Clinical Study Report Synopsis

Drug Substance	AZD2516
Study Code	D2080C00002
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A Single Centre Two Part Randomized Phase I Study to Assess the Pharmacokinetics of an ER Formulation of AZD2516 and to Assess the Safety, Tolerability and Pharmacokinetics of AZD2516 after Multiple Ascending Doses in Healthy Volunteers

Study dates: First subject enrolled: 01 June 2010
Last subject last visit: 10 July 2010

Phase of development: Clinical Pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives[a]	Outcome variables	Type
Primary	**Primary**	
To investigate the relative bioavailability and pharmacokinetic (PK) profile of extended release (ER) and immediate release (IR) formulations of AZD2516 (Part A).	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2, \lambda z}$, t_{lag}, CL/F, λ_z, V_Z/F, F_{rel}, MDT, MRT	PK
To investigate the safety and tolerability of AZD2516 after multiple dosing in healthy volunteers (Part B).	AEs; laboratory variables, vital signs, ECG, psychiatric interview, Columbia Suicide-Severity Rating Scale	Safety
Secondary	**Secondary**	
To investigate the safety and tolerability of AZD2516 ER and IR formulations after single dosing in healthy volunteers (Part A).	AEs; laboratory variables, vital signs, ECG, psychiatric interview, Columbia Suicide-Severity Rating Scale	Safety
To investigate the effect of food on the rate and extent of absorption of AZD2516 ER formulation (Part A) and PK profile of AZD2516 (Part B)	AUC, $AUC_{(0-t)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, $t_{1/2, \lambda z}$, t_{lag}, CL/F, λ_z, V_Z/F, F_{rel}, MRT, $C_{max,ss}$, $C_{min,ss}$, $t_{max,ss}$, $AUC_{(0-\tau),ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, CL_{ss}/F, $t_{lag,ss}$, TD, $C_{avg,ss}$, RC_{max}, $RAUC_{(0-\tau)}$, %Fluct	PK

[a] Exploratory objectives are not listed.
Note: Part B was not conducted due to early study termination.

Study design

This was a Phase I randomized, single centre study to be conducted in 2 parts, Part A and Part B. The study was terminated early for safety reasons after Part A was completed, but before the start of Part B.

Part A investigated the PK of extended release (ER) and immediate release (IR) formulations of AZD2516 in healthy young male and female volunteers of non-child bearing potential (aged 20 to 45 years). The effect of food on the ER formulation of AZD2516 was also investigated. Part A was conducted open label and was comprised of a 4-period, 4-treatment crossover design with a single dose of AZD2516 being given in each period.

Target subject population and sample size

Healthy male and non-fertile female volunteers aged 20 to 45 years with a body mass index of 19 to 30 kg/m^2

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

Investigational product, AZD2516, consisted of two ER formulations of oral tablets (10 mg and 50 mg strengths) and one IR formulation of oral capsule (10 mg strength).

Each healthy volunteer received the following oral treatments in one of 4 treatment sequences:

- Treatment A: 50 mg AZD2516 ER formulation in fasted state (Lot 10-001246AZ)
- Treatment B: 50 mg AZD2516 ER formulation in fed state (Lot 10-001246AZ)
- Treatment C: 10 mg AZD2516 ER formulation in fasted state (Lot 10-001249AZ)
- Treatment D: 10 mg AZD2516 IR formulation in fasted state (Lot 08-003388AZ)

There were 16 healthy volunteers in Part A. Subjects were randomized according to a Williams design with 4 sequence groups, for 4 treatments and 4 periods. Four healthy volunteers were randomized to each of the following 4 treatment sequences: A-B-C-D, B-D-A-C, C-A-D-B, and D-C-B-A.

Duration of treatment

Each volunteer received four single treatments with AZD2516. Following a screening period (Visit 1, within 30 days before Visit 2) there were 4 treatment periods (Visit 2 to Visit 5). In each treatment period the healthy volunteers were admitted to the clinical unit the day before dosing started (Day -1) and were discharged on Day 2. The time between doses was at least 3 days to ensure no carry-over effect between treatment periods.

Statistical methods

Pharmacokinetic concentrations and parameters for AZD2516 in plasma were summarized using descriptive statistics and graphic displays. Comparisons between treatments were evaluated by an analysis of the primary PK parameters (AUC, $AUC_{(0-t)}$ and C_{max}) by fitting a linear mixed model. Geometric mean ratios and 90% CI for these ratios were presented.

The safety data were summarized by treatment using descriptive statistics or frequency counts in tables and listings.

The sample size was based on the desire to obtain adequate safety, tolerability, PK and PD data to achieve the objectives of the study whilst exposing as few healthy volunteers as possible to study medication and procedures.

Subject population

In total, 15 male and one non-fertile female healthy volunteers were randomised into the study at one study site, each received four administrations of study drug during the planned treatment visits. All 16 healthy volunteers randomised to treatment completed Part A of the study. There were no important protocol deviations and no healthy volunteers were excluded from the PK analysis set. The safety analysis set included all randomised healthy volunteers. Only one healthy volunteer had a significant medical or surgical history reported (urinary tract infection).

Summary of pharmacokinetic results

Compared to the median t_{max} following a single-dose oral administration of the 10 mg IR formulation, 1 hour, the median t_{max} of the 10 and 50 mg ER formulations, 2.5 hours, was delayed but inter-individual variability was high. A high-fat meal further delayed the median t_{max} of the 50 mg ER formulation to 5 hours. Following administration of the IR formulation, AZD2516 plasma concentrations declined in a monophasic manner with geometric mean terminal half-life ($t_{1/2, \lambda z}$) of 1.7 hours. Following administration of the ER formulation, the geometric mean $t_{1/2, \lambda z}$ values were similar among the ER formulations ranging from 5.1 hours for the 50 mg ER fed treatment and 7.1 to 7.7 hours in the 50 and 10 mg ER fasted treatments, respectively.

The statistical analysis of effect of formulation on key AZD2516 plasma pharmacokinetic parameters, normalized to a 10-mg dose, is presented in Table S2. When AZD2516 was delivered as the ER formulation, C_{max} and AUC values were 16% and 67% (10 mg ER: 10 mg IR), respectively, and 16% and 81%, respectively (50 mg ER: 10 mg IR) when compared to the 10 mg IR formulation.

Table S2 Statistical comparison of key AZD2516 PK parameters (normalized to a 10-mg dose) between the two ER formulations and IR formulation (fasted)

Parameter	AZD2516 Dose/Treatment	N	Geometric LS Mean	Ratio	90% CI for the Ratio
AUC (nmol*h/L)	50 mg ER	13	559.4	80.67	(69.66, 93.41)
	10 mg IR	16	693.5		
	50 mg ER	13	559.4	119.88	(103.38, 139.02)
	10 mg ER	15	466.7		
	10 mg ER	15	466.7	67.29	(58.56, 77.32)
	10 mg IR	16	693.5		

Table S2 Statistical comparison of key AZD2516 PK parameters (normalized to a 10-mg dose) between the two ER formulations and IR formulation (fasted)

Parameter	AZD2516 Dose/Treatment	N	Geometric LS Mean	Ratio	90% CI for the Ratio
C_{max} (nmol/L)	50 mg ER	16	54.28	15.56	(12.28, 19.71)
	10 mg IR	16	348.9		
	50 mg ER	16	54.28	97.71	(77.11, 123.82)
	10 mg ER	16	55.55		
	10 mg ER	16	55.55	15.92	(12.56, 20.18)
	10 mg IR	16	348.9		
$AUC_{(0-t)}$ (nmol*h/L)	50 mg ER	16	462.8	67.32	(58.26, 77.78)
	10 mg IR	16	687.5		
	50 mg ER	16	462.8	113.83	(98.52, 131.53)
	10 mg ER	16	406.6		
	10 mg ER	16	406.6	59.13	(51.18, 68.33)
	10 mg IR	16	687.5		

The statistical analysis of effect of food on key AZD2516 plasma pharmacokinetic parameters is presented in Table S3. The administration of a high fat meal with the ER formulation increased AZD2516 C_{max} by 127%, AUC by 11%, and $AUC_{(0-t)}$ by 29%, respectively.

Table S3 Statistical comparison of key AZD2516 PK parameters with and without food (ER formulation)

Parameter	AZD2516 Dose/Treatment	n	Geometric LS Mean	Fed/Fasted Ratio	90% CI for the Ratio
AUC (nmol*h/L)	50 mg ER (Fed)	16	622.4	111.25	(96.07, 128.83)
	50 mg ER (Fasted)	13	559.4		
$AUC_{(0-t)}$ (nmol*h/L)	50 mg ER (Fed)	16	596.4	128.87	(111.53, 148.90)
	50 mg ER (Fasted)	16	462.8		
C_{max} (nmol/L)	50 mg ER (Fed)	16	123.4	227.40	(179.45, 288.16)
	50 mg ER (Fasted)	16	54.28		

Summary of safety results

There were no deaths, no discontinuations of IP due to adverse events, or any other significant adverse event in the study. Most of the AEs were of mild/moderate intensity. There was one adverse event reported, which met the criteria for seriousness (SAE) following the last of four doses of AZD2516 (10 mg ER fasted). The healthy volunteer had first experienced the event of anxiety after his third of four individual doses of AZD2516 (50 mg ER administered in the fed state). At Visit 1, the subject was negative for anxiety in the Spielberger Trait Anxiety Index assessment. As the event occurred following study drug administration, the investigator could not exclude a causal relationship to study drug.

Small decreases in mean platelet counts from baseline of up to 5% were recorded on Study Days 1 and 3 (ranging from 4 to 12 $x10^9$ cells/L in all treatment groups). Overall, there were no clinically relevant treatment-related changes or trends in any laboratory (haematology, clinical chemistry, and urinalysis) parameter measured in healthy volunteers exposed to AZD2516 during the study.

There were no clinically relevant treatment related changes or trends in pulse rate, diastolic blood pressure or systolic blood pressure during the study in healthy volunteers exposed to AZD2516. QT prolongations were observed in 2 healthy volunteers during the study. One volunteer had outlier values for QT increase from baseline greater than 30 ms but less than or equal to 60 ms, at 1.5, 2, 2.5, 3, and 4 hours after 10 mg AZD2516 ER fasted administration. Another volunteer had a QT increase from baseline greater than 30 ms but less than or equal to 60 ms at 12 hours after AZD2516 10 mg IR fasted administration. No Fridericia-corrected QT (QTcF) or other ECG outlier values were noted for any healthy volunteers after exposure to AZD2516.

In the Columbia Suicide Severity Rating Scale assessment at Visit 5, all healthy volunteers responded “No” to the questions regarding suicidal ideation and behaviour, except for the subject who described the suicidal intensity as “Easily able to control thoughts” and “Fleeting – few seconds or minutes less than once a week”.