AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1940
Study Code	D3120C00003
Edition Number	1
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A Phase I, Multi-Centre, Randomised, Double-blind, Placebo-controlled Study to Investigate the Safety, Tolerability and Pharmacokinetics of AZD1940, Including an Interaction Study, After Administration of Oral Multiple Ascending Doses in Adult Subjects with Chronic Low Back Pain

Study dates: First patient enrolled: 18 March 2008
Last patient completed: 19 November 2008

Phase of development: Clinical pharmacology (I)

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

Study centres

The study was conducted at 3 centres in Sweden: Quintiles AB, Uppsala, Quintiles-Hermelinen AB, Luleå and Berzelius Clinical Research Centre AB, Linköping. The first patient consented for the study on 18 March 2008 and the last patient's last visit was on 19 November 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective was to investigate safety and tolerability of AZD1940 after administration of oral multiple ascending doses in male and non-fertile female chronic low back pain subjects by assessment of adverse events (AEs) occurring during the study, blood pressure (supine and standing), pulse rate, respiratory rate, body temperature, laboratory variables and electrocardiogram (ECG).

The secondary objectives of the study were:

1. To investigate the central nervous system effects after multiple dosing of AZD1940 by assessment of psychometric rating scales (Visual Analogue Mood Scale [VAMS], Cognitive Drug Research Ltd [CDR] test battery, Drug Effects Questionnaire, Addiction Research Center Inventory and Bond-Lader)

2. To investigate the pharmacokinetic (PK) profile (including dose proportionality) of AZD1940 by assessment of plasma concentrations

3. To investigate the cytochrome P450 (CYP) 3A4 induction of AZD1940 by use of plasma levels of midazolam and 4β-hydroxycholesterol and 6β-hydroxycortisol:cortisol urine excretion ratio as markers

Exploratory objectives were:

1. To investigate the potential relationships between exposure and safety/tolerability

2. To explore the variability of pain measures in subjects with chronic low back pain using Numerical Rating Scale (NRS), Oswestry Disability Questionnaire and Roland Morris Disability Questionnaire

3. An optional blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and pharmacodynamic (PD), safety and tolerability related to AZD1940 treatment. (Any results will be reported separately from the clinical study report.)

Study design

This was a randomised, double-blind, placebo-controlled, multiple ascending dose study.

Target subject population and sample size

White, male and non-fertile female patients with chronic low back pain, aged between 20 and 65 years.

Up to 60 patients in six dose panels (8 active: 2 placebo per panel) were planned to be included. However, the study was stopped after completion of 5 dose panels. Thus, 50 patients were included and analysed in the study.

Investigational product: dosage, mode of administration and batch numbers

The starting dose of AZD1940 was 130 μg and doses were escalated to 250, 400, 650 and 1000 μg in subsequent dose panels before the study was stopped.

AZD1940 was given as an oral solution at 0.05 mg/mL (Batch H2003-01-01-01; 3957-3-2) or 0.5 mg/mL (Batch H2004-02-01-01; 3973-3-2) together with 240 mL water. Placebo was given as an oral solution (Batch nos. H2006-02-01-02; 4073-5-2 and H2006-02-01-01; 4073-2-2) and midazolam 0.2 mg was given an oral solution at 1 mg/mL (Batch 2250100).

Duration of treatment

Patients were given once daily doses of AZD1940/placebo for 12 days. Midazolam was administered once in the morning on Day -1 and on Day 14 (2 days after the last dose of AZD1940/placebo), as a marker to study CYP3A4 induction.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Plasma PK parameters of AZD1940 including C_{max}, $C_{ss,max}$, C_{trough}, AUC_{τ}, t_{lag}, t_{last}, t_{max} and $t_{1/2\lambda z}$

Plasma PK parameters of midazolam including C_{max}, AUC, AUC_{last}, t_{lag}, t_{last}, t_{max} and $t_{1/2\lambda z}$

Plasma concentrations of 4β-hydroxycholesterol

6β hydroxycortisol: cortisol urine excretion ratio

Plasma and urine concentrations of the metabolite AZ12444854

Criteria for evaluation – patient reported outcome variables

Variability in pain was assessed using NRS, Oswestry Disability Questionnaire and Roland Morris Disability Questionnaire.

Criteria for evaluation – pharmacodynamics

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

Cognitive assessments including simple reaction time, digit vigilance, choice reaction time, numeric working memory, immediate word recall, delayed word recall, word recognition, picture recognition, Bond Lader visual analogue scale of mood and alertness, Drug Effects Questionnaire and Addiction Research Center Inventory

Criteria for evaluation - safety (main variables)

AEs, vital signs, orthostatic blood pressure (supine and standing), pulse rate, respiratory rate, body temperature, laboratory variables and ECG

Genetics

Genetic samples were collected for future, possible research to identify/explore genetic variations that may affect AZD1940 PK, receptor occupancy and safety. The results are not reported in this clinical study report.

Statistical methods

Safety, tolerability and PK data were mainly analysed using descriptive statistics. PK dose proportionality was explored by analysis of covariance using a power model.

CYP3A4 induction potential was assessed by calculation of 90% confidence intervals for the geometric mean ratios of the observed PK measures pre and post AZD1940 administration (C_{max} and AUC of midazolam, 4β-hydroxycholesterol and 6β-hydroxycortisol:cortisol urine excretion ratio).

The PD and patient reported outcome variables were analysed using descriptive statistics.

The number of subjects per dose was chosen to have enough subjects to evaluate tolerability and safety based on experience from other studies.

Subject population

This study was stopped due to elevations in liver enzymes in 2 patients in dose panels 4 (650 μg) and 5 (1000 μg). Five of the 6 planned dose panels were completed before the study was stopped. The patients of the planned 6th dose panel were at the clinic for one day (Day -1) before the study was stopped. The 10 patients in panel 6 received a single dose of midazolam but did not receive AZD1940/placebo before being withdrawn from the study. Data from panels 1 to 5 are included in this report.

In total, 145 patients (including the patients recruited for panel 6) were enrolled in the study at 3 study sites, 50 were randomised and treated in panels 1 to 5 and 45 completed the study. Five patients were withdrawn from the study. The reasons for withdrawal were AE (severe headache) in 1 patient in the 130 μg group, safety reasons (elevated transaminase) in 1 patient in the 650 μg group, and incorrect enrolment for 3 patients (belonging to the 130 μg, 250 μg and 400 μg groups).

All patients were white. There was an uneven distribution of females between the groups.

Summary of pharmacokinetic results

At steady-state the median t_{max} of AZD1940 was 2.5 h and the average (maximum) $t_{½\lambda z}$ was 5 days (14 days). The highest average and individual $C_{ss,max}$ of AZD1940 were 38 nmol/L and 57 nmol/L (at 1000 µg), respectively. The corresponding mean C_{trough} was 28 nmol/L. According to the power model, exposures increased proportionally with increasing dose. The dose-corrected exposures at the highest dose were, however, approximately 15 to 20% lower than for the 400 and 650 µg doses. AZ12444854 could not be quantified in plasma at 130 to 400 µg doses. At 1000 µg AZD1940, the median t_{max} of this metabolite was 6 h, the average (maximum) $t_{½\lambda z}$ was 7 days (5 weeks) and the average (maximum) $C_{ss,max}$ was 0.16 nmol/L (0.22 nmol/L). The fraction of dose excreted in urine as AZ12444854 was in the per mille range. No signs of CYP3A4 induction were demonstrated.

Summary of efficacy results (patient reported outcome assessments)

Changes, both increases and decreases, were observed for NRS ratings from day to day for most patients. The range of individual changes from baseline of NRS ratings was at most -7 to +1 in the 650 µg group and -4 to +4 in the 130 µg group (-5 to +2 in the placebo group).

The individual Oswestry Disability scores ranged from approximately 0 to 60% within each dose group (0 to 46% in the placebo group). This parameter appeared to be stable within each patient over time, showing very small variability from day to day.

The individual scores from Roland Morris Disability Questionnaire ranged at most from 1 to 22 in the 1000 µg group (0 to 16 in the placebo group). This parameter appeared quite stable within each patient over time, showing only small variability from day to day.

Summary of pharmacodynamic results

According to the CDR results, this multiple dosing study identified impairments to both the quality of episodic memory and speed of memory in these patients. These impairments were largely seen with the highest 2 doses, with little evidence seen for impairment at the lowest dose. In terms of self-ratings, the patients on the highest 2 doses felt less alert, more sedated and less 'intellectually efficient' and could detect a drug-like effect, though there was no evidence of an increase in 'drug-wanting'. Patients administered the lowest dose level were the only ones that did not rate their experience of AZD1940 as 'marijuana-like'.

A sedative effect of AZD1940 was also indicated by the observed changes of mean VAMS sedation scores in the 2 highest dose groups.

Summary of safety results

There were no serious adverse events in the study but 2 patients had treatment discontinued due to AEs (for 1 of these patients the reason for withdrawal from the study was termed safety reasons). Most AEs were of mild to moderate intensity. The most common AEs were dry mouth, fatigue, postural dizziness, headache, dizziness and somnolence.

Two patients (1 in the 650 µg and 1 in the 1000 µg group) had alanine transaminase elevations of more than 3 x upper limit of normal. For 1 patient this led to discontinuation of study treatment and withdrawal from the study for safety reasons.

Body weight appeared to increase with dose and there was a blood pressure decrease in the 2 highest dose groups.

Shorter QTcF vs placebo was observed at single time points in the 3 highest dose groups, but this was not judged to be clinically significant by the investigator.

There were no clinically significant findings in any other safety variables (pulse rate, respiratory rate, body temperature or physical examinations).