AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2624
Study Code	D0970C00002
Edition Number	Final
Date	8 September 2008

A Phase I, Single-center, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD2624 When Given in Multiple Ascending Oral Doses in Healthy Male and Healthy Female Volunteers of Non-child-bearing Potential

Study dates:	First subject enrolled: 29 October 2007 Last subject completed: 16 April 2008
Phase of development:	Clinical pharmacology (I)
Principal Investigator:	
Sponsor's Responsible Medical Officer:	

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

Study center

This study was conducted in 1 center in the United States, Parexel International, Harbor Hospital, 3001 South Hanover Street, Baltimore, MD 21225. The first subject was enrolled on 29 October 2007 and the last subject completed the study on 16 April 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate the safety and tolerability of AZD2624 when given orally in multiple ascending doses to healthy male subjects and healthy female subjects of non-child-bearing potential by assessment of adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECG), clinical laboratory assessments, and assessments of extrapyramidal symptoms (EPS).

The secondary objectives of this study were:

1. To evaluate and characterize the pharmacokinetics (PK) of AZD2624 (parent) and its metabolites when given orally in multiple ascending doses by assessment of concentrations in plasma

2. To evaluate the pharmacodynamic (PD) effects of AZD2624 (parent) on selected psychometric (cognitive and psychomotor) assessments and subjective effect measures using CogState battery and a 24-item Bond-Lader visual analog scale (VAS).

Study design

This was a single-center, double-blind, placebo-controlled, randomized within each dose group, multiple ascending dose study. Up to 3 dose groups were planned with 12 subjects allocated to each dose group and randomized to receive repeated doses for a total of 7 days (with a washout period of 2 days between Days 1 to 4) of either AZD2624 (n=9) or placebo (n=3); a reserve group of subjects using a different dose or dose regimen could be used as a 4th dose group if deemed necessary based on emerging safety and PK data from the preceding groups. Four cohorts of subjects were enrolled in this study.

Target healthy volunteer population and sample size

Approximately 36 healthy male and female subjects of non-child-bearing potential aged 18 to 65 years inclusive were to be enrolled. For each dose group of 12 subjects, 9 subjects were to receive AZD2624, and 3 subjects were to receive placebo (active: placebo = 3:1). This sample size per dose group was thought to provide sufficient information to gather initial safety and PK data in human subjects while at the same time exposing a minimum number of subjects to AZD2624. In addition, with the criteria for stopping dose escalation based on the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE), if the true

incidence of dose-limiting toxicity events was 30%, then the probability that 2 or more subjects out of 9 subjects treated with active treatment reporting such an event would be 80%. In this study, a total of 47 male subjects were randomized to dose administration with AZD2624 (n=35) or placebo (n=12) in 1 of 4 cohorts. All subjects completed the study through the follow-up assessment.

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

AZD2624 was provided as a powder (1000 mg) for oral suspension in Ora-Plus® (a proprietary oral suspending vehicle) containing 0.05% w/v Sodium Lauryl Sulphate as a wetting agent. Study treatment was administered as single and multiple doses of 5 mg, 15 mg, 15 mg, and 30 mg (batch numbers 2000112357). Matching placebo (vehicle only) was provided for each dose strength of AZD2624.

Subjects in the first dose panel were administered 5-mg AZD2624 or placebo once daily (QD) on Day 1 and on Days 4 through 9 (with a washout period on Days 2 and 3). The dose of study treatment for the remaining panels (15 mg or placebo QD, 15 mg or placebo twice daily (BID), and 30 mg or placebo BID) were determined by the AstraZeneca Safety Review Committee; total daily doses were not to exceed the maximum tolerated dose (MTD) established in the single ascending dose (SAD) study, however, the CSP stated that a different dose regimen could be used in the 2^{nd}, 3^{rd}, and/or the 4^{th} dose group (BID or TID) if necessary based on emerging data in the multiple ascending dose (MAD) study.

Duration of treatment

The duration of each subject's participation was approximately 53 days including: 30-day screening period, 14 days/13 nights in the clinical research center (CRC), and a follow-up visit 7 to 10 days postdischarge from the CRC.

Criteria for evaluation - pharmacokinetics (main variables)

Primary PK parameters for AZD2624 and its metabolites included:

- C_{max}: maximum plasma concentration
- AUC: area under the plasma concentration-time curve from zero to infinity or AUC_{τ} (area under the total plasma concentration-time curve during a dosing interval, τ=24 or 12 for once or twice daily regimen)
- t_{max}: time to reach maximum plasma concentration following oral administration
- $t_{1/2}$: apparent terminal half life
- $R_{AC\ (AUC)}$: accumulation ratio based on AUC
- $R_{AC\ (Cmax)}$: accumulation ratio based on C_{max}

- TCP: temporal change parameter
- CL/F: apparent oral clearance of drug.

Criteria for evaluation - pharmacodynamics (main variables)

PD endpoints were included for exploratory purposes only. Cognitive/psychomotor assessments: The potential effect of AZD2624 on cognition, reaction time, and attention was assessed using a computerized neurocognitive test battery (CogState). In addition, potential effects on mood, mental status, and alertness were assessed using a 24-item variation of the Bond-Lader visual analog scale (a paper and pencil self-reported rating scale task).

Criteria for evaluation - pharmacogenetics

All subjects randomized into the study had the option to donate blood for possible future pharmacogenetic analysis. Subjects were not excluded from participating in the study if they refused to consent to the genetic analysis. A blood sample for this analysis was taken only after the subject gave informed consent for the study. The results of any analyses of the genes involved in the PK, PD, safety, and tolerability related to AZD2624 treatment will be reported separately.

Criteria for evaluation – biomarker panel profile

These samples were collected and stored for future rules-based medicine metabolic profiling. The analysis and results of this profiling will be handled and reported separately from the main study.

Criteria for evaluation - safety (main variables)

Safety and tolerability, the primary objective of the study, were evaluated by the assessment of the nature and incidence AEs, vital signs, physical examinations, ECGs, clinical laboratory assessments, and EPS based on data from the Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scales (BARS).

Statistical methods

Given the exploratory nature, no formal statistical hypothesis testing was performed in this study.

Data were presented by dose regimen (not the group), and subjects receiving placebo were pooled across dose panels for the purposes of summarization of safety and PD results.

To achieve the primary objective, the safety and tolerability data were evaluated in terms of AEs, vital signs, physical examinations, ECGs, and clinical laboratory assessments. AEs were listed as well as summarized by system organ class and dose. Vital signs (including orthostatic vitals), SAS, BARS, clinical laboratory measures, and dECGs were summarized using descriptive statistics by protocol time and dose.

To achieve the secondary objectives, the PK of AZD2624, AZ12592232, and AZ12430220 were evaluated by assessment of drug concentrations in plasma and urine. If possible, individual PK and PD parameters were calculated and tabulated along with descriptive statistics for each dosing group. Confidence intervals were provided only for accumulation ratios $R_{AC\ (AUC)}$, $R_{AC\ (Cmax)}$, and TCP.

Descriptive summary statistics for continuous variables included N, arithmetic mean, standard deviation, median, minimum, and maximum, geometric mean, and coefficient of variation. Descriptive summary statistics for categorical data included the frequency and proportion. Graphical methods were used to explore PK and safety data (dECG, SAS, BARS, and clinical laboratory results). There was no filling-in for missing data, unless otherwise specified, such as for the plasma concentration level and SAS total score.

Complete exploratory analysis of PD variables, and possible PK/PD relationship, will be reported separately from the main study, and will not form part of the CSR for this study. Bond-Lader VAS is summarized in Section 11 of the CSR by regimen and protocol time.

Subject population

In total, 47 male subjects were randomized into the study at 1 study site. The inclusion criteria allowed female subjects of non-child-bearing potential; however, no female subjects were enrolled. All subjects randomized to treatment completed the study. Of the minor deviations reported, none led to exclusion of data from the PK or safety analyses. The safety analysis included all 47 randomized subjects, the PK analysis included all 35 subjects treated with AZD2624 (9 subjects in the 5-mg QD, 15-mg BID, and 30-mg BID groups respectively, and 8 subjects in the 15-mg QD group). Note: Only 8 subjects were enrolled into the 15-mg QD group because on the day of randomization the 9th subject did not meet requirements in the opinion of the investigator, and neither did any of the alternates.

Overall, the treatment groups were well balanced and comparable with regard to demographic characteristics. The demographic and key baseline characteristics of study subjects are summarized in Table S1.

Table S1 Demographic and baseline characteristics

			AZD2624				
		Placebo (n=12)	5 mg QD (n=9)	15 mg QD (n=8)	15 mg BID (n=9)	30 mg BID (n=9)	Total (n=47)
Demographic characteristics							
Sex (n and [%])	Male	12 (100)	9 (100)	8 (100)	9 (100)	9 (100)	47 (100)

Table S1 Demographic and baseline characteristics

			AZD2624				
		Placebo (n=12)	5 mg QD (n=9)	15 mg QD (n=8)	15 mg BID (n=9)	30 mg BID (n=9)	Total (n=47)
Race, ethnicity	Asian, Hispanic or Latino	0	0	1 (12.5)	0	0	1 (2.1)
(n and [%])	Black or African American, not applicable	8 (66.7)	3 (33.3)	2 (25.0)	2 (22.2)	5 (55.6)	20 (42.6)
	Black or African American, African American	1 (8.3)	0	3 (37.5)	0	0	4 (8.5)
	Black or African American, Hispanic or Latino	1 (8.3)	2 (22.2)	0	1 (11.1)	0	4 (8.5)
	White, not applicable	0	2 (22.2)	1 (12.5)	3 (33.3)	3 (33.3)	9 (19.1)
	White, Hispanic or Latino	2 (16.7)	2 (22.2)	1 (12.5)	3 (33.3)	1 (11.1)	9 (19.1)
Age (years)	n	12	9	8	9	9	47
	Mean (SD)	33.7 (7.9)	36.0 (10.2)	27.9 (7.1)	36.0 (10.1)	28.4 (7.6)	32.6 (9.0)
	Range	21-47	22-55	23-45	21-51	22-46	21-55
Baseline characteristics							
Height (cm)	n	12	9	8	9	9	47
	Mean (SD)	176.6 (6.9)	174.9 (8.3)	179.1 (5.5)	178.4 (6.7)	175.9 (8.7)	176.9 (7.2)
	Range	166-186	165-187	170-187	170-190	164-187	164-190
Weight (kg)	n	12	9	8	9	9	47
	Mean (SD)	81.7 (7.7)	77.7 (8.5)	77.3 (10.6)	77.6 (12.7)	76.8 (8.3)	78.5 (9.4)
	Range	70-95	68-91	63-91	66-106	68-93	63-106
BMI	n	12	9	8	9	9	47
	Mean (SD)	23.6 (2.9)	25.5 (3.2)	24.0 (1.9)	24.4 (3.5)	24.8 (1.9)	25.1 (2.8)
	Range	21-30	20-30	22-27	19-29	22-29	19-30

BMI Body mass index; SD Standard Deviation.

Summary of pharmacokinetic results

The PK of AZD2624 and AZ12592232 (the AZD2624 ketone metabolite) were well characterized after oral administration following single and repeated dose administration of AZD2624 (5-mg and 15-mg QD, and 15-mg and 30-mg BID) (Table S2 and Table S3). The PK of AZ12430220 was not characterized in this study as the plasma and urine concentrations of AZ12430220 were all below the lower limit of quantification.

Following single and multiple oral dose administration under fasted conditions, AZD2624 appeared to be rapidly absorbed at each dose level. Median peak plasma concentrations were reached approximately 2 to 3 hours postdose. AZD2624 C_{max} and AUC, following single dose administration, increased approximately proportionately with dose over the range of 5 mg to 30 mg AZD2624. $T_{1/2}$ and CL/F were independent of dose. These results indicate that AZD2624 exhibits linear PK. Following multiple dose administration steady-state was achieved within 4 days. The accumulation of AZD2624 in the plasma was minimal and was greater following BID dosing as compared to QD dosing. The TCP was approximately 1 for all dose groups indicating that AZD2624 pharmacokinetics are time independent (Table S4). Renal elimination of AZD2624 was negligible.

Exposure to AZ12592232 increased with increasing dose. Based on a comparison of geometric mean AUC values, exposure to AZ12592232 was approximately 50–66% that of AZD2624. Geometric mean $t_{1/2}$ values for the metabolite were longer than that observed for AZD2624. Based on the longer $t_{1/2}$ for AZ12592232 compared to AZD2624 plasma, accumulation of this metabolite was greater than AZD2624, and was greater following BID dosing compared to QD administration. Renal elimination of AZ12592232 was negligible.

Table S2 Summary of the PK parameters for AZD2624 for Days 1 and 9 (PK analysis set)

Variable	Dose (unit)	n	Day 1	Day 9
			Geometric Mean (CV [%])	Geometric Mean (CV [%])
AUC (ng.hr/mL)	5 mg QD	9	451 (32.5)	561 (34.0)
	15 mg QD	8	1362 (36.4)	1581 (45.3)
	15 mg BID	9	1634 (50.7)	2843 (48.2)
	30 mg BID	9	2837 (47.4)	4383 (55.3)
$AUC_{(0-t)}$ (ng.hr/mL)	5 mg QD	9	435 (33.3)	537 (35.4)
	15 mg QD	8	1346 (36.7)	1559 (45.6)
	15 mg BID	9	1617 (51.1)	2812 (48.8)
	30 mg BID	9	2801 (47.8)	4353 (55.4)
$AUC_{(0-24)}$ (ng.hr/mL)	5 mg QD	9	424 (29.2)	526 (29.5)
	15 mg QD	8	1242 (35.2)	1436 (41.2)
$AUC_{(0-12)}$ (ng.hr/mL)	15 mg BID	9	1136 (36.8)	1896 (33.4)
	30 mg BID	9	1704 (46.3)	2852 (49.9)
C_{max} (ng/mL)	5 mg QD	9	58.9 (23.0)	74.0 (20.2)
	15 mg QD	8	153 (33.6)	152 (35.2)
	15 mg BID	9	164 (29.2)	253 (27.3)
	30 mg BID	9	231 (53.0)	376 (41.6)

Table S2 Summary of the PK parameters for AZD2624 for Days 1 and 9 (PK analysis set)

Variable	Dose (unit)	n	Day 1	Day 9
			Geometric Mean (CV [%])	Geometric Mean (CV [%])
$t_{1/2}$ (hr)	5 mg QD	9	5.47 (39.9)	5.37 (39.0)
	15 mg QD	8	6.34 (31.0)	6.43 (26.3)
	15 mg BID	9	6.33 (22.9)	6.97 (22.7)
	30 mg BID	9	7.61 (23.2)	7.45 (27.8)
t_{max} (hr)	5 mg QD	9	2.02[a]	2.00[a]
	15 mg QD	8	3.00[a]	3.00[a]
	15 mg BID	9	3.00[a]	2.02[a]
	30 mg BID	9	2.00[a]	2.00[a]
CL/F (L/hr)	5 mg QD	9	11.1 (32.5)	9.50 (29.5)
	15 mg QD	8	11.0 (36.4)	10.7 (39.1)
	15 mg BID	9	9.18 (50.7)	7.91 (33.4)
	30 mg BID	9	10.6 (47.4)	10.5 (49.9)

[a] Median.

A_e Cumulative amount of unchanged AZD2624 excreted into urine up to 72 hours postdose; AUC Area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$ Area under the plasma concentration-time curve from zero to t; $AUC_{(0-12)}$ Area under the plasma concentration-time curve from zero to 12 hours; $AUC_{(0-24)}$ Area under the plasma concentration-time curve from zero to 24 hours; CL/F Apparent oral clearance of drug; CV Coefficient of variation; C_{max} Maximum plasma concentration; F_e Apparent fraction of the total dose excreted as AZD2624 in urine; NA Not applicable; t_{max} Time to reach C_{max} following drug administration; $t_{1/2}$ Apparent terminal half-life in plasma; V_z/F Apparent volume of distribution.

Table S3 Summary of the PK parameters for AZ12592232 for Days 1 and 9 (PK analysis set)

Variable	Dose (unit)	n	Day 1	Day 9
			Geometric Mean (CV [%])	Geometric Mean (CV [%])
AUC (ng.hr/mL)	5 mg QD	9	300 (33.1)	424 (35.0)
	15 mg QD	8	790 (38.6)	1078 (50.6)
	15 mg BID	9	1015 (43.1)	2521 (42.1)
	30 mg BID	9	1385 (42.0)	3126 (57.9)

Table S3 Summary of the PK parameters for AZ12592232 for Days 1 and 9 (PK analysis set)

Variable	Dose (unit)	n	Day 1	Day 9
			Geometric Mean (CV [%])	Geometric Mean (CV [%])
$AUC_{(0-t)}$ (ng.hr/mL)	5 mg QD	9	273 (36.0)	387 (38.3)
	15 mg QD	8	756 (40.4)	1054 (51.0)
	15 mg BID	9	974 (41.7)	2472 (41.6)
	30 mg BID	9	1330 (38.8)	3081 (56.9)
$AUC_{(0-24)}$ (ng.hr/mL)	5 mg QD	9	223 (22.8)	321 (31.5)
	15 mg QD	8	575 (31.9)	800 (38.4)
$AUC_{(0-12)}$ (ng.hr/mL)	15 mg BID	9	370 (17.4)	1118 (27.9)
	30 mg BID	9	483 (31.1)	1544 (42.1)
C_{max} (ng/mL)	5 mg QD	9	15.0 (15.7)	21.3 (23.8)
	15 mg QD	8	36.5 (29.8)	49.9 (28.5)
	15 mg BID	9	43.4 (13.9)	109 (25.3)
	30 mg BID	9	57.1 (30.5)	155 (37.9)
$t_{1/2}$ (hr)	5 mg QD	9	10.1 (26.2)	10.3 (20.8)
	15 mg QD	8	10.2 (22.4)	9.27 (20.9)
	15 mg BID	9	10.3 (35.0)	10.6 (25.6)
	30 mg BID	9	10.8 (34.6)	9.79 (23.7)
t_{max} (hr)	5 mg QD	9	6.00[a]	6.00[a]
	15 mg QD	8	7.01[a]	6.00[a]
	15 mg BID	9	8.00[a]	4.00[a]
	30 mg BID	9	8.00[a]	4.00[a]

[a] Median.

A_e Cumulative amount of unchanged AZD2624 excreted into urine up to 72 hours postdose; AUC Area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$ Area under the plasma concentration-time curve from zero to t; $AUC_{(0-12)}$ Area under the plasma concentration-time curve from zero to 12 hours; $AUC_{(0-24)}$ Area under the plasma concentration-time curve from zero to 24 hours; CV Coefficient of variation; C_{max} Maximum plasma concentration; NA Not applicable; t_{max} Time to reach C_{max} following drug administration; $t_{1/2}$ Apparent terminal half-life in plasma.

Table S4 Statistical analysis of plasma PK parameters for AZD2624 and AZ12592232(PK analysis set)

			AZD2624			AZ12592232		
				95% CI			95% CI	
PK parameter	Treatment group	N	Geometric mean	Lower	Upper	Geometric mean	Lower	Upper
$R_{AC(AUC)}$	5 mg QD	9	1.24	1.08	1.43	1.44	1.28	1.62
	15 mg QD	8	1.16	0.931	1.44	1.39	1.09	1.77
	15 mg BID	9	1.67	1.34	2.08	3.02	2.52	3.62
	30 mg BID	9	1.67	1.47	1.90	3.20	2.42	4.23
$R_{AC(Cmax)}$	5 mg QD	9	1.26	1.12	1.41	1.42	1.24	1.63
	15 mg QD	8	1.00	0.752	1.33	1.36	1.06	1.76
	15 mg BID	9	1.54	1.25	1.90	2.51	2.14	2.95
	30 mg BID	9	1.63	1.31	2.03	2.71	2.21	3.34
TCP	5 mg QD	9	1.17	1.01	1.34	1.07	0.959	1.19
	15 mg QD	8	1.05	0.865	1.28	1.01	0.823	1.25
	15 mg BID	9	1.16	0.872	1.54	1.10	0.868	1.40
	30 mg BID	9	1.01	0.924	1.09	1.11	1.05	1.18

AUC Area under the plasma concentration-time curve from zero to infinity; BID Twice daily; CI Confidence interval; C_{max} Maximum plasma concentration; QD Once daily; $R_{AC(AUC)}$ Accumulation ratio based on AUC; $R_{AC(Cmax)}$ Accumulation ratio based on C_{max}; TCP Temporal change parameter.

Summary of pharmacodynamic results

The exploratory analysis of PD variables may be presented in a separate report.

Summary of pharmacokinetic/pharmacodynamic relationships

Possible PK/PD relationships will be reported separately from this CSR.

Summary of safety results

Forty-seven healthy men were enrolled into the study; 35 subjects received AZD2624 and 12 subjects received placebo. There were no deaths, serious adverse events, AEs leading to discontinuation, or other significant adverse events reported in the study. An MTD was not achieved in this study. All AEs were considered Grade 1 using the NCI CTCAE criteria. Of the total 64 AEs (experienced by 23 subjects), 30 of the events (experienced by 11 subjects) were considered by the investigator to be related to study treatment. The incidence of AEs did not appear to be dose-related. There were no clinically significant findings noted in vital signs, clinical laboratory assessments, or ECG assessments during the study.

There was a reduction in testosterone during the dosing period, most notably in the 15-mg BID and 30-mg BID groups compared to placebo. The testosterone reduction was reversible, and the mean total testosterone retuned to baseline by the Day 12 assessment (72 hours after last dose) and was not associated with any clinical symptoms.

The number and percentage of subjects who had an AE in any category are summarized in Table S5.

Table S5 Number (%) of subject who had at least 1 AE in any category (All dosed subjects)

		AZD2624				
	Placebo	5 mg QD	15 mg QD	15 mg BID	30 mg BID	Total[b]
AE category[a]	n=12	n=9	n=8	n=9	n=9	n=47
Any AE	5 (41.7)	5 (55.6)	1 (12.5)	8 (88.9)	4 (44.4)	23 (48.9)
Treatment-related AEs[c]	3 (25.0)	0	1 (12.5)	4 (44.4)	3 (33.3)	11 (23.4)
Any AE with outcome = death	0	0	0	0	0	0
Any SAE (including events with outcome = death)	0	0	0	0	0	0
Any AE leading to discontinuation of study	0	0	0	0	0	0
Any other significant AE[d]	0	0	0	0	0	0

a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
b Total number of subjects on AZD2624 and placebo
c As assessed by the investigator
d Any AE that led to dose of treatment being changed or temporarily stopped, or deemed by the sponsor to be significant, excluding AEs reported as SAEs or AEs that led to discontinuation of treatment.
AE Adverse event; BID Twice daily; QD Once daily; SAE Serious adverse event.

Date of the report

8 September 2008