AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00011
Edition Number	1
Date	5 December 2011

A Single-Centre, Double-Blind, Double-Dummy, Randomised, Placebo-Controlled, 4-Period Cross-Over Study in Healthy Male Subjects to Assess the Effect on QT/QTc Interval of Single Oral Doses of AZD1981 (200 mg and 2000 mg) using Moxifloxacin (Avelox®) as a Positive Control

Study Dates: First subject enrolled: 12 January 2011
Last subject last visit: 21 April 2011

Phase of Development: Clinical Pharmacology (1)

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

Study centre

One study centre in the

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the change in time-matched QTcF intervals after administration of a single supra therapeutic dose of AZD1981 (2000 mg) compared with placebo	QTcF	PD
Secondary	**Secondary**	
To evaluate the change in time-matched QTcF intervals after administration of a single assumed therapeutic dose of AZD1981 (200 mg) compared with placebo	QTcF	PD
To evaluate the change in time-matched electrocardiogram parameters (QTcB, RR, PR and QRS) after administration of single doses of AZD1981 200 mg and 2000 mg compared with placebo	QTcB, RR, PR, and QRS	PD
Supporting comparison: To evaluate the change in time-matched QTcF intervals after administration of moxifloxacin 400 mg compared with placebo	QTcF	PD
To evaluate the safety and tolerability of single doses of AZD1981 200 mg and 2000 mg	Adverse events, laboratory assessments[a], vital signs, electrocardiogram, and physical examination	Safety
To describe the PK of single doses of AZD1981 200 mg and 2000 mg, and moxifloxacin 400 mg	AUC, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2\lambda z}$, CL/F, V_z/F, and MRT	PK

Objectives	Outcome variables	Type
Exploratory	**Exploratory**	
To investigate the relationship between plasma AZD1981 concentrations and changes in QTc parameters	NA	PK
To assess the PK of any significant AZD1981 metabolite(s) and their relationship to changes in QT interval, if an effect on QT is found[b]	NA	PK
To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence response ie, PK, tolerability, and safety of AZD1981 and that may explain some of the variability observed in the QT interval of AZD1981 and moxifloxacin[b]	NA	Pharmacogenetic

a Laboratory assessments are listed in Table 5 of the CSP.
b Reported separate from the Clinical Study Report, if conducted.

AUC: Area under the plasma concentration-time curve from zero to infinity; AUC_{0-t}: Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; CL/F: Apparent plasma clearance; C_{max}: Maximum plasma concentration; CSP: Clinical Study Protocol; MRT: Mean residence time; NA: Not applicable; PD: Pharmacodynamics; PK: Pharmacokinetics; $t_{1/2\lambda z}$: Terminal half-life; t_{max}: Time of maximum plasma concentration; V_z/F: Volume of distribution during the terminal phase.

Study design

This was a double-blind, double-dummy, randomised, placebo-controlled, 4-way cross-over study in 43 healthy male subjects. The study consisted of 6 visits and 4 treatment periods. During each 3-day treatment period, each subject was to receive a single dose of 1 of the 4 treatments (AZD1981 2000 mg [Treatment A], AZD1981 200 mg [Treatment B], moxifloxacin 400 mg [Treatment C], and placebo [Treatment D]) in 1 of the 4 treatment sequences (ADBC, BACD, CBDA, or DCAB) as determined by the randomisation schedule.

Target subject population and sample size

44 healthy male subjects

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

The study centre was provided with subject-specific kits containing all investigational products.

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
AZD1981	Tablet, 100 mg, oral	AstraZeneca	10-006358AZ
Avelox® (moxifloxacin)	Encapsulated tablet, 400 mg, oral	Bayer	10-006358AZ
Placebo matched to AZD1981	Tablet, 0 mg, oral	AstraZeneca	10-006358AZ
Placebo matched to Avelox®	Encapsulated tablet, 0 mg, oral	AstraZeneca	10-006358AZ

Duration of treatment

This was a cross-over study with a single dose in each of 4 treatment periods, separated by a wash-out period of at least 7 days.

Statistical methods

The analysis of change from baseline for QTcF (primary) was performed using a repeated measures linear mixed model with fixed effects for treatment, period, time, period*time, treatment*time and the baseline value as covariate. Subject was treated as a random effect. Time was treated as repeated effect within subject-period using an appropriate covariance. At each of the post-dose electrocardiogram (ECG) nominal times, the least-squares means with corresponding 2-sided 90% confidence interval (CI) for the treatment compared to placebo were computed. To test the treatment effect for each dose level of AZD1981, the upper bounds of these intervals were compared against the 10 ms threshold under an intersection-union test. To conclude that a dose showed no effect on the QTcF interval, all upper confidence bounds needed to be less than 10 ms. Sensitivity analyses were also conducted, including analysis using separate models for each time point.

To test the assay sensitivity of the study, the treatment effect of moxifloxacin (from the model above) was evaluated by estimating the mean difference to placebo for the mean of QTcF during the 1 to 4 hour period post-dose with a corresponding 2-sided 90% CI. The lower bound of this 2-sided interval was evaluated against the 5 ms threshold, and assay sensitivity concluded if the lower bound was above this.

The analyses of safety and tolerability data were summarised descriptively including tables, listings and graphs, as appropriate.

Subject population

Planned: 44 subjects

Enrolled: 43 subjects

Randomised: 43 subjects

Completed: 42 subjects

All subjects were male with an age range of 19 to 54 years (mean 32 years, median 31 years) and a body mass index (BMI) range of 19.0 to 29.2 kg/m^2 (mean 24.7 kg/m^2, median 24.8 kg/m^2), in accordance with the inclusion criteria.

Summary of pharmacokinetic results

The maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to infinity (AUC) achieved in this study by AZD1981 were consistent with the expected PK profile of AZD1981. The plasma concentrations and PK variables of moxifloxacin in this study were consistent to previously reported values.

Summary of pharmacodynamic results

Statistical analysis of baseline-adjusted QTcF revealed that all upper bound 2-sided 90% CIs were well below 10 ms, and all point estimates for the contrast between 2000 mg and 200 mg AZD1981 and placebo were <5 ms. There were no increases from baseline of >30 ms for QTcF at any time point over the 24 hours period after dosing. The results of the analyses based on QTcB were in alignment with the results of the analyses based on QTcF. No relevant changes were observed in any other ECG parameter after AZD1981 200 mg and 2000 mg. Assay sensitivity was confirmed in the study: the lower bound of the 2-sided 90% CI of baseline-adjusted between moxifloxacin and placebo was above the 5 ms threshold during a 1 hour to 4 hour post-dose time period.

Table S3 **Estimate and 2-sided 90% CI of the difference in mean of QTcF (ms) for the comparison of AZD1981 versus placebo by time point, adjusted for baseline, repeated measures linear mixed model (PD analysis set)**

			Difference to placebo	
Treatment	**Time (h)**	**n**	**LS mean**	**90% CI**
AZD1981 200 mg	0.50	43	0.635	(-1.17, 2.44)
	1.0	43	0.522	(-1.28, 2.33)
	2.0	43	0.458	(-1.35, 2.26)
	3.0	43	0.984	(-0.820, 2.79)
	4.0	43	0.897	(-0.907, 2.70)
	8.0	43	-1.65	(-3.45, 0.154)
	12	43	0.450	(-1.35, 2.25)
	24	43	0.886	(-0.917, 2.69)
AZD1981 2000 mg	0.5	42	0.623	(-1.19, 2.44)
	1.0	42	1.18	(-0.636, 2.99)
	2.0	42	0.769	(-1.04, 2.58)
	3.0	42	1.48	(-0.336, 3.29)
	4.0	42	0.947	(-0.867, 2.76)
	8.0	42	0.508	(-1.31, 2.32)
	12	42	0.913	(-0.900, 2.73)
	24	42	0.691	(-1.12, 2.50)

LS: least squares; CI: confidence interval. Results based on repeated measures linear mixed model (LLM) with fixed effects for treatment, period, time, period*time, treatment*time and baseline as covariate. Subject was included in the model as random effect and time as a repeated effect within subject-period. A first-order autoregressive covariance structure was used.

Summary of pharmacokinetic/pharmacodynamic relationships

No statistically or clinically significant effect of AZD1981 plasma concentration on QTcF was observed. This was a negative thorough QT study.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of the investigational product due to adverse events (DAEs), or any other significant adverse events (OAEs) in the study. The highest incidence of subjects with at least 1 adverse event (AE) was reported after moxifloxacin 400 mg and after AZD1981 200 mg. No safety concerns, based

on the AEs reported, laboratory measurements, vital signs, ECG, and physical examination, were reported.