AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1704
Study Code	D0980C00001
Edition Number	1
Date	22 September 2008

A Phase I, First Time in Man, Single-Centre, Randomised, Double-Blind (within panels), Placebo-Controlled Study to Investigate Safety, Tolerability and Pharmacokinetics of AZD1704 after Administration of Oral Single Ascending Doses in Healthy Volunteers

Study dates: First healthy volunteer enrolled: 28 March 2008
Last healthy volunteer completed: 9 June 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(s)

AstraZeneca CPU, Queens Medical Center, Nottingham, NG7 2UH, UK

Study dates

First healthy volunteer enrolled	28 March 2008
Last healthy volunteer completed	9 June 2008

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate the safety and tolerability of AZD1704 following single ascending doses in healthy male and non-fertile female volunteers by assessment of adverse events (AEs), orthostatic blood pressure (BP) (supine and standing), pulse rate, body temperature, respiratory rate, safety laboratory variables and 12-lead electrocardiography (ECG).

The secondary objectives of the study were to investigate

1. the subjective cannabinoid central nervous system (CNS) effects of orally administered AZD1704 on a psychometric rating scale by assessment of specific adjectives (stimulated, anxious, sedated, down and high) rated on the Visual Analogue Mood Scale (VAMS)

2. the pharmacokinetic (PK) profile and dose proportionality of AZD1704 following single ascending doses by assessment of drug concentration in plasma and urine

An exploratory objective of the study was to investigate the relationships between exposure (drug concentrations in plasma) and safety/tolerability.

Furthermore, a blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK, pharmacodynamics (PD), safety and tolerability related to AZD1704 treatment. Genetic results are not included in this clinical study report.

Study design

This was a first time in man study to investigate the safety, tolerability and pharmacokinetics of single ascending doses of AZD1704 administered to healthy volunteers aged 20 to 45 years. The study was a single-centre, randomised, double-blind (within panels), placebo controlled study.

Target healthy volunteer population and sample size

The target population was to be healthy Caucasian males and non-fertile females between the ages of 20 and 45 years. The study was to include up to 8 panels each containing 8 volunteers (6 randomised to AZD1704 and 2 to placebo) with the possibility to include up to 2 additional panels within the dose range considered to be tolerated.

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

AZD1704 (batch number 4102-3-2) or placebo was administered in a single oral dose. The doses of AZD1704 administered in the study were 200 µg, 400 µg, 800 µg, 1600 µg and 2400 µg.

Duration of treatment

Single dose

Variables

Safety: Adverse events, vital signs, orthostatic blood pressure (supine and standing), pulse rate, respiratory rate, body temperature, safety laboratory assessment and ECG

Pharmacokinetic: C_{max}, $t_{max,}$ t_{last}, t_{lag}, AUC_{last}, AUC, λ_z, number of points for λ_z, $t_{½\lambda z}$, CL/F, V_z/F, MRT and fraction of oral dose excreted unchanged in urine.

Pharmacodynamic: VAMS scores of different adjectives (stimulated, anxious, sedated, down and high)

Statistical methods

The analysis of safety, tolerability, PK and PD data was mainly descriptive with listings, summary statistics and graphs as appropriate.

Subject population

The first healthy volunteer entered the study on 28 March 2008 and the last volunteer finished the study on 9 June 2008. In total, 39 volunteers were randomised into the study at 1 study centre. Each subject received 1 administration of AZD1704 or placebo during the planned treatment visit. All volunteers randomised to treatment completed the study. In panel 5, only 7 healthy volunteers were randomised (6 volunteers were randomised to AZD1704 and 1 volunteer to placebo). There were no protocol deviations that led to exclusion of data from the PK, PD or safety analyses. The safety analysis included all randomised healthy volunteers.

Overall, the treatment groups were well balanced and comparable with regards to demographic characteristics. All of the volunteers were white males. The mean age of the study population was 31.3 years, the mean weight was 81.2 kg and the mean BMI was 25.3 kg/m^2. The mean age in the 400 µg dose group was younger (25.5 years) and the mean

weight was lower (75.2 kg) than the other dose groups. However, it is not expected that these differences significantly influence the results or their interpretation.

Summary of pharmacokinetic results

AZD1704 was rapidly absorbed with t_{max} occurring at approximately 1 h for all dose panels. The geometric mean C_{max} at the MTD (1600 µg) was 28.9 nmol/L (range 23.6 to 33 nmol/L). The systemic exposure (AUC and C_{max}) increased in proportion to dose for the dose range studied. The $t_{1/2}$ was approximately 7 h with a geometric mean range of 5.76 to 8.14 h across the 5 dose panels. The geometric mean total oral plasma clearance (CL/F) for the 5 dose panels ranged from 14 to 22 L/h and appeared to be dose-independent. The geometric mean volume of distribution ranged from 136 to 207 L. The mean fraction of unchanged AZD1704 excreted in urine was low (range 0.7-1.6% of dose) and was dose independent.

Summary of pharmacodynamic results

The volunteers were asked to rate the extent to which they felt stimulated, sedated, anxious, high and down on the VAMS following the administration of AZD1704 or placebo. Overall, there were no systematic findings related to AZD1704 administration observed in the VAMS scores.

Summary of safety results

Based on preclinical data and previous clinical experience with the target, the safety findings in this study were as expected. There were no deaths, SAEs, DAEs or OAEs. A total of 29 volunteers reported 80 AEs. Of these, 23 volunteers (70 AEs) received AZD1704. The most common AEs were postural dizziness, orthostatic hypotension and dry mouth. The severe AEs in the study were postural dizziness (reported from 11 volunteers), orthostatic hypotension (reported from 7 volunteers) and hypotension (reported from 1 volunteer). None of these AEs were ongoing at the follow-up visit.

There were no clinically relevant changes in any laboratory safety variable. There was a transient decrease in mean testosterone, LH and FSH levels at some time points, however, there was no clear dose response nor a clear time course of these changes. There was an increase in supine pulse with increasing dose and concentration of AZD1704. Several standing measurements of pulse rate, DBP and SBP were missing due to the postural dizziness experienced by several of the volunteers in this study. All ECG data were within the normal physiological range.

The postural dizziness and orthostatic hypotension following AZD1704 administration limited dose escalation. Thus, the MTD for single dose administration of AZD1704 to healthy white male volunteers was considered to be 1600 µg.