AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3199
Study Code	D0570C00004
Edition Number	1
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A single-centre, randomised, double-blind, double-dummy, placebo-controlled, 4-way crossover Phase I study to investigate the effect of 2 single doses (400 µg and 1200 µg) of inhaled AZD3199 on QT/QTc interval, compared to placebo, using moxifloxacin (Avelox®) as a positive control, in healthy male volunteers

Study dates: First subject enrolled: 01 November 2010
Last subject last visit: 14 February 2011

Phase of development: Clinical Pharmacology (1)

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

Publications

None at the time of writing this Clinical Study Report (CSR).

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary		
To investigate the effect of AZD3199 on the QT interval	Primary variable: QTcF Secondary variables: -QTcI and QTcB -Holter-Bin QT	Pharmaco-dynamics (PD)
Secondary		
To investigate the effect of AZD3199 on additional electrocardiogram (ECG) variables	RR interval, PQ interval, and QRS duration	PD
To assess the pharmacokinetics (PK) of single doses of AZD3199	AZD3199 plasma concentrations, $AUC_{(0-24)}$, C_{max}, and t_{max}	PK
To evaluate the safety and tolerability of single doses of AZD3199	Adverse events (AEs), safety laboratory variables (clinical chemistry, haematology, urinalysis), vital signs (blood pressure, pulse rate) and ECG parameters	Safety
To assess effects on serum potassium concentration of single doses of AZD3199	Serum potassium concentrations, E_{av} (for 0 to 4 hours), and E_{min}	PD
Exploratory		
To explore the relationship between AZD3199 plasma concentrations and the QT interval	Analysis will be performed at a future date and results will be reported outside of this study report	PK
To explore the relationship between serum potassium concentrations and the QT interval	ΔQTc versus change-from-baseline serum potassium concentrations	PD

$AUC_{(0-24)}$ Area under the plasma concentration-time curve from time zero to 24 hours
C_{max} Maximum plasma concentration
E_{av} Average effect
E_{min} Minimum effect
PQ ECG interval measured from the beginning of the P wave to the beginning of the Q wave, or as PR to the beginning of the R wave if Q wave not present
QRS ECG interval measured from the beginning of the Q wave (or the R wave if Q is missing) to the J point
QT ECG interval measured from the beginning of the Q wave (or the R wave if Q is missing) to the end of the T wave

QTcB QT interval corrected for heart rate using Bazett's formula
QTcF QT interval corrected for heart rate using Fridericia's formula
QTcI QT interval, individually corrected for heart rate
RR The time between corresponding points on 2 consecutive R waves on ECG
t_{max} Time to maximum concentration
Note: QTcB was not a primary variable but had been included and reported in the Clinical Study Report for historical comparisons.

Study design

This was a double-blind, double-dummy, randomised, placebo-controlled, 4-way crossover study evaluating single delivered doses of AZD3199 400 µg and 1200 µg compared with placebo and a single 400 mg dose of oral moxifloxacin as a positive control. The primary variable was defined by an algorithm-driven choice between QTcF and QTcI.

The 2 doses of AZD3199 investigated in this study, 400 µg and 1200 µg, were selected to represent the upper limit of the dose interval considered of clinical relevance and a substantial multiple of this dose.

Each treatment visit consisted of 3 study days (Day -1, Day 1 and Day 2 [24 hour measurements]). All treatment visits started with a "dummy-day" (Day -1) without investigational product administration, where ECG measurements were performed according to same schedule as on the dosing day to record the individual QT intervals at different RR intervals. Randomisation to treatment group was done in the morning of Day 1, Period 1 (Visit 2). Treatments were administered on Day 1 of each treatment visit (Visits 2 to 5).

Target subject population and sample size

The study was restricted to healthy male subjects aged 18 to 45 years, inclusive. It is known that female subjects have greater inter- and intra-individual variation for QT interval, but since the objective of the study was to study a model situation, it was considered appropriate to exclude female subjects to maximise precision. Healthy volunteers were chosen to avoid interference from disease processes or other drugs.

In total, 41 healthy male subjects were randomised.

A sample size of 40 subjects was considered sufficient to reliably characterise the QTc effect profile in this pilot study. For example, under the assumptions of a within-subject standard deviation (SD) of 8 milliseconds (ms) in the ΔQTc, α=0.05, a hypothetical mean time-matched, placebo-corrected QTc profile of (1, 1, 3, 3, 2, 2, 2, 2, 1) for the 9 planned ECG assessments, and constant within-day correlation of 0.5 for a subject, 40 completing subjects would provide greater than 80% power to conclude that a single dose level of AZD3199 does not prolong QTc beyond 10 ms under inter-section union testing.

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

Each subject received the 4 treatments (expressed as delivered dose from a Turbuhaler inhaler) in a randomised order.

- Treatment A: AZD3199 400 µg + moxifloxacin placebo
- Treatment B: AZD3199 1200 µg + moxifloxacin placebo
- Treatment C: AZD3199 placebo + moxifloxacin 400 mg
- Treatment D: AZD3199 placebo + moxifloxacin placebo

Batch numbers: AZD3199 200 µg (09-002574AZ), AZD3199 400 µg (09-002575AZ), AZD3199 placebo (09-002533AZ), moxifloxacin 400 mg (09-004206AZ), moxifloxacin placebo (10-004623AZ)

Duration of treatment

The study comprised 6 visits: Visit 1 (enrolment and screening), Visits 2 to 5 (treatment visits), and Visit 6 (follow-up). The screening visit took place within 21 days prior to Visit 2. Between each treatment there was a washout period of at least 14 days but not more than 26 days.

Statistical methods

The primary variable, either QTcF or QTcI, was chosen by an algorithm-driven decision prior to inference. The QTc variable not selected as primary became the secondary variable in addition to all remaining digital ECG (dECG) intervals. All other dECG intervals (uncorrected QT, heart rate [HR], RR, PR and QRS) were defined as secondary variables. In addition, Holter-Bin methods for the uncorrected QT interval were used as a secondary analysis.

Primary analysis: Analysis of change-from-baseline QTcF was carried out using a repeated measures linear mixed model.

To test the treatment effect on primary variable for each dose level of AZD3199, the upper bounds of the 2-sided 90% confidence interval (CI) for treatment contrasts were evaluated against the 10 ms threshold. The null hypothesis was that AZD3199 prolongs QTc (QTcI/QTcF) relative to placebo by at least 10 ms for at least 1 postdose assessment. The alternative hypothesis was that AZD3199 does not prolong QTcI/F by 10 ms or more for any postdose assessment.

Secondary analyses: To test the treatment effect of AZD3199 on the secondary QTc (QTcI or QTcF) intervals, the model described above was used and the upper bounds of the 2-sided 90% CI for the AZD3199 contrasts at all postdose time points was evaluated against the margin of 10 ms. Analysis of secondary ECG intervals was completed in a method similar to the methods described above and contrasts for QT, RR, PR, and QRS were not subject to a specific threshold for interpretation.

Holter-Bin analysis: The analyses were done ad-hoc separately from the other Clinical Study Protocol analyses, using R version 2.11.0. Dummy-day-adjusted Holter-Bin 12-lead overall

QT values were compared across treatments using t-tests on moving average smoothed data and time-specific t-tests for each minute interval. Estimates and 2-sided 95% CIs of differences versus placebo were presented.

Assay sensitivity: To test the assay sensitivity, the treatment effect of moxifloxacin was evaluated for the primary QTc interval and assay sensitivity was concluded if the lower bound excluded 5 ms.

Categorical analysis: The number and percentage of subjects on treatment exceeding International Conference on Harmonisation (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 summarised by treatment for QTcF, and QTcI.

Serum potassium analysis: Observed and change-from-baseline serum potassium concentrations at each time point and serum potassium PD parameters (E_{av} [for 0 to 4 hours] and E_{min}) were summarised by treatment.

Serum potassium parameters E_{av} and E_{min} were compared between the two AZD3199 dose levels and moxifloxacin relative to placebo using linear mixed models. As an exploratory assessment, ΔQTc were plotted against change-from-baseline serum potassium concentrations with the former as the dependent variable.

Adverse events are summarised using the Medical Dictionary for Regulatory Activities (MedDRA). Continuous variables (haematology, clinical chemistry, thyroid function, and vital signs) were summarised using descriptive statistics by treatment group and scheduled assessment point. Categorical variables (eg, urinalysis) were summarised in frequency tables by treatment group and scheduled assessment point. Further, safety data were judged regarding low/high values or large changes from predose using the AstraZeneca extended reference limits. Abnormalities found on physical examination are listed.

Subject population

In total 41 healthy male subjects aged 20 to 44 years participated in the study consistent with the study enrolment criteria.

Five (5) subjects prematurely discontinued the study.

Summary of pharmacokinetic results

The $AUC_{(0-24)}$ and C_{max} were 3.6-fold higher for 1200 µg AZD3199 when compared to the 400 µg dose group. The estimated median t_{max} was similar between the dose groups. The PK for both AZD3199 and moxifloxacin were comparable to the historical data.

Summary of pharmacodynamic results

QTcF was determined as the primary variable over QTcI due to better correction for RR under placebo treatment.

The table below highlights only the largest placebo-corrected change-from-baseline results and the time at which they occurred for QTcF, QTcI and QTcB.

Table S2 Largest time-matched, placebo-corrected change-from-baseline results for secondary QTc variables

				Comparison to placebo	
QTc Variables	**Treatment**	**Time of Largest ΔΔQTc (h)**	**N**	**Difference**	**90% CI**
QTcF	AZD3199 400 µg	0.5	38	2.4	(0.5, 4.4)
	AZD3199 1200 µg	1.0	38	10.3	(8.4, 12.2)
	Moxifloxacin 400 mg	4.0	38	10.9	(9.0, 12.8)
QTcI (ms)	AZD3199 400 µg	0.5	38	2.5	(0.6, 4.4)
	AZD3199 1200 µg	1.0	38	9.6	(7.7, 11.5)
	Moxifloxacin 400 mg	4.0	38	10.2	(8.3, 12.1)
QTcB (ms)	AZD3199 400 µg	0.5	38	5.0	(2.7, 7.4)
	AZD3199 1200 µg	0.5	38	17.4	(15.0, 19.8)
	Moxifloxacin 400 mg	2.0	38	12.6	(10.3, 15.0)

ΔΔ placebo-corrected change-from-baseline; CI confidence interval.

- For the AZD3199 1200 µg single dose (supra-therapeutic dose), the largest mean time-matched, baseline-adjusted, difference compared to placebo in QTcF was an increase of 10.3 ms (90% CI of 8.4, 12.2 ms) at 1 hour postdose, that is, after the C_{max} (t_{max} of 0.5 hours postdose) of AZD3199 was achieved. Also, the 90% CI did not exceed 10 ms at any other time point after 1 hour following administration of 1200 µg of AZD3199

- At the AZD3199 400 µg single dose (assumed maximum therapeutic dose), the largest mean time-matched, baseline-adjusted, difference compared to placebo in QTcF was an increase of 2.4 ms (90% CI of 0.5, 4.4 ms) at 0.5 hour postdose

- For the moxifloxacin 400 mg single dose, the largest mean time-matched, baseline-adjusted, difference compared to placebo in QTcF was an increase of 10.9 ms (90% CI of 9.0, 12.8 ms) at 4 hours (estimated t_{max} about 1.5 hours). Since the lower bound of the 2-sided 90% CI excluded 5 ms threshold, the assay sensitivity was considered to be established for this study

- Results for QTcI and Holter-Bin were essentially in line with the results obtained on QTcF. On Holter-Bin, estimated maximum mean difference compared to placebo was 7.3 ms (at 28 minutes postdose) for AZD3199 1200 µg, 2.7 ms (at 51 minutes

postdose) for AZD3199 400 µg and 11.0 ms (at 169 minutes postdose) for moxifloxacin 400 mg

- No subjects reached the threshold of QTcF >450 ms or the change-from-baseline threshold of an increase in QTcF >30 ms, for any treatment

- The largest baseline-adjusted difference compared to placebo in HR was 7.3 bpm after 1200 µg and 2.7 bpm after 400 µg AZD3199; both occurred at 0.5 hours and coincided with or preceded the maximum effect on QTcF. Compared to placebo, the uncorrected QT was increased for moxifloxacin but decreased for AZD3199

- For serum potassium, a statistically significant but not clinically meaningful decrease was observed, with a change-from-baseline E_{min} between AZD3199 1200 µg and placebo: -0.074 mmol/L, 95% CI (-0.124,-0.025) but no difference was observed for E_{av}. No difference was shown between AZD3199 400 µg and placebo

Summary of pharmacokinetic/pharmacodynamic relationships (not applicable)

Summary of pharmacogenetic results (not applicable)

Summary of safety results

- No deaths, serious adverse events (SAEs), discontinuation of investigational product due to an AE (DAEs), or other significant adverse events (OAEs) were reported during the study

- Somewhat more subjects in the AZD3199 1200 µg group (supra-therapeutic dose) reported AEs compared to the other treatment groups. However, there were no clinically important differences between the treatment groups regarding the nature or severity of the AEs. No AEs of severe intensity were reported

- There were no clinically significant changes for laboratory values, vital signs, or the investigator's interpretation of ECGs