AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2624
Study Code	D0970C00006
Edition Number	1.0
Date	27 February 2009

A Phase I, Single-Center, Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD2624 when given in multiple ascending oral doses in young healthy male Japanese subjects.

Study dates:
Phase of development:

Principle Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

This study was conducted in 1 center in Japan, Kitasato University School of Medicine, 2-1-1 Asamizo-dai, Sagamihara, Kanagawa 228-8520. The first subject was enrolled on 27 May 2008 and and the last subject completed the study on 28 August 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective was to assess the safety and tolerability of multiple ascending oral doses of AZD2624 in young healthy male Japanese subjects compared to placebo by assessment of adverse events, vital signs, physical examinations, laboratory parameters, ECGs and EEGs.

The secondary objectives of the study were:

1. To evaluate and characterize the pharmacokinetics of AZD2624 and its metabolites when given orally in multiple ascending doses of AZD2624 to young healthy male Japanese subjects by assessment of drug concentration in plasma.

2. Defensive sampling for genetic analysis.

Study design

This was a double-blind, randomized, placebo controlled study. There were three ascending dose groups randomized in such a way that 7 subjects received AZD2624 and 3 subjects receive placebo in each dose group. The dose levels for Groups A, B and C were 10 mg, 30 mg and 40 mg, respectively. Once daily administrations were given in the morning at Day 1 through in the morning at Day 6 on fasting condition. For Group C, single dose at Day 1 and once daily from morning at Day 6 to morning at Day 11 were given.

Target healthy volunteer population and sample size

Thirty (30) healthy male Japanese subjects aged 20 to 45 years inclusive were to be randomised. For each dose group of 10 subjects, 7 subjects were to receive AZD2624, and 3 subjects were to receive placebo. This sample size per dose group was considered sufficient to characterize the PK characteristics and provide safety and tolerability data in humans. In this study, a total of 30 healthy male Japanese subjects were randomized to dose administration with AZD2624 (n=21) or placebo (n=9) in 1 of 3 cohorts. Twenty-nine (29) 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 (100 mg and 1000 mg) for oral suspension in Ora-Plus® (a proprietary oral suspending vehicle) includes Sodium phosphate monobasic (<1%), Sodium

carboxymethylcellulose (<1%), Microcrystalline cellulose (<1%), Xanthan gum (<1%), Carrageenan (<1%) and Water. Batch numbers of AZD2624 100 mg, AZD2624 1000 mg and matching placebo (i.e Ora-Plus®) were ST76091, ST76092 and 7513795, respectively.

In Group A and B the dose was administered once daily from the morning at Day 1 through in the morning at Day 6 on fasting condition. In Group C, single dose at Day 1 and once daily from the morning at Day 6 through in the morning at Day 11 were dosed.

Duration of treatment

In Group A and B the maximum duration of each subject's participation was approximately 50 days including: 30-day screening period, 10 days/9 nights in the study center, and a follow-up visit 7 to 10 days post discharge from the study center. In Group C the maximum duration of each subject's participation was approximately 55 days including: 30-day screening period, 15 days/14 nights in the study center, and a follow-up visit 7 to 10 days post discharge from the study center.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary PK parameters for AZD2624 and its metabolites included:

- C_{max}: maximum plasma concentration
- AUC: (area under 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 hours for once daily administration)
- t_{max}: time to reach peak or maximum concentration
- $t_{1/2}$: apparent terminal half life
- $R_{AC\ (AUC)}$: accumulation ratio based on AUC
- $R_{AC\ (Cmax)}$: accumulation ratio based on C_{max}

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 of adverse events (AEs), vital signs, physical examinations, laboratory assessments, ECGs, EEGs and results reported on the Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scales (BARS).

Statistical methods

Due to the exploratory nature of the study, no formal sample size calculation was made and the sample size was not based on any formal statistical criteria.

Safety, tolerability and PK data were listed and summarised for each dose using descriptive statistics. Placebo for each group was combined for summarising results. Graphical methods were used in exploring PK and safety (dECG, SAS, BARS, and laboratory) results. There was no filling-in for missing data unless specified otherwise, such as for the plasma concentration level and for SAS Total score.

Subject population

In total, 94 subjects were enrolled at 1 study centre. Thirty (30) subjects were randomised, and 29 randomised subjects completed the study. One (1) subject was discontinued from the study due to voluntary discontinuation by subject. The subjects participating in the study were healthy male Japanese subjects aged 20 to 44 years, which were considered to be appropriate for this Phase I clinical pharmacology study. The demographic characteristics of study subjects are summarized in Table S 1.

Table S 1 Demographic characteristics (All randomised subjects)

Demographic characteristics		Placebo	AZD2624			Total
			10 mg	30 mg	40 mg	
		n=9	n=7	n=7	n=7	n=30
Age (years)	Mean	29.4	35.1	29.7	32.3	31.5
	SD	6.4	7.0	8.6	6.6	7.1
	Median	27.0	37.0	31.0	34.0	32.0
	Min	22	24	20	21	20
	Max	38	44	39	40	44
Sex	Male	9 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	30 (100.0%)
Ethnic group	Japanese	9 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	30 (100.0%)
Weight (kg)	Mean	62.48	66.83	63.56	61.11	63.43
	SD	4.97	3.81	3.95	6.65	5.16
	Median	63.30	68.70	62.90	58.40	63.45
	Min	54.8	61.4	59.0	54.3	54.3
	Max	69.8	70.6	70.0	71.8	71.8
Height (cm)	Mean	172.28	169.81	171.24	172.44	171.50
	SD	5.86	4.21	5.38	5.74	5.20
	Median	171.10	171.60	173.10	171.40	171.50
	Min	163.9	160.9	162.2	164.8	160.9
	Max	181.5	172.8	177.9	182.7	182.7
BMI (kg/m^2)	Mean	21.2	23.3	21.9	20.7	21.7
	SD	2.5	1.4	2.1	1.4	2.1
	Median	20.0	24.0	23.0	20.0	21.5
	Min	19	21	19	19	19
	Max	26	25	24	23	26

SD: standard deviation

Summary of pharmacokinetic results

Pharmacokinetic parameters of AZD2624 and AZ12592232 (the AZD2624 ketone metabolite) are summarised (geometric mean and CV%) in Table S 2 and Table S 3, respectively.

Following first dose administration, AZD2624 was rapidly absorbed after 10 mg, 30 mg and 40 mg with a median t_{max} value ranging from 2 to 3 hours. The geometric mean $t_{1/2}$ for the 40 mg dose group was 7.8 hours. The $t_{1/2}$ for 10 mg and 30 mg was not calculated since utilizable plasma concentration data were up to 24 hours after dosing. Following multiple dose administration, AZD2624 was rapidly absorbed after 10 mg, 30 mg and 40 mg with median t_{max} values ranging from 1.75 to 3 hours. Following last dose, the geometric mean $t_{1/2}$ for the 10 mg, 30 mg and 40 mg was 6.43, 6.59 and 7.33 hours, respectively.

AZ12592232 was formed after the first dosing with median t_{max} values ranging from 4 to 6 hours. The geometric mean $t_{1/2}$ for the 40 mg dose group was 8.5 hours. Following multiple dose administration, the median t_{max} was approximately 4 hours in all dose groups. The geometric mean $t_{1/2}$ of AZ12592232 for the 10 mg, 30 mg and 40 mg was 10.02, 8.46 and 8.83 hours, respectively. The $t_{1/2}$ of AZ12592232 is longer than that of AZD2624. The exposure to AZ12592232 was approximately 40-60% that of AZD2624 in terms of AUC and 20-30% that of AZD2624 in terms of C_{max}.

Table S 2 Descriptive statistics of pharmacokinetics parameters of AZD2624 (PK analysis set)

Treatment	Period	Statistic	AUC_{0-24h} (ng*h/mL)	AUC_{0-inf} (ng*h/mL)	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)
AZD2624 10 mg	First dose	n	7	NC	7	7	NC
		G-mean	1050.64	NC	141.95	2.00	NC
		CV (%)	39.3	NC	17.2	1.5 to 4.0	NC
	Last dose	n	6	6	6	6	6
		G-mean	1184.84	1307.39	154.89	1.75	6.43
		CV (%)	50.7	60.9	31.3	1.5 to 2.0	39.7
AZD2624 30 mg	First dose	n	7	NC	7	7	NC
		G-mean	2057.87	NC	234.56	3.00	NC
		CV (%)	33.1	NC	39.0	2.0 to 4.0	NC
	Last dose	n	7	7	7	7	7
		G-mean	2534.37	2887.90	289.17	3.00	6.59
		CV (%)	28.8	31.7	34.0	1.5 to 4.0	34.1
AZD2624 40 mg	First dose	n	7	7	7	7	7
		G-mean	2250.58	2542.95	287.67	3.00	7.80
		CV (%)	27.4	23.0	26.2	1.5 to 4.0	46.4
	Last dose	n	7	7	7	7	7
		G-mean	2861.38	3209.70	356.11	3.00	7.33
		CV (%)	28.7	26.7	23.0	2.0 to 4.0	24.8

a: Median and Range, G-mean: Geometric mean, NC: Not calculated

Table S 3 Descriptive statistics of pharmacokinetics parameters of AZ12592232 (PK analysis set)

Treatment	Period	Statistic	AUC_{0-24h} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)
AZD2624 10 mg	First dose	n	7	NC	7	7	NC
		G-mean	434.24	NC	28.87	4.00	NC
		CV (%)	26.0	NC	14.8	4.0 to 12.0	NC
	Last dose	n	6	6	6	6	6
		G-mean	651.02	893.65	41.81	4.00	10.02
		CV (%)	51.5	73.2	35.7	3.0 to 4.0	28.1
AZD2624 30 mg	First dose	n	7	NC	7	7	NC
		G-mean	886.92	NC	57.52	6.00	NC
		CV (%)	34.4	NC	33.8	4.0 to 8.0	NC
	Last dose	n	7	7	7	7	7
		G-mean	1383.09	1841.32	89.25	4.02	8.46
		CV (%)	35.4	41.9	28.7	4.0 to 8.0	23.1
AZD2624 40 mg	First dose	n	7	7	7	7	7
		G-mean	1180.57	1497.72	84.84	4.00	8.50
		CV (%)	23.1	21.4	21.6	4.0 to 8.0	34.5
	Last dose	n	7	7	7	7	7
		G-mean	1800.67	2265.12	123.80	4.00	8.83
		CV (%)	29.7	31.0	19.1	4.0 to 8.0	11.6

a: Median and Range, G-mean: Geometric mean, NC: Not calculated

Accumulation ratios of AZD2624 and AZ12592232 based on AUC and C_{max} are summarised (estimate and 95% confidence interval) in Table S 4.

Accumulation ratios of AZD2624 for AUC and C_{max} were 1.09 (95%CI: 0.94 to 1.27) and 1.10 (95%: 0.91 to 1.34) following 10 mg dose, 1.23 (95%CI: 1.07 to 1.41) and 1.23 (95%: 1.03 to 1.47) following 30 mg dose, and 1.27(95%CI: 1.11 to 1.46) and 1.24 (95%CI: 1.04 to 1.48) following 40 mg dose, respectively. There was limited accumulation of AZD2624 in plasma in all dose groups except for 10 mg dose group.

Accumulation ratios of AZ12592232 for AUC and C_{max} were 1.47(95%CI: 1.21 to 1.79) and 1.44 (95%CI: 1.18 to 1.76) following 10 mg dose, 1.56 (95%CI: 1.30 to 1.87) and 1.55 (95%CI: 1.29 to 1.87) following 30 mg dose, and 1.53 (95%CI: 1.27 to 1.83) and 1.46 (95%CI: 1.21 to 1.76) following 40 mg dose, respectively. There was limited accumulation of AZ12592232 in plasma in all dose groups.

Table S 4 Estimates and 2-sided 95% confidence intervals of accumulation ratio for AZD2624 and AZ12592232 on the ANOVA model (PK analysis set)

Accumulation ratio	Treatment	AZD2624			AZ12592232		
		Estimate	95% CI		Estimate	95% CI	
			Lower	Upper		Lower	Upper
R_{ac} (AUC)	AZD2624 10 mg	1.09	0.94	1.27	1.47	1.21	1.79
	AZD2624 30 mg	1.23	1.07	1.41	1.56	1.30	1.87
	AZD2624 40 mg	1.27	1.11	1.46	1.53	1.27	1.83
R_{ac} (C_{max})	AZD2624 10 mg	1.10	0.91	1.34	1.44	1.18	1.76
	AZD2624 30 mg	1.23	1.03	1.47	1.55	1.29	1.87
	AZD2624 40 mg	1.24	1.04	1.48	1.46	1.21	1.76

CI: confidence interval

Summary of safety results

In total, 48 adverse events were reported for 21 of the 30 subjects in the study. Six (6) AEs were reported for 4 of 7 subjects in 10 mg group, 11 AEs were reported for 5 of 7 subjects in 30 mg group, 19 AEs were reported for 7 of 7 subjects in 40 mg group, and 12 AEs were reported for 5 of 9 subjects in placebo group. The incidence of AEs appeared to be dose-related. There were no deaths, SAEs, DAEs, OAEs in the study. The majority of AEs were of mild intensity. Overall, the highest frequency of AEs when summarized by system organ class were investigations (12 of 30 subjects [40.0%]) including blood testosterone decreased, electroencephalogram abnormal, blood triglycerides increased and white blood cell count decreased, gastrointestinal disorders (5 of 30 subjects [16.7%]) including diarrhoea, abdominal pain, abdominal discomfort, salivary hypersecretion, epigastric discomfort, general disorders and administration site conditions (5 of 30 subjects [16.7%]) including application site pruritus, feeling hot and vessel puncture site pain, vascular disorders (5 of 30 subjects [16.7%]) including orthostatic hypotension. No clinically significant changes in vital signs, clinical laboratory results, ECGs or EEGs were observed.

There was a reduction in total testosterone during the dosing period in the AZD2624 groups compared to placebo. The testosterone reduction was reversible, and the total testosterone returned to baseline within 72 hours after last dose and was not associated with any clinical symptoms. No subjects met the predefined stopping criteria of 2 sampled AM total testosterone values falls below an absolute value of 150 ng/dL (or 100 ng/dL for AM and PM values) during the dosing period.

The number and percentage of subjects who had an AE in any category are summarized in Table S 5.

Table S 5 Number (%) of subjects who had at least 1 AE in any category (Safety analysis set)

AE category	Number (%) of subject [a]				
	Placebo	AZD2624			Total
		10 mg	30 mg	40 mg	
	n=9	n=7	n=7	n=7	n=30
Any AEs	5 (55.6)	4 (57.1)	5 (71.4)	7 (100.0)	21 (70.0)
Mild	4 (44.4)	4 (57.1)	5 (71.4)	6 (85.7)	19 (63.3)
Moderate	1 (11.1)	0	0	1 (14.3)	2 (6.7)
Severe	0	0	0	0	0
Any drug-related AEs [b]	5 (55.6)	3 (42.9)	5 (71.4)	7 (100.0)	20 (66.7)
Any AEs with outcome = death	0	0	0	0	0
Any SAEs not leading to death	0	0	0	0	0
Any AEs leading to discontinuation of treatment	0	0	0	0	0
Any other significant AEs	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 As assessed by the investigator

Date of the report

27 February 2009

An aminoquinoline species (AZ12430220) were not quantifiable in any of sampling points for all subjects.