AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2624
Study Code	D0970C00008
Edition Number	1
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A Phase I, Randomized, Open-label, Two-way Crossover Study in Healthy Subjects to Assess the Relative Bioavailability of AZD2624 (Tablet Versus Liquid Suspension) Followed by an Additional Period to Assess the Food Effect on the Tablet

Study dates: First subject enrolled: March 2009
Last subject last visit: April 2009

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Introduction

As there is no expectation of submitting AZD2624 data in support of an application for marketing approval, the report for this study is submitted as a synopsis format clinical study report.

Study center

This was a single-center study. Sixteen healthy male and female subjects were randomized.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the pharmacokinetics of AZD2624 as a tablet formulation vs. AZD2624 as a liquid suspension in a fasting state	Assessed by estimates of relative bioavailability	Pharmacokinetic
Secondary	**Secondary**	
To compare the pharmacokinetics of AZD2624 as a tablet formulation administered in a fed vs. fasting state	Assessed by estimates of relative bioavailability	Pharmacokinetic
To monitor the safety and tolerability of AZD2624 in healthy male and female subjects	Assessed by adverse event reports, clinical safety laboratory values, ECG abnormalities, physical examination findings, vital sign values, and the Columbia Suicide Severity Rating Scale (C-SSRS)	Safety

Study design

This was an open-label, randomized, pharmacokinetic study of AZD2624, intended for the treatment of schizophrenia, with a 2-period crossover design, followed by an additional period in which all subjects received the tablet in the fed state. The treatments consisted of either a tablet or suspension formulation, administered in a fasting state, followed by tablet administration in the fed state.

Target subject population and sample size

Approximately 16 healthy male and female subjects, of non-childbearing potential, 18 to 65 years of age, were randomized in the study.

Investigational product: dosage, mode of administration and batch numbers

Healthy subjects were randomly assigned to receive AZD2624 in a randomized sequence in the fasted state (AB or BA):

- **Treatment A:** Oral dose of 40 mg AZD2624 (manufactured by AstraZeneca) from a 10-mg/mL concentration liquid suspension (1000-mg bottle Lot # 09-001173AZ; formulation F13550).

- **Treatment B**: Oral dose of two 20-mg tablets (Lot # 09-001174AZ; formulation F13685).

Both treatment sequences were followed by Treatment C**:**

- **Treatment C:** Oral dose of two 20-mg tablets 30 minutes following administration of a high-fat meal.

Duration of treatment

Healthy subjects received a single 40-mg dose of AZD2624 in each treatment period. Dosing for the first 2 treatments occurred after an overnight fast of at least 8 hours. All subjects received the tablet formulation 30 minutes following a high-fat meal during the third treatment period. There was a washout period of at least 5 days between treatment periods.

Statistical methods

No formal statistical hypothesis testing was performed in this study. Relative bioavailability was evaluated by analyzing ratios of the area under the plasma concentration curve (AUC), AUC from time zero to the time of the last quantifiable plasma concentration ($AUC_{(0-t)}$), and maximum plasma concentration (C_{max}) between formulations with a mixed-effect model. In addition, a 2-sided 90% confidence interval (CI) was provided as a descriptive measure. The food effect was assessed by ratios of AUC, $AUC_{(0-t)}$, and C_{max} between fasted and fed conditions and in safety data. Estimates of geometric mean ratios (fed versus fasting) in AUC, $AUC_{(0-t)}$, and C_{max} and corresponding 2-sided 95% CIs were produced.

Due to the exploratory nature of the study, the sample size was not based on the precision of a formal statistical comparison. For point estimates of the relative bioavailability parameters ranging from 0.8 to 1.25, the 90% CI would be not wider than 0.19 below/above the point estimate.

Subject population

A total of 14 subjects (87.5%) completed the study with 2 subject discontinuations due to positive urine drug screening results. There were no discontinuations due to adverse events.

For evaluations of safety, 15 subjects from suspension/fasting treatment, 16 subjects from the tablet/fasting treatment, and 14 subjects from the tablet/fed treatment were analyzed. A summary of demographic and baseline characteristics is presented in Table S2.

Table S2 Demographic and baseline characteristics (all dosed subjects)

Demographic or baseline characteristics		
Demographic characteristics (N=16)		
Gender	Male, n (%)	13 (81.3%)
	Female, n (%)	3 (18.8%)
Race	White, n (%)	10 (62.5%)
	Black or African American, n (%)	5 (31.3%)
	American Indian or Alaska Native, n (%)	1 (6.3%)
Age (yr)	Mean (SD)	50.38 (8.156)
	Range	29.0-64.0
Baseline characteristics		
Height (cm)	Mean (SD)	173.25 (11.902)
	Range	150.0-191.0
Weight (kg)	Mean (SD)	77.44 (10.973)
	Range	57.0-99.0
BMI (kg/m^2)	Mean (SD)	25.75 (2.720)
	Range	21.0-30.0

BMI Body Mass Index. n Number of subjects in group. N Number of subjects on study. SD Standard deviation.

Summary of efficacy results

Efficacy was not evaluated in this study.

Summary of pharmacokinetic results

All pharmacokinetic parameters were similar for all conditions. Summary statistics for pharmacokinetic parameters compared by formulation are shown in Table S3. The tablet and liquid formulations exhibited similar bioavailability. Summary statistics of pharmacokinetic parameters compared by AZD2624 tablet administration state are shown in Table S4. The absorption of AZD2624 was greater following a high-fat meal than in the fasted state, but clearance was similar in the two conditions.

Table S3 Summary statistics of pharmacokinetic parameters between suspension and tablet formulations of AZD2624 under fasting conditions

PK Parameter	N[a]	Suspension Formulation[b] GLS Mean	Tablet Formulation[c] GLS Mean	GLS Mean Ratio (LL, UL)
AUC (ng/mL*hr)	15	4244.459	4268.049	0.994 (0.929,1.064)
C_{max} (ng/mL)	15	310.137	330.468	0.938 (0.855, 1.030)
$AUC_{(0-t)}$ (ng/mL*hr)	15	4046.329	4123.748	0.981 (0.924, 1.042)

[a] Number of PK evaluable subjects.
[b] One 40-mg dose of AZD2624 in liquid formulation was administered to fasted subjects.
[c] Two 20-mg tablets of AZD2624 were administered to fasted subjects.
AUC Area under the plasma concentration-time. $AUC_{(0-t)}$ AUC from time zero to the time of the last quantifiable plasma concentration. C_{max} Maximum plasma concentration. GLS Geometric least squares mean. LL Lower limit of 90% confidence interval. N Number of evaluable subjects in treatment group. PK Pharmacokinetic. UL Upper limit of the 90% confidence interval.

Table S4 Summary statistics of pharmacokinetic parameters of tablet formulations of AZD2624 between fed and fasting conditions

PK Parameter	N[a]	Tablet Formulation[b]/Fed[c] GLS Mean	Tablet Formulation[b]/Fasting GLS Mean	GLS Mean Ratio (LL, UL)
AUC (ng/mL*hr)	14	4566.981	4052.258	1.127 (1.034, 1.228)
C_{max} (ng/mL)	14	553.197	316.968	1.745 (1.626, 1.873)
$AUC_{(0-t)}$ (ng/mL*hr)	14	4457.771	3912.580	1.139 (1.047, 1.240)

[a] Number of PK evaluable subjects.
[b] Two 20-mg tablets of AZD2624 were administered to subjects.
[c] Subjects were administered AZD2624 30 minutes following a high-fat meal.
AUC Area under the plasma concentration-time. $AUC_{(0-t)}$ AUC from time zero to the time of the last quantifiable plasma concentration. C_{max} Maximum plasma concentration. GLS Geometric least squares mean. LL Lower limit of 90% confidence interval. N Number of evaluable subjects in treatment group. PK Pharmacokinetic. UL Upper limit of the 90% confidence interval.

Summary of pharmacodynamic results

There were no pharmacodynamic results in this study.

Summary of pharmacokinetic/pharmacodynamic relationships

Pharmacokinetic/pharmacodynamic relationships were not analyzed in this study.

Summary of pharmacogenetic results

There were no pharmacogenetic results.

Summary of safety results

There were few adverse events reported across all study treatments. No serious adverse events occurred, and no adverse event led to a discontinuation. A summary of adverse event findings is reported in Table S5. The most common adverse events are reported by the Medical Dictionary for Regulatory Activities (MedDRA) terms in Table S6. The most common treatment-related effect was somnolence for all groups.

Overall, there were no differences among treatment groups in any clinical laboratory or hematology values that were deemed to be clinically relevant.

Table S5 Subjects who had an adverse event in any category (all dosed subjects)

	Treatment		
	Suspension/Fasting[a]	**Tablet/Fasting[b]**	**Tablet/Fed[c]**
Category of adverse event	**N=15**	**N=16**	**N=14**
Any adverse event, n (%)	5 (33.3%)	4 (25.0%)	3 (21.4%)
Serious adverse event, n (%)	0	0	0
Serious adverse event leading to death, n (%)	0	0	0
Treatment-related adverse event, n (%)	3 (20%)	1 (6.3%)	3 (21.4%)
Adverse events leading to discontinuation, n (%)	0	0	0

[a] One 40-mg dose of AZD2624 in liquid formulation was administered to fasted subjects.
[b] Two 20-mg tablets of AZD2624 were administered to fasted subjects.
[c] Subjects were administered AZD2624 30 minutes following a high-fat meal.
n Number of subjects reporting adverse event. N Number of dosed subjects in group.
Note: Percentages are calculated as n/N*100.

Table S6 Number of adverse events by preferred term frequency (all dosed subjects)

	Treatment		
	Suspension/Fasting[a]	**Tablet/Fasting[b]**	**Tablet/Fed[c]**
MedDRA preferred term	**N=15**	**N=16**	**N=14**
Somnolence, n (%)	2 (13.33%)[d]	1 (6.25%)[d]	2 (14.29%)[d]
Pain in extremity, n (%)	1 (6.67%)	2 (12.50%)	0
Headache, n (%)	0	0	1 (7.14%)[d]
Back pain, n (%)	2 (13.33%)	0	0
Tenderness, n (%)	1 (6.67%)	0	0
Skin irritation, n (%)	0	1 (6.25%)	0
Nausea, n (%)	0	0	1 (7.14%)[d]
Hematoma, n (%)	1 (6.67%)	0	0
Fatigue, n (%)	1 (6.67%)[d]	0	0
Abdominal distension, n (%)	0	0	1 (7.14%)[d]

[a] One 40-mg dose of AZD2624 in liquid formulation was administered to fasted subjects.
[b] Two 20-mg tablets of AZD2624 were administered to fasted subjects.
[c] Subjects were administered AZD2624 30 minutes following a high-fat meal.
[d] Treatment-related adverse event.

MedDRA Medical Dictionary of Regulatory Activities. n Number of subjects reporting adverse event.
N Number of dosed subjects in group.
Note: Percentages are calculated as n/N*100.

Date of the report

14 September 2008