AstraZeneca

Clinical Pharmacology Study Report

Drug Substance	AZD7371
Study Code	D1803C00002
Date	19 October 2006

A double-blind randomized placebo controlled crossover study of AZD7371 ER 5 mg bid, 20 mg bid and placebo treatment for one week on visceral perception and symptoms in patients with Irritable Bowel Syndrome

The previous drug substance code for AZD7371 was NAD-299.

Study dates: First subject enrolled: 13 September 2004
Last subject completed: 18 April 2005

Phase of development: Clinical Pharmacology (I)

[redacted]

This study was performed in compliance with Good Clinical Practice

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Drug Substance(s)	AZD7371	**SYNOPSIS**	(For national authority use only)
Study Code	D1803C00002		
Date	19 October 2006		

A double-blind randomized placebo controlled crossover study of AZD7371 ER 5 mg bid, 20 mg bid and placebo treatment for one week on visceral perception and symptoms in patients with Irritable Bowel Syndrome

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Study dates		**Phase of development**
First subject enrolled	13 September 2004	Clinical pharmacology (I)
Last subject completed	18 April 2005	

The study was prematurely terminated due to adverse events reported as hallucinations/hallucination-like in studies with AZD7371. The enrolment was halted on March 30, 2005 in order to perform a detailed analysis of these adverse events. The Medical Products Agency (MPA) stopped the study April 8, 2005 while awaiting information about the details of the adverse events.

Objectives

The primary objective of this study was to evaluate the effect of AZD7371 20 mg bid, AZD7371 5 mg bid and placebo on rectal sensitivity during rectal distension by assessment of discomfort by using a newly developed Sensitivity Index (SI).

Secondary objectives of the study were

- to evaluate the effect of AZD7371 20 mg bid, AZD7371 5 mg bid and placebo on rectal sensitivity during rectal distension by assessment of discomfort and pain using a newly developed Electronic Analogue Scale (EAS).
- to evaluate the effect of AZD7371 20 mg bid, AZD7371 5 mg bid and placebo on volumetric measures (maximum volume, compliance, accommodation), on autonomic response (heart rate and blood pressure), and on visceromotor response (electromyogram (EMG) and autonomic nervous system (ANS) measures) during rectal distension.

- to evaluate the effect of AZD7371 20 mg bid, AZD7371 5 mg bid and placebo by assessment of the proportion of patients with complete relief of overall IBS symptoms after one week of treatment.

- to evaluate the effect of AZD7371 20 mg bid, AZD7371 5 mg bid and placebo by assessment of the proportion of patients with adequate relief of overall IBS symptoms after one week of treatment.

- to evaluate the effect of AZD7371 20 mg bid, AZD7371 5 mg bid and placebo on abdominal symptoms and stool frequency/consistency day by day during one week as assessed by diary cards.

- to evaluate the safety and tolerability of AZD7371 20 mg bid and AZD7371 5 mg bid by assessment of adverse events, laboratory parameters, blood pressure and heart rate.

Study design

This was a randomized, double-blind, placebo-controlled, single-centre crossover study in male and female patients previously diagnosed with IBS according to the Rome II criteria. Eligible patients entered a one-week baseline period followed by randomization to two of the following treatment groups; AZD7371 20 mg bid, AZD 7371 5 mg bid or placebo, each treatment period lasting one week. The two treatment periods were separated by a one-week washout period and a one-week baseline period.

Target subject population and sample size

Patients were selected based on the inclusion and exclusion criteria. Only patients that fulfilled the Rome II criteria for IBS were eligible for inclusion into the study. When the study was prematurely terminated, only 15 evaluable patients, out of a planned 30, had completed.

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

- AZD7371, extended release tablets, 5 mg bid for oral use, batch number 2602-278-4

- AZD7371, extended release tablets, 20 mg bid for oral use* batch number (20 mg tablets) ST76033-001-FA02

- Matching placebo tablets for oral use, batch number ST76033-001-FA01

* Patients randomized to 20 mg bid received escalating doses in increments of 5 mg bid on Days 1-3, (Day 1 at 5 mg bid, Day 2 at 10 mg bid, Day 3 at 15 mg bid) and 20 mg bid thereafter.

Duration of treatment

Each patient was randomized to two different study treatments for seven days in each treatment period. The time between the two treatment periods was 14 days.

Variables

Pharmacokinetic

The plasma concentration of AZD7371 2 hours post dose on visits 3 and 5.

Pharmacodynamic

- Rectal sensitivity test (SI, EAS)
- ANS and EMG recordings
- Assessment of IBS Symptom variables
- Adequate relief of symptoms
- Variables derived from diary cards

Safety

Adverse events (AEs), electrocardiogram (ECG), vital signs including blood pressure (BP) and pulse, physical examination and laboratory parameters.

Pharmacogenetics

DNA was collected, with appropriate informed consent, for potential retrospective exploratory research into genes that may influence response to AZD7371 and the diagnosis or prognosis of IBS and related functional gastric disorders.

Statistical methods

The mean change from baseline in outcome variables was analysed using mixed models.

The mean change from baseline in symptom score of consistency of bowel movements after one week of treatment, the proportion of patients with complete relief, and the proportion of patients with adequate relief from overall IBS symptoms after one week of treatment, were analysed using descriptive statistics.

Adverse events were summarized descriptively.

Subject population

In total, 47 patients (15 males, 32 females) were enrolled in the study. 26 patients (9 males, 17 females) between the age of 25 and 61 were randomized. Mean age (SD) was 45.3(12.1) and median age was 48. Mean BMI(SD) was 24(2.3), max 28.6, min 19.8 and median 24.2. All patients were Caucasian.

Out of the 26 patients randomized, 21 patients completed the study. 5 patients were discontinued, 2 of them due to adverse events not causally linked to the investigational products, 3 of them due to the premature termination of the study.

The safety population included all 26 randomized patients and 15 patients with evaluable data at the termination of the study were included in the per protocol analysis population.

Table S1 Summary of baseline disease characteristics of randomized subjects

		Randomized (n=26)
Time since IBS diagnose	<1 year	2
	1 - 2 years	5
	2 - 3 years	5
	3 - 10 years	8
	>10 years	6
IBS diagnosis obtained from gastroenterologist[a]	Yes	18
IBS diagnosis obtained from other provider/primary care physician[a]	Yes	9
First episode of IBS symptoms	3 months - 1 year ago	0
	1 year - 5 years ago	5
	> 5 years ago	21
Family history of IBS	No	12
	Yes	4
	Do not know	10
Did the IBS start with symptoms of or verified gastroenteritis	No	18
	Yes	3
	Do not know	5
Frequency of consultations with a doctor for IBS symptoms (past 12 months)	Never	16
	Occasionally	10

Table S1 Summary of baseline disease characteristics of randomized subjects

		Randomized (n=26)
Consultations with a doctor/psychiatrist for psychiastric or psychologocal problems during the past 5 years	Yes	4
Diagnosis of fibromyalgia	Yes	0
Past or current urogenital problems	Yes	8
Past or current alternative treatment for IBS symptoms	Yes	1
IBS Symptoms	Diarrhoea	14
	Constipation	6
	Alternating	6

[a] One patient reported that diagnosis was obtained from both gastroenterologist and other provider/primary care physician

Summary of pharmacokinetic results

Descriptive statistics of the plasma concentrations of AZD7371 are given in the table below. Blood samples for determination of plasma concentrations were taken 2 hours post dose on the days of the colorectal distensions.

Table S2 Descriptive statistics of plasma concentrations (nmol/L) of AZD7371

Treatment	N	Mean	SD	Min	Max	Median
AZD7371 20 mg	17	341.16	209.97	164.70	935.20	262.60
AZD7371 5 mg	15	87.81	50.22	30.12	239.80	78.45

Summary of pharmacodynamic results

Primary outcome variable

No significant differences were seen between the treatment groups with respect to the primary variable, SI.

Secondary outcome variables

- EAS discomfort and pain

The maximum discomfort and maximum pain during rectal distension were measured using the electronic analogue scale (EAS). There were no significant differences between the treatment groups with respect to either change from baseline in maximum discomfort or change from baseline in maximum pain as measured by the EAS scale.

- Volumetric measures, autonomic response and visceromotor response

No significant changes could be seen for either compliance or accommodation in any of the groups, and there were no significant changes in the percent change in heart rate.

- Symptomatology

The proportion of patients with complete relief (defined as no symptoms assessed according to the Likert scale) was small in all treatment groups, with the highest proportion observed in the placebo group. The proportions of patients reporting adequate relief were similar in the placebo group (6/15), the 5 mg AZD7371 group (5/15) and the 20 mg AZD7371 group (4/17). The proportions of patients reporting an improvement in symptoms after treatment compared to baseline were similar across treatment groups.

Summary of pharmacogenetics

The genotyping samples were stored so that analysis could be performed at a later date, and has not been included in this report.

Summary of safety results

There were no deaths, serious adverse events or other significant adverse events. Two patients were discontinued due to adverse events not causally linked to the treatment. There were no clinically relevant abnormalities or changes with respect to laboratory variables, vital signs, ECG or physical examination.

The majority of adverse events were from the organ class “Gastrointestinal signs and symptoms” and were reported by patients randomized to all treatment arms as well as baseline/wash-out and follow-up periods. Adverse events in the class “Neurological disorders” were reported by patients randomized to AZD7371 20 mg bid. One patient, randomized to AZD7371 20 mg bid and not on concomitant antidepressant medication, reported a visual hallucination. All adverse events were transient.

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