AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3355
Study Code	D9120C00025
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A Single-blind, Randomized, Placebo-controlled, Single-centre Phase I Study to Investigate the Safety, Tolerability and Pharmacokinetics after 7 Days Repeated Administration of Escalating Oral Doses of AZD3355 solution in Healthy Japanese Male Subjects

Study dates: First subject enrolled: 11 February 2008
Last subject completed: 28 April 2008

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This study was conducted at 1 centre, Guy's Drug Research Unit, in UK.

Study dates		**Phase of development**
First subject enrolled	11 February 2008	Clinical pharmacology (I)
Last subject completed	28 April 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate the safety and tolerability after once daily repeated oral doses of AZD3355 solution in healthy Japanese male subjects by assessment of adverse events, electrocardiogram, blood pressure, pulse rate, urine weight and osmolality, body temperature and laboratory variables.

The secondary objective of the study was to investigate the pharmacokinetics, including dose proportionality, after once daily repeated oral doses of AZD3355 solution in healthy Japanese male subjects by assessment of plasma and urine concentration of AZD3355 and AUC, AUC_t, $AUC_{0\text{-}24h}$, C_{max}, $C_{ss,max}$, C_{24h} (C_{trough}), t_{max}, $t_{½}$, CL/F, CL_R and A_e.

Study design

This was a single-blind, randomized, placebo-controlled, single centre phase I study to assess the safety, tolerability and pharmacokinetics after 7 days repeated administration of escalating doses of AZD3355 in healthy Japanese male subjects.

Twenty-seven (27) healthy Japanese male subjects were included and divided into three different dose groups. Six subjects received AZD3355 and three subjects received placebo in each dose group. The subject only belonged to one of three dose groups.

Target healthy volunteer population and sample size

Twenty-seven (27) healthy Japanese male subjects aged 20 to 45 years were planned to take part in this study. A sample size of 9 subjects (6 in AZD3355 and 3 in placebo) per dose panel was considered sufficient to characterize the PK characteristics and provide safety and

tolerability data in healthy Japanese male subjects. In this study, a total of 27 Japanese subjects were randomized to dose administration with AZD3355 (n=18) or placebo (n=9). All subjects completed the study through the follow-up assessment.

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

Repeated, oral doses of AZD3355 solution and matching placebo.

The following investigational products were supplied:

- AZD3355 oral solution 2 mg/mL (Batch number: H 1912-01-01-01 and H 1912-01-02-01)
- Placebo for AZD3355 oral solution (Batch number: H 1913-01-01-01)

The dose was administered as oral solution and matching placebo solution. The 65 mg dose was given directly at one occasion. The 250 mg and 500 mg doses were given in fractions, where four low start doses were given every 30 minutes before the main dose which was given 2 hours later, on study Day 1 and Day 3. The subsequent doses (study Day 4 to Day 8) were given as a single dose e.g. without the initial low doses.

Duration of treatment

The treatment period was 8 days. A single dose was given on study Day 1 followed by a washout period (study Day 2). Thereafter, a repeated dose (once daily) was given for 6 days (study Day 3 to Day 8).

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Pharmacokinetic parameters for AZD3355 were assessed and included the following secondary study variables:

- Single dosing (study Day 1): AUC, AUC_t, AUC_{0-24h}, CL/F, C_{max}, t_{max} and $t_{½}$ [CL_R and Ae; only at the highest dose]
- Repeated dosing (study Day 8): AUC_{0-24h}, CL/F, $C_{ss,max}$, t_{max} and $t_{½}$ [CL_R and Ae; only at the highest dose]

Criteria for evaluation - safety (main variables)

Safety and tolerability were assessed by the nature and incidence of AEs, ECG, BP, pulse rate, urine weight and osmolality, body temperature and laboratory variables.

Statistical methods

Descriptive statistics and graphs were used for the evaluation of the safety and pharmacokinetic profiles of AZD3355. In addition, the dose proportionality of AUC and C_{max} on study Day 1 and AUC_{0-24h} and $C_{ss,max}$ on study Day 8 were evaluated using a power model.

Subject population

In total, 40 subjects were enrolled at 1 study centre. Twenty-seven (27) subjects were randomised, and all randomised subjects completed the study. All 27 subjects who were randomised and received the study drug (AZD3355 or placebo) were included in the safety and PK analysis set. Mean age of the randomised subjects was 26.2 years (range: 20 to 45) with a BMI of 19.2 to 26.2 kg/m^2 (Table S 1).

Table S 1 Summary of baseline characteristics of subjects included in the safety population

Statistics	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
n	27	27	27	27
Mean	26.2	172.4	62.9	21.1
SD	4.9	5.8	8.3	2.0
Min	20	164	53	19.2
Median	25	173	61	20.4
Max	45	189	85	26.2

Summary of pharmacokinetic results

Steady state was reached within 3 days repeated dosing (i.e. Day 6). This was confirmed by comparing AZD3355 plasma concentration immediately before each dose (C_{trough}) of AZD3355 over time. Pharmacokinetic parameters of AZD3355 on Day 1 and Day 8 are summarised (geometric mean and 95% confidence interval) in Table S 2. There were no apparent dose related differences in $t_{1/2}$ or CL/F on Day 1 and Day 8. The t_{max} did not show any substantial dose related differences on Day 1 and Day 8 considering dosing regimen (i.e. direct and fractionated dosing). There was no deviation of dose proportional increases in AUC and C_{max} except for $AUC_{0\text{-}24h}$ on Day 8 in the investigated dose ranges of 65-500 mg. The deviation from dose proportionality in $AUC_{0\text{-}24h}$ on Day 8 was very small. A 2-fold increase in dose of AZD3355 was estimated to result in 2.16 (95%: CI: 2.02 to 2.31) increase in $AUC_{0\text{-}24h}$ and 2.20 (95%: CI: 1.99 to 2.43) increase in $C_{ss,\,max}$ on Day 8. The corresponding increase in AUC on Day 1 were 2.03 (95%: CI: 1.89 to 2.19) and 2.16 (95%: CI: 1.92 to 2.44) for C_{max}. There was no apparent time-dependency in AUC and limited accumulation of AZD3355 in plasma following 6 days once daily dosing of AZD3355 65 mg to 500 mg. The geometric mean ratios of $AUC_{0\text{-}24h}$ (Day 8)/AUC (Day 1) for 65 mg, 250 mg and 500 mg doses were 0.92 (95% CI: 0.69 to 1.22), 0.99 (95% CI: 0.78 to 1.26) and 1.10 (95% CI: 0.90 to 1.35), respectively. The geometric mean ratios of $C_{ss,max}$ (Day 8)/C_{max} (Day 1) for 65 mg dose was 1.11 (95% CI: 0.83 to 1.47).

Table S 2 Geometric mean with 95% confidence interval for pharmacokinetic variables of AZD3355 on Day 1 and Day 8 (PK analysis set)

		Estimated mean (95% confidence interval)					
Parameter	**Day**	**65 mg (n=6)**		**250 mg (n=6)**		**500 mg (n=6)**	
AUC (µmol*h/L)	Day 1	16.0	(12.8-20.1)	75.0	(66.5-84.5)	124.5	(110.8-139.8)
	Day 8	18.0	(15.0-21.5)	94.9	(84.9-106.2)	182.8	(160.7-207.9)
AUC_{0-24h} (µmol*h/L)	Day 1	13.4	(10.5-17.1)	62.0	(54.0-71.3)	100.6	(89.5-113.0)
	Day 8	14.7	(12.2-17.6)	74.4	(61.5-90.0)	137.1	(123.8-151.8)
AUC_t (µmol*h/L)	Day 1	15.4	(12.2-19.5)	72.3	(64.1-81.5)	119.4	(106.1-134.3)
	Day 8	14.7	(12.2-17.6)	74.4	(61.5-90.0)	137.1	(123.8-151.8)
C_{max} (µmol/L)	Day 1	1.9	(1.3-2.7)	9.7	(6.9-13.5)	17.8	(14.1-22.4)
$C_{ss,max}$ (µmol/L)	Day 8	2.1	(1.7-2.6)	11.8	(8.8-15.8)	20.4	(16.3-25.5)
t_{max} (h) [a]	Day 1	1.01	(0.75-1.25)	3.00	(2.73-4.00)	3.00	(2.75-3.50)
	Day 8	1.00	(0.75-1.25)	0.75	(0.50-0.75)	1.13	(0.50-1.25)
$t_{1/2}$ (h)	Day 1	10.4	(9.0-12.0)	10.2	(9.0-11.7)	10.5	(9.9-11.0)
	Day 8	10.8	(9.2-12.6)	12.2	(9.9-15.1)	13.3	(10.6-16.8)
CL/F (L/h)	Day 1	28.7	(22.9-36.1)	23.6	(21.0-26.6)	28.5	(25.3-32.0)
	Day 8	31.4	(26.1-37.6)	23.8	(19.7-28.8)	25.9	(23.3-28.6)

a: Median and range

Summary of safety results

This study did not identify any safety or tolerability issues. AZD3355 was safe and well tolerated in healthy Japanese male subjects after 7 days repeated oral administration up to 500 mg. There were no deaths, serious AEs, discontinuations due to AE or any other significant AE in the study. The most commonly reported adverse events during the active treatment and wash-out/follow-up periods were diarrhoea, postural dizziness, headache, dry skin, application site reaction and epistaxis. All adverse events were of mild or moderate intensity. A transient increase in urine weight and a corresponding decrease in urine osmolality were seen 0-2 hour after the direct dosing of AZD3355 65 mg and 2-4 hour after the first fraction of AZD3355 250 mg and 500 mg (corresponding to 0-2 hour after the last fraction) on Day 1, and 0-2 hour after the direct dosing of AZD3355 65 mg, 250 mg to 500 mg on Day 8. No major changes in urine weight or osmolality were seen during the entire collection period 0-24 hours. The slight orthostatic decrease in SBP and DBP, and orthostatic increase in pulse rate were observed in AZD3355 groups compared to placebo on Day 1 but was not obvious on Day 8. Overall the orthostatic changes in SBP, DBP and pulse rate were small. There were no clinically relevant abnormalities in clinical laboratory, vital signs or electrocardiograms.