AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3480
Study Code	D3691C00001
Edition Number	1
Date	03 September 2009

A single-centre, double-blind, randomised, parallel group study of repeated oral doses of AZD3480/placebo and a single dose of aripiprazole to evaluate the pharmacokinetic interaction between AZD3480 and aripiprazole in healthy subjects (phase I)

Study dates: First healthy volunteer enrolled: 12 March 2008
Last healthy volunteer completed: 14 April 2009

Phase of development: Clinical pharmacology (I)

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

Study centre

The study was conducted at one study centre at ICON Development Solutions, Skelton House, Manchester Science Park, UK.

The first subject was enrolled on 12 March 2008.

The last subject completed on 14 April 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate the effect of AZD3480 at steady state on the pharmacokinetics (PK) of aripiprazole, given as a single dose, in healthy male CYP2D6 extensive metabolisers (EMs) and poor metabolisers (PMs).

The secondary objectives of this study were:

1. To investigate the effect of aripiprazole on the steady state PK of AZD3480 in healthy male CYP2D6 EMs and PMs.

2. To investigate the safety and tolerability of AZD3480 in combination with a single dose of aripiprazole by assessments including, but not limited to, adverse events (AEs), vital signs and laboratory variables.

In addition, a blood sample for deoxyribonucleic acid (DNA) analysis was collected and stored for potential future research into genes that could influence drug response (PK profile, safety and tolerability) of AZD3480 and/or aripiprazole.

Study design

This was a double-blind, placebo-controlled (AZD3480 versus placebo, open for aripiprazole), randomised, parallel group, single-centre study.

Target healthy volunteer population and sample size

Healthy male subjects aged ≥18 to ≤45 years were recruited to ensure that 48 subjects were randomised onto the study, of which 40 subjects were EMs and 8 subjects were PMs.

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

AZD3480 or placebo capsules (batch number H 1814-02-01-01) were administered at doses of 50 mg (1 x 50 mg capsule, batch number H 1813-02-01-01) to PMs and 125 mg (2 x 50 mg, batch number H 1813-02-01-01 and 1 x 25 mg capsule, batch number H 1812-02-01-01) to

EMs once daily from Day 1 to Day 22. Doses were given under fasting conditions on Days 4 and 5.

Aripiprazole (Abilify®) was administered as a 5 mg single dose to both EMs and PMs in the morning of Day 5 in both arms of the study. Aripiprazole was dosed under fasting conditions.

Duration of treatment

The study consisted of an enrolment visit, within 28 days of first dosing, followed by a treatment period of 24 days (Day -1 to Day 23). A follow-up visit occurred 7 to 10 days after the last dose of AZD3480/placebo.

Criteria for evaluation - pharmacokinetics (main variables)

Primary PK variables were C_{max} and $AUC_{(0-t)}$ of aripiprazole and dehydro-aripiprazole

Secondary PK variables were $C_{ss,max}$ and AUC_{τ} of AZD3480 and TC-1784 (the inactive N-dealkyl metabolite).

Criteria for evaluation - safety (main variables)

The safety variables were AEs, laboratory assessments (chemistry, haematology, urinalysis), physical examination, 12-lead ECG, vital signs (supine blood pressure and pulse).

Statistical methods

In order to show that AZD3480 did not interact with the PK of aripiprazole, the parameters $AUC_{(0-t)}$ and C_{max} of aripiprazole and dehydro-aripiprazole and the dehydro-aripiprazole/ aripiprazole ratios for $AUC_{(0-t)}$ and C_{max} on Day 5 were analysed using an analysis of variance (ANOVA). The parameters were $\log_e$ transformed and compared between co-administration of aripiprazole with AZD3480 (Test) and co-administration of aripiprazole with placebo (Reference) using ANOVA.

In order to show that aripiprazole did not affect the PK of AZD3480, AUC_{τ} and $C_{ss,max}$ of AZD3480 and TC-1784 were analysed using an ANOVA procedure. The parameters were $\log_e$ transformed and compared between co-administration of AZD3480 with aripiprazole (Test) and AZD3480 given alone (Reference) using ANOVA.

Subject population

Fifty-two subjects were randomised onto the study and received at least one dose of study medication. Forty-eight subjects successfully completed the study and 4 were withdrawn.

Table S1 Summary of demographic data

Demographic and baseline characteristic		Overall (N=52)
Sex n (%)	Male	52 (100.0%)
Age (years)	Mean (SD)	31.6 (7.7)
	Minimum	19
	Median	29.5
	Maximum	45
Race n (%)	Asian	1 (1.9%)
	Black	5 (9.6%)
	Caucasian	45 (86.5%)
	Mixed	1 (1.9%)

Summary of pharmacokinetic results

For EMs the geometric mean ratio and associated 90% confidence interval (CI) indicated there was no statistically significant effect of AZD3480 on C_{max} or $AUC_{(0-t)}$ of aripiprazole. For PMs, C_{max} and $AUC_{(0-t)}$ of aripiprazole the geometric LSmean ratios were 1.60 and 1.40 indicating that in PMs AZD3480 was possibly a weak inhibitor of aripiprazole metabolism. However, these results must be viewed with caution due to the small number of PM subjects (n=4).

Table S2 PK of aripiprazole: Summary of statistical analysis (PK population)

CYP2D6 Population	Parameter	n Test	n Reference	Geometric LSmean Test	Geometric LSmean Reference	Geometric LSmean Ratio (Test/ Reference)	90% CI for Geometric LSmean Ratio [Lower - Upper]
EM	C_{max}	22	19	45.582	46.565	0.979	[0.826 - 1.160]
	$AUC_{(0-t)}$	22	19	2893.125	2770.171	1.044	[0.883 - 1.235]
PM	C_{max}	4	4	57.291	35.761	1.602	[1.091 - 2.353]
	$AUC_{(0-t)}$	4	4	5200.467	3715.907	1.400	[0.959 - 2.042]

Test = Aripiprazole + AZD3480
Reference = Aripiprazole + Placebo

In both EMs and PMs, the geometric mean ratios for both $C_{ss,max}$ and AUC_{τ} were close to 1, indicating there was no overall effect of aripiprazole on the PK of AZD3480. However, for PMs, these results must be viewed with caution due to the small number of subjects (n=4).

Table S3 PK of AZD3480: Summary of statistical analysis (PK population)

CYP2D6 Population	Parameter	n Test	n Reference	Geometric LSmean Test	Geometric LSmean Reference	Geometric LSmean Ratio (Test/ Reference)	90% CI for Geometric LSmean Ratio [Lower - Upper]
EM	$C_{ss,max}$	22	22	341.263	309.572	1.102	[0.928 - 1.309]
	AUC_{τ}	22	22	1583.152	1475.149	1.073	[0.977 - 1.179]
PM	$C_{ss,max}$	4	4	588.249	526.813	1.117	[0.746 - 1.670]
	AUC_{τ}	4	4	7767.367	7364.667	1.055	[0.846 - 1.315]

Test = AZD3480 + Aripiprazole (Day 5)
Reference = AZD3480 (Day 4)

Summary of safety results

There were 4 pre-treatment AEs reported in 3 subjects (5.8%). There were no deaths or SAEs during the study. Two subjects were withdrawn due to AEs, one following AEs of moderate headache, moderate sleep disorder and mild decreased appetite after dosing with placebo and aripiprazole and one following an AE of mild dizziness after dosing with AZD3480. No other significant AEs were reported in this study. The most common TEAEs (number and % of subjects) were dizziness and headache following AZD3480 alone, dizziness and nausea following AZD3480 and aripiprazole, headache, dizziness, fatigue and back pain following placebo and dizziness and nausea following placebo and aripiprazole. The TEAEs experienced by the PMs were similar to those experienced by the EMs with nervous system disorders and gastrointestinal disorders being the most commonly reported affected system organ class in both groups. The number of EM subjects reporting dizziness, but not headache, was increased following AZD3480 compared to placebo, and following AZD3480 and aripiprazole compared to placebo and aripiprazole. The number of EM subjects reporting nausea was increased following AZD3480 and aripiprazole compared to placebo and aripiprazole. The number of EM subjects reporting all other TEAEs was comparable between AZD3480 and placebo, and AZD3480 and aripiprazole and placebo and aripiprazole. The number of PM subjects reporting adverse events in the system organ class gastrointestinal disorders (including nausea and vomiting) was increased following AZD3480 and aripiprazole compared to placebo and aripiprazole. The number of PM subjects reporting dizziness and dizziness postural was increased following AZD3480 compared to placebo. The number of PM subjects reporting dizziness was also increased following AZD3480 and aripiprazole

compared to placebo and aripiprazole. The number of PM subjects reporting all other TEAEs was comparable between AZD3480 and placebo, and AZD3480 and aripiprazole and placebo and aripiprazole. The majority of TEAEs were mild or moderate in severity. There were 6 severe AEs, 5 following AZD3480 and aripiprazole and 1 following placebo and aripiprazole.

There were no clinically relevant changes in safety laboratory variables, vital signs, ECG and physical examination.