin' represents Day 12 (Period II)
C_{max}= maximum plasma concentration; AUC_{ss}= area under the plasma concentration-time curve at steady-state; CI= confidence interval; geomean= geometric mean; n= number of observations.

Geometric mean plasma concentrations of AZD5672 after administration of AZD5672 50 mg with digoxin in Group A tended to be lower than without digoxin, but tended to be slightly higher after dosing AZD5672 150 mg with digoxin in Group B, however these differences were small relative to the inter-subject variability.

The PK parameters of AZD5672 50 mg showed lower geometric mean AUC_{ss} and $C_{ss\ max}$ values after co-administration of AZD5672 50 mg with digoxin. Three subjects showed unusually flat concentration-time profiles indicative for little or no significant absorption of AZD5672 after combination of AZD5672 50 mg and digoxin compared with AZD5672 alone. A post-hoc sensitivity analysis showed no evidence for a relevant effect of digoxin on the PK of AZD5672 at steady-state in the remaining subjects. The geometric mean PK parameters of AZD5672 after administration of AZD5672 150 mg with and without digoxin revealed also no remarkable effect on the PK of AZD5672.

For the AZD5672 50 mg dose (Group A), using data from all 12 subjects, the point estimates of the geometric mean ratios for both, AZD5672 $C_{ss\ max}$ and AUC_{ss}, were below unity and the lower limits of the 90% CIs were both below the interval of 0.67 and 1.5. Whereas, the post-hoc sensitivity analysis, omitting the data of the 3 outliers provided point estimates slightly above unity and 90% CIs that were both within the pre-defined interval of 0.67 and 1.5 ($C_{ss\ max}$ ratio: 1.10; 90% CI: 0.85,1.42 and AUC_{ss} ratio: 1.06; 90%CI: 0.96,1.16). Since these low AZD5672 exposures are much lower than seen in these subjects in Period I or in the other subjects in Periods 1 or 2, these low exposures are thought to be outliers. The reason for these low exposures is currently unknown. The results from the post-hoc analysis, is consistent with that seen following 150 mg AZD5672. For the AZD5672 150 mg dose (Group B), the geometric mean ratios for both, AZD5672 $C_{ss\ max}$ and AUC_{ss} after dosing AZD5672 150 mg with and without digoxin, were also slightly above unity and the 90% CIs were both entirely within the interval of 0.67 and 1.5.

Overall, there was no indication of an effect of a single dose of digoxin 0.5 mg on AZD5672 $C_{ss\ max}$ and AUC_{ss} after dosing AZD5672 50 or 150 mg.

Summary of safety results

A total of 2 AEs were reported by 2 (17%) subjects during administration of AZD5672 50 mg (Group A) and 8 AEs by 4 (33%) subjects on AZD5672 150 mg (Group B), alone or in combination with digoxin. Treatment with digoxin alone was followed by 6 AEs in 1 (8%) subject. Adverse events considered by the Investigator to be causally related to IP comprised only headache, one was reported after AZD5672 50 mg in Group A and one after AZD5672 150 mg in Group B. All AEs were of mild intensity except for one headache (Group B) of moderate intensity. No AE was of severe intensity, and no SAE, discontinuation due to AE, or other significant AEs were observed.

There were no clinically relevant changes in safety laboratory variables, vital signs, ECG, and physical examination.