AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	AZD1704
Study Code	D0980C00005
Edition Number	1
Date	14 January 2009

A Phase 1, 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 Japanese Male and Non-Fertile Female Volunteers

Study dates:	First healthy volunteer enrolled: 04 August 2008 Last healthy volunteer completed: 21 September 2008
Phase of development:	Clinical pharmacology (I)

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

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Study centre

The study was conducted at Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, London SW17 0RE, UK.

The first healthy volunteer was enrolled on to the study on 04 August 2008.

Publications

There were no publications at the time of writing this report.

Objectives

Primary objective

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

Secondary objectives

The secondary objectives were:

- To investigate the subjective cannabinoid CNS effects of orally administered AZD1704 in healthy Japanese male and non-fertile female volunteers on a psychometric rating scale by assessment of specific adjectives (stimulated, anxious, sedated, down and high) rated on visual analogue mood scale (VAMS).

- To investigate the pharmacokinetic profile of AZD1704 following single ascending doses in healthy Japanese male and non-fertile female volunteers.

Study design

This was a Phase I study in Japanese volunteers to investigate the safety, tolerability and PK of single ascending doses of AZD1704 or placebo administered to healthy Japanese male and non-fertile female volunteers. The study was a placebo-controlled, single-centre, randomised, double-blind study.

Target healthy volunteer population and sample size

Healthy young male Japanese volunteers between 20 and 45 years of age were included in the study. A maximum of 32 volunteers were to be included in up to 4 panels with 8 healthy volunteers (6 active and 2 placebo) in each dose panel. The volunteers were administered single doses of AZD1704 or placebo, following an escalation scheme based on results from the GSAD AZD1704 study (D0980C00001), that was to continue until significant intolerance occurred or until the predefined maximal allowed exposure had been reached or was predicted to be reached or until any of the other stopping criteria had been reached.

The sample size was not based on any statistical criteria but based on previous experience from other similar studies.

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

Single oral doses of AZD1704 (200 µg and 600 µg) diluted and/or dispensed from a suspension of 10 mg/mL with a starting dose of 200 µg.

Batch number - AZD1704 (Oral suspension, 10 mg/mL) - 4102-3-2

Batch number – Diluent for AZD1704 oral suspension (Solution) - 4114-1-1

Batch number – Placebo (Oral suspension) - 3941-6-7

Duration of treatment

A single dose of AZD1704 was administered on Day 1 and volunteers were discharged from the unit on Day 3. The study consisted of 3 visits for the volunteers within a time frame of approximately 48 days including Visit 1 (Enrolment).

Safety variables

Adverse events, vital signs, respiratory rate, body temperature, laboratory tests, urinanalysis, hormone analysis and ECG.

Pharmacokinetics variables

C_{max}, t_{max}, AUC_{last}, AUC, λ_z, number of points for λ_z, $t_{½,\lambda z}$, CL/F, V_z/F

Pharmacodynamic variables

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 study was discontinued after completion of the first 2 dose panels. All healthy volunteers randomised to treatment in these 2 dose panels completed the study. All 16 randomised healthy volunteers received one dose of study drug and were included in the PK and safety analysis sets. Twelve randomised healthy volunteers were included in the PD analysis set. All volunteers included in the study and receiving AZD1704 were male and Japanese volunteers and were aged from 20 to 32 years with a BMI ranging from 19 to 25 kg/m2. Overall, all treatment groups were well balanced in terms of age and BMI.

Summary of safety results

During the conduct of the study it was decided by AstraZeneca to stop the development of AZD1704 and therefore, the study was halted after the first two dose panels. It was concluded

that AZD1704 had essentially similar PK profiles in Japanese volunteers compared to Caucasian volunteers in the D0980C00001 study and that volunteers would need to be exposed to higher concentrations compared to those in study D0980C00001 in order to obtain beneficial data.

In this study, administration of AZD1704 to healthy Japanese volunteers was well tolerated with no safety concerns raised. Postural dizziness, one of the known typical AEs associated with cannabinoid compounds, was the most common AE reported on active treatment in this study (Table S1). No clinically relevant changes were observed in any laboratory variables. It should be noted that the slight changes seen in hormone parameters, particularly decreases from baseline in testosterone and total T4 (both 200 µg and 600 µg AZD1704) are consistent with previous findings in cannabinoids which are known to have some transient depression effects on gonadotropin, gonadal hormones, and TSH levels.

Table S1 Number (%) of volunteers in the safety population who had at least 1 adverse event during active treatment

System organ class and preferred term	Placebo (N=4)	AZD1704 200µg (N=6)	AZD1704 600µg (N=6)	AZD1704 Total (N=12)
General disorders and administration site conditions				
Fatigue	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (8.3%)
Pyrexia	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (8.3%)
Nervous system disorders				
Dizziness postural	0 (0.0%)	2 (33.3%)	3 (50.0%)	5 (41.7%)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (8.3%)
Skin and subcutaneous tissue disorders				
Rash	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (8.3%)

Summary of pharmacokinetic results

AZD1704 was rapidly absorbed with t_{max} occurring at approximately 1.5 h. The geometric mean terminal half-life was 3.65 h (200 µg) and 5.49 h (600 µg) (Table S2). Following administration of AZD1704 both C_{max} and AUC appeared to increase in proportion to dose in the dose range 200 µg and 600 µg. However, as only two dose levels (200 µg and 600 µg) were administered dose proportionality should be interpreted with caution since doses greater than 600 µg were not investigated.

Table S2 Summary of pharmacokinetic parameters of AZD1704 - single dose (PK analysis set)

Parameter	Treatment	n	Geometric Mean	Geometric CV(%)	Min	Median	Max
C_{max} (nmol/L)	200µg	6	3.54	19	2.46	3.66	4.11
	600µg	6	7.61	13	6.25	7.77	9.00
T_{max} (h)	200µg	6	1.57	67	0.75	1.53	3.03
	600µg	6	1.57	49	1.03	1.38	3.03
AUC (nmol*h/L)	200µg	6	20.71	30	14.85	20.02	30.50
	600µg	6	53.95	27	37.00	61.14	68.32
$t_{1/2}$ (h)	200µg	6	3.65	28	2.77	3.61	5.47
	600µg	6	5.49	32	3.75	5.70	8.02
CL/F (L/h)	200µg	6	19.61	30	13.31	20.31	27.35
	600µg	6	22.58	27	17.83	19.92	32.92
Vz/F (L)	200µg	6	103.36	13	87.99	104.58	119.32
	600µg	6	178.88	21	123.40	181.92	229.04

Summary of pharmacodynamic results

Psychometric assessment did not show any obvious trends during the study. However, higher sedation scores were reported by volunteers randomised to 200 µg AZD1704 compared to 600 µg and placebo. Sedation is a common initial CNS effect of many cannabinoid compounds.