AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3551C00002
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Date	
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An Open-label, Single Centre Relative Bioavailability Study With an Adaptive Design Comparing up to 5 Solid Oral AZD5069 Formulations After Single Dose Administration to Healthy Volunteers

Study dates: First subject enrolled: 24 January 2014
Last subject last visit: 16 April 2014

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 centre(s)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To assess the relative bioavailability of AZD5069 from the putative Phase III formulation in comparison with the formulation used in the Phase IIb study following oral administration of single doses of 45 mg.	AUC, C_{max}, and C_{12h}.
Secondary	PK	To assess the bioavailability of AZD5069 from up to 3 Phase III formulation variants relative to the 45 mg putative Phase III formulation.	For AZD5069: $AUC_{(0\text{-last})}$, AUC, C_{max}, C_{12h}, C_{max}/C_{12h} ratio, C_{max}/AUC ratio, λ_z, $t_{½\lambda z}$, t_{max}, CL/F, and V_z/F.
Secondary	Safety	To further assess the safety and tolerability, particularly blood neutrophil counts, of single administrations of AZD5069 in healthy volunteers.	ANC, ratio to baseline, and change from baseline, ANC_{min}, ANC_{tmin}, ANC_{mean}, $ANC_{min,ratio}$, $ANC_{mean,ratio,}$ adverse events, safety laboratory evaluations, physical examination, electrocardiograms, and vital signs.
Exploratory[a]	PK	To understand the relationship between the in vitro dissolution rate and the in vivo plasma concentration profile of AZD5069.	-
Exploratory[a]	Pharmaco-genetic	To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (eg, disposition, safety, and tolerability) to AZD5069.	-

λ_z: Terminal rate constant; ANC: Absolute neutrophil count; ANC_{mean}: Mean of ANC values from predose to 24 hours postdose; $ANC_{mean,ratio}$: Mean of ANC ratio values calculated from baseline to 24 hours postdose; ANC_{min}: Minimum of absolute neutrophil count; $ANC_{min,ratio}$: Minimum of ANC ratio values; $ANCt_{min}$: Time to minimum absolute neutrophil count; AUC: Area under plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0\text{-last})}$: Area under plasma concentration-time curve from time zero to the time of last quantifiable analyte concentration; C_{12h}: Plasma concentration measured at 12 hours; CL/F: Apparent systemic clearance; C_{max}: Observed maximum plasma concentration; DNA: Deoxyribonucleic acid; $t_{½\lambda z}$: Terminal half-life; t_{max}: Time to maximum plasma concentration; PK: Pharmacokinetic; V_z/F: Apparent volume of distribution

[a] Reported separate from the Clinical Study Report, if performed.

Study design

This open-label, single centre, study including single administrations of up to 5 different formulations was to be conducted in up to 2 parts, with Part I consisting of a randomised 4 period 4-way crossover study. Part II could have occurred following an interim analysis of Part I pharmacokinetic (PK) data and, if so, would have comprised a single administration of 1 additional formulation. All treatments were administered as single oral administrations, capsules or tablets.

The screening (Visit 1) took place within 35 days of the first treatment administration in Period 1 (Part I).

Part I

Part I was a randomised, 4-way randomised crossover study design, where healthy volunteers were randomised to 1 of 4 different treatment sequences receiving each of the following treatments in 4 periods:

Treatment A: Phase IIb formulation, 45 mg, 3 capsules (solid state form A) (20 mg+20 mg+5 mg)

Treatment B: Tablet formulation B (solid state form D), 45 mg (putative Phase III formulation)

Treatment C: Tablet formulation C (solid state form D), 45 mg (slow dissolution variant 1)

Treatment D: Tablet formulation D (solid state form D), 45 mg (slow dissolution variant 2)

Healthy volunteers were admitted to the study centre on Day -1 of each of the 4 periods as per the randomisation scheme. Healthy volunteers received the treatment on Day 1 of each period, followed by safety and serial PK and blood neutrophil assessments. Healthy volunteers remained resident until discharge on Day 2 of each period, if there were no safety concerns. All periods were separated by a washout period of at least 5 days between administrations of the treatment (ie, washout period of 5 days between Day 1 of a period to Day 1 of the following period).

The study had an adaptive design with an interim analysis following Part I (4-way crossover). Interim analyses of Part I PK data were to be performed to determine which formulation (ie, Treatment E) to study in Part II, or whether to stop the study. A visit was scheduled 3 to 4 weeks following Period 4, which could have either been used for Period 5 (if it was decided to continue with the study) or for the follow-up visit (if it was decided to stop the study).

Data from 12 completed healthy volunteers were required and up to approximately 16 healthy volunteers may have been randomised to achieve this. All of the healthy volunteers received

up to 5 of the formulations. If less than 12 randomised healthy volunteers completed the study, additional healthy volunteers could have been screened, in order to achieve 12 completed healthy volunteers. The maximum total duration of the study for each healthy volunteer was approximately 10 weeks.

Target subject population and sample size

Healthy male and/or female volunteers aged 18 to 50 years (inclusive).

Planned: Up to 16 healthy volunteers

Randomised: 16 healthy volunteers

Treated: 16 healthy volunteers

Completed: 15 healthy volunteers

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

Table S2 Details of treatments

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD5069	Capsules 5 mg (Phase IIb) (A) (solid state form A)	AstraZeneca	12-002894AZ
AZD5069	Capsules 20 mg (Phase IIb) (A) (solid state form A)	AstraZeneca	13-000398AZ
AZD5069	Tablet putative Phase III 45 mg (B) (solid state form D)	AstraZeneca	13-002297AZ
AZD5069	Tablet 45 mg (C) (solid state form D)	AstraZeneca	13-001932AZ
AZD5069	Tablet 45 mg (D) (solid state form D)	AstraZeneca	13-002445AZ

Duration of treatment

Single dose.

Statistical methods

A listing of PK blood sample collection times as well as derived sampling time deviations were provided. A listing of all concentration-time data was presented. Figures of arithmetic mean (standard deviation) concentration-time data were presented on linear and semi-logarithmic scales. Individual healthy volunteer concentration-time data were graphically presented on linear and semi-logarithmic scales. Geometric mean and individual

area under plasma concentration-time curve from time zero extrapolated to infinity (AUC), plasma concentration measured at 12 hours (C_{12h}), and observed maximum plasma concentration (C_{max}) values for AZD5069 were presented versus treatment in scatter plots.

Analyses of AZD5069 PK parameters were performed by fitting a linear mixed effects model, using ln-transformed AUC, C_{max}, and $C_{12h,}$ as the response variables. Transformed back from the logarithmic scale, the estimates of the geometric means from the fitted model, together with corresponding 95% confidence intervals (2-sided) were presented. Also, the ratios of the geometric means were presented together with corresponding 90% confidence intervals (2-sided).

All adverse events (AEs) were collected for each healthy volunteer from admission until the follow-up visit. Adverse events were summarised by Preferred Term and System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities by treatment group. Furthermore, listings of serious adverse events (SAEs) and discontinuation of treatment due to an AE were made and the number of healthy volunteers who had any AEs, SAEs, discontinuation of treatment due to an AE, and AEs with severe intensity were summarised.

Tabulations and listings of data for vital signs (blood pressure and pulse rate), clinical laboratory tests, electrocardiograms, and physical examination findings were presented. Where applicable, data were summarised for the absolute value at each scheduled assessment, and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each healthy volunteer were presented with abnormal or out-of-range values flagged. Clinical laboratory data were reported in Système International units.

For blood neutrophil counts, line plots of individual and arithmetic mean absolute values (±standard deviation) versus time were presented. Individual healthy volunteer blood neutrophil count data (absolute value and change from baseline) were plotted with arithmetic mean, one plot per treatment. Descriptive summaries of the minimum of absolute neutrophil count (ANC_{min}) and the time to minimum absolute neutrophil count ($ANCt_{min}$) were presented by treatment.

Analyses of ln-transformed ANC_{min} were performed by fitting a linear mixed effects model. Transformed back from the logarithmic scale, the estimates of the geometric means from the fitted model, together with corresponding 95% confidence intervals (2-sided) were presented.

Subject population

Sixteen healthy volunteers were randomised in the study and all healthy volunteers (100.0%) received at least 1 treatment. Fifteen healthy volunteers (93.8%) completed the study. One healthy volunteer (6.3%) was withdrawn due to an AE and only received Treatment B.

Summary of pharmacokinetic results

AZD5069 mean plasma concentration-time profiles were similar between treatments in Part I. Median time to maximum plasma concentration (t_{max}) for Treatment B (2.00 h) occurred approximately 1 hour earlier than Treatment A (2.98 h). Median t_{max} was similar between

Treatments B, C and D (1.50 to 2.00 h). Geometric mean estimates of $t_{½\lambda z}$ (range of 4.74 to 5.44 hours) were similar between the 4 treatments.

The table below summarizes the point estimates of the geometric least-squares mean ratios and associated 90% confidence intervals for the comparison of AZD5069 primary PK parameters between treatments.

Table S3 Statistical comparison of primary AZD5069 pharmacokinetic parameters

					Statistical Pairwise comparison		
Parameter	**Treatment[a]**	**n**	**Geometric LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI (%)**
AUC	A	15	11570	(9425, 14200)			
(nmol ·h/L)	B	16	12080	(9846, 14820)	B/A	104.43	(99.50, 109.60)
	C	15	10710	(8725, 13140)	C/B	88.65	(84.46, 93.04)
	D	15	10870	(8861, 13350)	D/B	90.03	(85.78, 94.49)
C_{max}	A	15	2595	(2200, 3060)			
(nmol/L)	B	16	3127	(2662, 3672)	B/A	120.50	(105.27, 137.93)
	C	15	2800	(2374, 3303)	C/B	89.56	(78.24, 102.51)
	D	15	2790	(2366, 3291)	D/B	89.25	(77.97, 102.16)
C_{12h}	A	15	118.1	(85.07, 164.1)			
(nmol/L)	B	16	95.58	(68.97, 132.4)	B/A	80.90	(70.35, 93.04)
	C	15	85.10	(61.28, 118.2)	C/B	89.04	(77.42, 102.39)
	D	15	80.77	(58.16, 112.2)	D/B	84.51	(73.49, 97.19)

CI: Confidence interval; LS: Least-squares
Results based on a linear mixed effects model with fixed effects for sequence, period, and treatment, plus a random effect for subject nested within sequence.

[a] Treatment A: Phase IIb formulation, 45 mg, 3 capsules (solid state form A) (20 mg+20 mg+5 mg); Treatment B: Tablet formulation B (solid state form D), 45 mg (putative Phase III formulation); Treatment C: Tablet formulation C (solid state form D), 45 mg (slow dissolution variant 1); Treatment D: Tablet formulation D (solid state form D), 45 mg (slow dissolution variant 2).

Source: Table 11.2.3.

Treatment B had similar overall AZD5069 exposure (AUC) to Treatment A, but its geometric mean C_{max} was approximately 21% higher and geometric mean C_{12h} was approximately
19% lower on average than that of Treatment A.

Treatments C and D exhibited approximately 10% to 11% lower geometric mean AZD5069 exposure (AUC and C_{max}) and approximately 11% to 15% lower geometric mean C_{12h} on average compared to Treatment B.

Following review of the Part I interim data, it was decided to end the study. This decision was made based on the conclusions drawn from review of the interim data (Table S3).

Summary of safety results

All 16 healthy volunteers received at least one of the treatments and were included in the safety analysis set.

No deaths or SAEs were reported during the study. One healthy volunteer (6.3%) reported a discontinuation of treatment due to an AE (Treatment B); the Investigator considered the reported event of moderate back pain to be not related to the treatment. A total of 5 healthy volunteers (31.3%) reported at least 1 AE during the study. The SOC with the most healthy volunteers reporting at least 1 AE was nervous system disorders (2 healthy volunteers [12.5%]).

Mean and median absolute neutrophil count (predose to 24 hours), change from baseline, and percentage change from baseline showed a steady decrease from predose values and reached a minimum at 6 or 8 hours postdose. Thereafter, the values increased again towards baseline. Mean and median minimum of absolute neutrophil count ratio values ($ANC_{min,ratio}$) and mean of absolute neutrophil count ratio values calculated from baseline to 24 hours postdose ($ANC_{mean,ratio}$) values were similar between the treatments.

No clinically important values or changes were reported for laboratory measurements (apart from the known and expected variation of neutrophils), vital signs, electrocardiograms, and physical examinations.

Conclusion(s)