AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00006
Edition Number	01
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A Single-centre, Double-blind, Double-dummy, Randomised, Placebo Controlled, Four-Period Crossover Study to Assess the Effect of Single Oral Doses of AZD5672 (600 mg and 150 mg) on QT/QTc Interval, Compared to Placebo, using Moxifloxacin (Avelox®) as a Positive Control, in Healthy Male Volunteers

Study dates: First healthy volunteer/patient enrolled: 30 March 2009
Last healthy volunteer/patient completed: 19 June 2009

Phase of development: Clinical pharmacology (1)

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

Study centre(s)

This study was conducted in the United Kingdom at Quintiles Drug Research Unit at Guy's Hospital.

The first healthy volunteer was enrolled on 30th March 2009 and the last healthy volunteer completed the study on 19th June 2009.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives and criteria for evaluation are summarised below.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the change in time-matched QTcF intervals of single dose AZD5672 600 mg compared to placebo.	QTcF	Pharmacodynamic (PD)
Supporting comparison: To evaluate the change in time-matched QTcF intervals of moxifloxacin 400 mg compared to placebo.	QTcF	PD
Secondary	**Secondary**	
To evaluate the change in time-matched QTcF intervals after administration of single dose AZD5672 150 mg compared to placebo.	QTcF	PD
To evaluate the change in time-matched ECG parameters (QTcB, QTcX, RR, PR, and QRS) of single dose AZD5672 600 mg and 150 mg compared to placebo.	QTcB, QTcX, RR, PR and QRS	PD
The relationship between plasma AZD5672 concentrations and changes in QTc parameters were investigated	Plasma concentrations of AZD5672, QTcB, QTcX, and QTcF	Pharmacokinetic (PK)/PD[a]
To further evaluate the safety and tolerability of single dose AZD5672 600 mg and 150 mg.	Adverse events; laboratory variables: haematology, clinical chemistry, urinalysis; physical examination; 12-Lead ECG; vital signs: blood pressure, pulse, body temperature, respiratory rate	Safety
To describe the pharmacokinetics of single dose AZD5672 600 mg and 150 mg in healthy volunteers.	Plasma concentrations of AZD5672, and PK variables AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_Z//F	PK

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Exploratory	**Exploratory**	
Possible assessment of PK of AZD5672 metabolite(s) and their relationship to changes in QT interval.	Plasma concentrations of AZD5672 metabolite, QTcB, QTcX, and QTcF	PK/PD[a]
To provide samples to allow investigation of genetic factors that may help explain some of the variability observed in the QT interval of AZD5672 and moxifloxacin, and the variability in the pharmacokinetics, tolerability, and safety of AZD5672.	Plasma concentrations of AZD5672, moxifloxacin, QTcB, QTcX, QTcF, phenotype, and genotype	PK/PD/PGX[a]

[a] These objectives were intended to be investigated separate from the CSR.

Study design

This was a double-blind, double-dummy, randomised, placebo-controlled, 4-way crossover study evaluating single doses of AZD5672 600 mg and 150 mg compared with placebo and a single-dose of 400 mg oral moxifloxacin as a positive control.

The study consisted of 6 visits. During each 5-day period, each healthy volunteer received 1 of the 4 treatments in 1 of 4 treatment sequences, using the sequences of ABCD, BDAC, CADB, and DCBA in a double-blind fashion determined by a randomisation schedule. The washout time between the treatment periods was at least 14 days.

Target subject population and sample size

Sixty-four subjects were enrolled onto the study.

Subjects were to be healthy males aged between 18 and 45 years (inclusive) of age, current non-smokers with a Body Mass Index (BMI) of ≥19 to ≤30 kg/m^2.

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

Investigational product: AZD5672 50 mg oral tablet, batch number 08-002434AZ; AZD5672 placebo matched to AZD5672 50 mg tablet, batch number 08-013515AZ.

Non-investigational products: Moxifloxacin 400 mg capsule; moxifloxacin placebo matched to moxifloxacin 400 mg oral capsule.

Duration of treatment

Each subject was to receive single doses of AZD5672 600 mg, AZD 5672 150 mg and moxifloxacin 400 mg.

Statistical methods

Pharmacodynamics

QTcF was used as the primary QTc variable for the assessment of QT/QTc prolongation. Secondary QTc variables included QTcB and QTcX. Other ECG parameters evaluated included QT, RR, PR, and QRS.

For the primary analysis of QT prolongation, the least-squares (LS) mean and 2-sided 90% CI for the treatment compared to placebo for the change in QTcF was estimated at each of the 9 post-dose timepoints. This analysis of QTcF was carried out using a repeated measures analysis of covariance (ANCOVA) model.

To test the treatment effect of AZD5672 600 mg and AZD5672 150 mg versus placebo, the upper bounds of the 2-sided 90% confidence intervals were evaluated against the margin of 10 ms. If all 9 upper bounds fell below 10 ms it was to be concluded that AZD5672 does not induce a prolongation of the QTc interval compared to placebo.

To test assay sensitivity, the linear contrast comparing moxifloxacin versus placebo for the mean QTcF across the first 1 to 4 hours post-dose (time points 1, 1.5, 2, 3, and 4 hours) was made and a 2-sided 90% confidence interval presented. The lower bound of the 2-sided 90% CI was evaluated against the 5 ms threshold.

The number and percentage of subjects exceeding ICH E14 recommended boundaries (ie, >450 ms, >480 ms, and >500 ms, for observed values; and >30 ms, and >60 ms, for change from baseline values) were summarized by treatment for QTcF, QTcB, and QTcX.

Pharmacokinetics

Pharmacokinetic parameters for AZD5672 and moxifloxacin were estimated by non-compartmental analysis using WinNonLin. Summary statistics of concentrations and PK parameters of AZD5672 and moxifloxacin were generated.

Safety

No formal statistical analysis of the safety data was done. Safety and tolerability data are summarized descriptively by treatment and presented in tabular form. All adverse event data are listed individually and summarized using MedDRA® terminology. Clinical laboratory and vital signs data were analyzed using descriptive statistics by treatment and protocol time point.

Subject population

Subjects were aged between 19 and 45 years of age, current non-smokers and had a Body Mass Index (BMI) between 19 and 29 kg/m^2. Some subjects had out-of-range values at baseline for laboratory safety tests, vital signs or ECG parameters; upon review of the data the investigator considered that these values were not clinically significant and that the subjects were healthy and eligible to participate in the study.

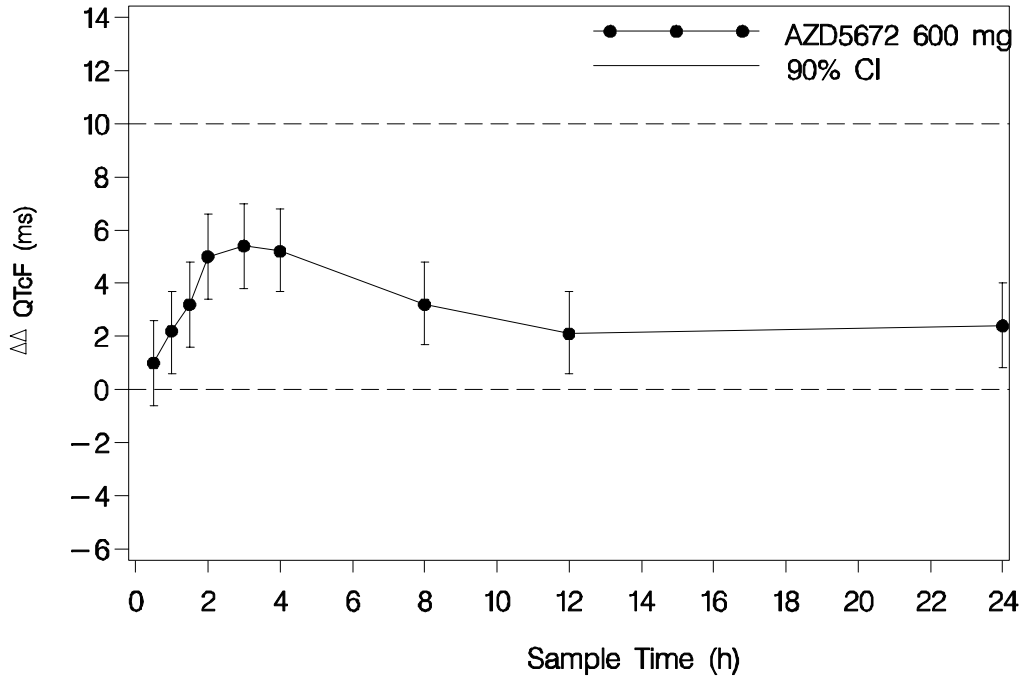
In total 59 healthy volunteers completed the study as planned. Five healthy volunteers discontinued study treatment. One subject was withdrawn due to a moderate adverse event of cellulitis; 1 subject was withdrawn due to a failure to meet inclusion/exclusion criteria for LFTs at admission to Period 4; 1 subject was withdrawn due to severe non-compliance with the protocol; 2 subjects withdrew consent.

Summary of pharmacodynamic results

Assay sensitivity was confirmed in the study: The lower bound of the 2-sided 90% CI for the difference between moxifloxacin 400 mg and placebo was above the 5 ms threshold across the pre-selected timepoints (1, 1.5, 2, 3, and 4-hours post-dose).

For the comparison of AZD5672 600 mg versus placebo, all upper bounds of the 2-sided 90% CI for the placebo-subtracted mean change from baseline in QTcF (ΔΔQTcF) were below 10 ms. Similar results were observed for QTcX and QTcB.

Figure S1 Placebo subtracted LS mean difference (2-sided 90% CI) in QTcF of AZD5672 600 mg by sample time, adjusted for baseline (Per protocol analysis set)



For the comparison of AZD5672 150 mg versus placebo, all upper bounds of the 2-sided 90% CI for the placebo-subtracted mean change from baseline in QTcF (ΔΔQTcF) were below 10 ms. Similar results were observed for QTcX and QTcB.

There were no increases from baseline of >30 ms for QTcF, or observed QTcF>450 ms, at any timepoint over the 24 h period after dosing.

There was no apparent effect of AZD5672 on other ECG variables such as RR, PQ, and QRS.

Summary of pharmacokinetic results

The PK data for AZD5672 showed that subjects were exposed to AZD5672, and exposure increased with dose. The QTc effects appeared to follow the AZD5672 concentration-time profile, with the maximal concentration and QTc both observed at 3 h post-dosing for the 600 mg dose.

The PK data for moxifloxacin showed that subjects were exposed to moxifloxacin. The QTc effects on moxifloxacin appeared to follow the general moxifloxacin concentration-time profile, and declined from 4h after dosing.

Summary of safety results

There were no deaths, serious adverse events or other significant adverse events during the study. No safety concerns were identified in this study up to the highest dose given (600 mg).

There was 1 discontinuation due to an adverse event (DAE). Subject E0001073 had a moderate adverse event of cellulitis beginning 81 hours and 37 minutes after the last dose of study drug. The cellulitis was not considered by the investigator to be related to study treatment.

The majority of adverse events (AEs) were of mild intensity. There were 4 subjects with AEs of moderate intensity, these were: ankle fracture, chest injury, headache and cellulitis. All moderate AEs were considered by the investigator to be not related to treatment. There were no AEs of severe intensity.

Five subjects had AEs considered by the investigator to be related to AZD5672. These were: dizziness, dry throat, gastritis, headache [2 subjects] and hot flush. One subject receiving placebo had an AE considered by the investigator to be related to treatment (hot flush), and 4 subjects had AEs considered by the investigator to be related to moxifloxacin (abdominal pain upper, dizziness, headache [2 subjects] and restlessness).