AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2551
Study Code	D1570C00001
Edition Number	1
Date	14 January 2010

A Double Blind, Randomised, Placebo-controlled, Phase I Trial to Assess the Safety, Tolerability and Pharmacokinetics of Single, Ascending, Oral Doses of AZD2551 in Healthy Male Subjects

Study dates:

First healthy volunteer enrolled: 27 February 2009
Last healthy volunteer last visit: 9 April 2009
Date of early study termination: 26 October 2009 for logistical reasons

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)

One centre in the United Kingdom.

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 assess the safety and tolerability of AZD2551 following administration of single ascending doses and to estimate the maximum tolerated dose, up to the predefined exposure and dose limits.	Adverse events, 12-lead electrocardiograms, laboratory variables (clinical chemistry, haematology and urinalysis), blood pressure, pulse rate, QT interval, and continuous cardiac monitoring using telemetry for 24 hours post-dose.	Safety
Secondary	**Secondary**	
To characterise the PK of AZD2551 and provisionally assess the dose proportionality of the PK following administration of single ascending doses of AZD2551.	C_{max}, t_{max}, $t_{½\lambda z}$, $AUC_{(0-t)}$, $AUC_{(0-24h)}$, AUC, CL/F, V_z/F and MRT.	PK

AUC Area under plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$ Area under plasma concentration-time curve from zero to the time of the last measurable concentration; $AUC_{(0-24h)}$ Area under plasma concentration-time curve from zero to 24 hours post-dose; CL/F Oral clearance; C_{max} Maximum plasma concentration; MRT Mean residence time; PK Pharmacokinetics; $t_{½\lambda z}$ Terminal half-life; t_{max} Time to reach maximum plasma concentration; V_Z/F Oral volume of distribution during the terminal phase.
Note: There were 3 exploratory objectives for this study (pharmacogenetic and metabolite analyses of plasma and urine); these are not presented in the clinical study report.

Study design

This was a Phase I, first time in man, randomised, double-blind, placebo-controlled, single ascending dose study in healthy male volunteers conducted at a single centre.

The study was terminated early; as a result, only 23 of the 81 planned healthy volunteers were randomised into 3 of the 9 planned cohorts (doses studied: 5 mg, 15 mg and 45 mg). In April 2009, a temporary halt (reported within 3 days to the Medicines and Healthcare products Regulatory Agency [MHRA], followed by a substantial amendment and 15 day report/update) was called to the study following adverse events (AEs) of ventricular extrasystoles (verbatim text: ventricular bigeminy) in 1 healthy volunteer in Cohort 3 (AZD2551 45 mg). Following extensive consultation of expert groups within the company, including the Cardiotoxicity Safety Knowledge Group, the Chief Medical Officer and the Human Exposure Limits Committee, AstraZeneca concluded that these AEs were unlikely to be due to the study drug. The persons consulted included senior individuals with expertise in both clinical and preclinical areas of drug development, including Cardiology, Clinical Pharmacology and

Patient Safety. In addition, with the exception of the Investigator, the Safety Review Committee felt that on the basis of the available evidence, the episode of ventricular extrasystoles observed was unlikely to be drug related. In the opinion of the Investigator, there remained a reasonable possibility that the AEs of ventricular extrasystoles were causally related to the administration of the study drug. Due to ongoing portfolio discussions within AstraZeneca, combined with logistical issues associated with the closure of AstraZeneca's Clinical Pharmacology Units, a decision was made in October 2009 not to restart this study but rather to terminate it. The study was not terminated for safety reasons.

Target subject population and sample size

The study included healthy male volunteers aged 18 to 45 years, who provided written informed consent, had suitable veins for cannulation or repeated venepuncture, and had clinically normal physical findings, laboratory values and electrocardiograms. Persons with underlying musculoskeletal symptoms or a history or presence of conditions known to interfere with the absorption, distribution, metabolism or excretion of the study drug were not eligible.

Up to 81 healthy male volunteers were planned to participate in 9 cohorts (with up to 9 healthy volunteers in each cohort). Healthy volunteers were randomised to receive either AZD2551 or placebo (6:3).

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

Table S2 Details of investigational product and other study treatments

Investigational product/ test drug	Dosage form, strength	Manufacturer	Formulation number	Batch number
AZD2551	Solution 0.5 mg/g	AstraZeneca	1774-3	08-002009AZ
AZD2551	Solution 5 mg/g	AstraZeneca	1774-2	08-002014AZ
AZD2551	Solution 25 mg/g	AstraZeneca	1774-1	08-002015AZ
Placebo	Matching solution 0.5 mg/g	AstraZeneca	P1774-3	08-002016AZ
Placebo	Matching solution 5 mg/g	AstraZeneca	P1774-2	08-002018AZ
Placebo	Matching solution 25 mg/g	AstraZeneca	P1774-1	08-002017AZ

Duration of treatment

Study drug (AZD2551 or placebo) was administered as a single oral dose.

Statistical methods

No formal statistical hypothesis testing was performed. All data were summarised descriptively including tables, listings and graphs, as appropriate.

Subject population

The first healthy volunteer entered the study on 27 February 2009 and the last healthy volunteer last visit was on 9 April 2009. In total, 23 of the planned 81 healthy male volunteers were randomised into the study at 1 study site; each received 1 administration of study drug (AZD2551 or placebo) during the planned treatment visit. Of the 23 healthy volunteers dosed, 16 received AZD2551 and 7 received placebo. Of the 9 planned cohorts, only 3 cohorts took place. Both the 5 mg and 15 mg cohorts dosed 9 healthy volunteers (6 with AZD2551 and 3 with placebo). The 45 mg cohort dosed 5 healthy volunteers (4 with AZD2551 and 1 with placebo) before the study was terminated.

There were no protocol deviations that led to exclusion of data from the PK or safety analyses. All 16 healthy volunteers who received AZD2551 were included in the PK analysis set. The safety analysis set included all 23 randomised healthy volunteers.

The demographic characteristics of the treatment groups were generally comparable. Medical and surgical history, and physical examination findings were as expected for a healthy volunteer population. The healthy volunteers were suitable for the study.

Summary of pharmacokinetic results

The plasma concentration versus time profiles, following administration of AZD2551 as an oral solution, were characterised by a rapid absorption phase. AZD2551 was measurable in plasma at the first sampling time (10 minutes post-dose) in all healthy volunteers across all dose levels. Mean AZD2551 plasma concentrations peaked between 41 and 53 minutes post-dose. Plasma concentrations of AZD2551 were quantifiable up to 12 hours post-dose in all healthy volunteers who received AZD2551 5 mg, up to 24 hours post-dose in all healthy volunteers who received AZD2551 15 mg and up to 32 hours post-dose in all healthy volunteers who received AZD2551 45 mg. Plasma concentrations of AZD2551 were below the lower limit of quantification (5 nM) in all pre-dose samples.

The predefined maximum exposure limits for area under plasma concentration-time curve from zero to infinity (AUC) (154 h*µmol/L) and maximum plasma concentration (C_{max}) (20 µmol/L) were not reached at any dose level investigated. Mean time to reach maximum plasma concentration (t_{max}) occurred at 41 to 53 minutes post-dose and the mean terminal half-life was 4.0 to 5.1 hours. The oral clearance (CL/F) and the oral volume of distribution during the terminal phase (V_z/F) did not change with ascending dose. Geometric mean CL/F ranged between 10.4 L/h and 13.6 L/h and V_z/F between 73.7 L and 88.6 L. The extrapolated part of AUC ranged between 0.6% and 14.0%, and did not exceed 2.5% in any of the healthy volunteers at the dose levels of 15 mg and 45 mg. The mean residence time (MRT) was approximately 5.9 hours.

The systemic exposure (AUC and C_{max}) seemed to increase linearly to the dose between 5 mg and 45 mg. The terminal half-life increased from 4.0 to 5.1 hours in the same dose range, indicating that the terminal phase may not have been reached. MRT remained unchanged at all 3 dose levels.

Summary of safety results

There were no deaths, serious AEs, severe AEs or discontinuations due to AEs. In total, 10 healthy volunteers had an AE; 4 of these received placebo and 6 received AZD2551. The total number of AEs reported was 20; 8 in healthy volunteers who received placebo and 12 in healthy volunteers who received AZD2551. The most common treatment emergent AE with AZD2551 (ie, reported by more than 1 healthy volunteer within any AZD2551 cohort) was application site rash (2 healthy volunteers in the AZD2551 5 mg cohort). Application site rash was also reported for 1 healthy volunteer who received placebo; no AE was reported for more than 1 healthy volunteer that received placebo. Four healthy volunteers had a total of 6 AEs that were moderate in intensity; 3 healthy volunteers received placebo and 1 healthy volunteer received AZD2551 15 mg. Two healthy volunteers had AEs considered to be other significant AEs (1 healthy volunteer had a fungal skin infection [verbatim text: fungal skin infection; axillary] of moderate intensity after receiving placebo and 1 healthy volunteer had ventricular extrasystoles [verbatim text: ventricular bigeminy] of mild intensity after receiving AZD2551 45 mg).

In April 2009, a temporary halt (reported within 3 days to the MHRA, followed by a substantial amendment and 15 day report/update) was called to the study (as described above). One healthy volunteer (AZD2551 45 mg cohort) experienced intermittent periods of ventricular extrasystoles (verbatim text: ventricular bigeminy) in the post-dose period; reported as 6 separate AEs (these were considered other significant AEs). The 39-year-old male had no relevant medical history. He was unaware of the onset of the arrhythmia and was asymptomatic throughout. He did not require medical intervention. Following extensive consultation of expert groups within the company, including the Cardiotoxicity Safety Knowledge Group, the Chief Medical Officer and the Human Exposure Limits Committee, AstraZeneca concluded that these AEs were unlikely to be due to the study drug. In the opinion of the Investigator, there remained a reasonable possibility that the AEs of ventricular extrasystoles were causally related to the administration of the study drug.

An additional healthy volunteer (AZD2551 5 mg cohort) was noted to have infrequent monomorphic ventricular ectopic beats pre-dose, which persisted throughout the 24-hour continuous electrocardiogram monitoring period (25 hours including the pre-dose period). The frequency of ventricular ectopic beats appeared to correlate with his sympathetic tone and reduced in frequency during sleep. These observations were not reported as AEs.

There were no clinically relevant changes in laboratory parameters (haematology, clinical chemistry or urinalysis) and there were no clinically relevant findings in vital signs in healthy volunteers exposed to AZD2551. No association between AZD2551 and critical electrocardiogram parameters including QT interval corrected for heart rate using Fridericia's formula was observed.