AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00033
Edition Number	1
Date	FINAL 24 October 2011

Randomized, Open, 4-way Crossover, Single Center, Phase I Relative Bioavailability Study in Type 2 Diabetes Mellitus Patients to Measure the Extent and Rate of Absorption of AZD1656 from Different Tablet Formulations

Study dates: First subject enrolled: 28 September 2010
Last subject last visit: 10 February 2011

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 performed at 1 center in the United States (Prism Research, 1000 Westgate Drive, #149, St. Paul, MN 55114).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary		
To measure the rate and extent of absorption of AZD1656 following single-dose administration of Tablets A, B, and C, administered before food intake and additionally following administration of Tablet B after food intake, by assessment of AUC, C_{max}, and t_{max} of AZD1656	AUC, C_{max}, and t_{max} of AZD1656	Pharmacokinetic
Secondary		
To evaluate the pharmacokinetics of AZD1656 following single-dose administration of Tablets A, B, and C administered before food intake and additionally following administration of Tablet B after food intake, by assessment of $AUC_{(0-t)}$, $t_{1/2}$, and CL/F of AZD1656	$AUC_{(0-t)}$, $t_{½}$, and CL/F of AZD1656	Pharmacokinetic
To evaluate the pharmacokinetics of the AZD1656 metabolite, AZD5658, following single-dose administration of Tablets A, B, and C, administered before food intake and additionally following administration of Tablet B after food intake, by assessment of AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, and $t_{1/2}$	AUC, $AUC_{(0-t)}$ C_{max}, t_{max}, and $t_{½}$ of AZD5658	Pharmacokinetic
To evaluate the pharmacodynamics of AZD1656 following single-dose administration of Tablets A, B, and C, administered before food intake and additionally following administration of Tablet B after food intake, by assessment of $AUC_{(0-4)}$ and $AUC_{(0-24)}$ for plasma glucose and $AUC_{(0-4)}$ for serum insulin	$AUC_{(0-4)}$, $AUC_{(0-24)}$, $AUC_{(0-4)}/T$, and $AUC_{(0-24)}/T$ for glucose and $AUC_{(0-4)}$ and $AUC_{(0-24)}/T$ for insulin	Pharmacodynamic
To evaluate the safety of AZD1656 by assessment of adverse events, physical examination, electrocardiogram, pulse, blood pressure, weight, and laboratory variables including plasma glucose	Adverse events, physical examination, electrocardiogram, pulse, blood pressure, body weight, and laboratory variables including plasma glucose	Safety

Objectives	Outcome variables	Type
Exploratory		
To collect and store deoxyribonucleic acid samples for potential future research into genes which may influence response (pharmacokinetics, efficacy, safety, and tolerability) to AZD1656 and/or metformin	Not applicable	Exploratory[a]

[a] Results from any genetic research, if performed, will be reported separately from this Clinical Study Report.

Study design

This was an open-label, randomized, 4-way crossover, bioavailability study in patients with type 2 diabetes mellitus. The relative bioavailability was assessed between 3 different formulations (Tablet A, Tablet B, and Tablet C) and in addition, the effect of food on the pharmacokinetics of AZD1656 was evaluated for Tablet B only.

Patients were randomly assigned to 1 of the 4 treatment sequences (ABCD, CADB, DCBA, and BDAC).

Treatment A= Tablet A, AZD1656 film-coated tablets, 2 x 50 mg prior to food
Treatment B= Tablet B, AZD1656 film-coated tablet, 100 mg prior to food
Treatment C= Tablet C, AZD1656 film-coated tablet variant, 100 mg prior to food
Treatment D= Tablet B, AZD1656 film-coated tablet, 100 mg after food

Any oral antidiabetic drugs other than metformin were stopped 7 to 10 days before randomization/intake of investigational product, and patients remained on their regular dose of metformin during the study. Patients stayed in the clinic until 48 hours postdose of each treatment period for pharmacokinetic and pharmacodynamic sampling and safety surveillance. There was at least a 72 hour washout before the patient returned to the clinic for the next treatment period.

Target subject population and sample size

The target population were males and females (of nonchildbearing potential) with type 2 diabetes mellitus on stable metformin, aged greater than or equal to 18 years, and with a body mass index of greater than or equal to 19 kg/m^2 and less than or equal to 42 kg/m^2.

Based on previous studies, an estimate of the within-patient SD for the logarithm of AUC is 0.09 for AZD1656 and AZD5658. To obtain a 90% confidence interval for AUC of AZD1656 within the interval (0.8; 1.25) with 90% power, 12 evaluable patients was considered sufficient.

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

- Tablet A, AZD1656 film-coated tablets, 50 mg, lot number 10-002614AZ
- Tablet B, AZD1656 film-coated tablet, 100 mg, lot number WK90546.001

- Tablet C, AZD1656 film-coated tablet variant, 100 mg, lot number 10-002624AZ

All investigation products were manufactured by AstraZeneca. All treatments were given with 240 mL of water. The patients took their regular metformin tablets as prescribed in the morning of Day 1 of each study period just prior to the AZD1656 administration.

Duration of treatment

Total length of the study for a patient was approximately 2 months and included a screening visit, oral antidiabetic drugs washout period (other than metformin), 4 treatment periods at the clinic during which patients received 4 single oral doses of 100 mg AZD1656, and a follow-up visit.

Statistical methods

Plasma concentrations of AZD1656, and the metabolite AZD5658 and their derived pharmacokinetic parameters were summarized by treatment using descriptive statistics.

The relative bioavailability was analyzed utilizing data from treatment with Tablet A administered in a fasting state as reference and treatment with the Tablet B and Tablet C variant administered in fasting states as test. Analyses were performed with a linear mixed-effect analysis of variance model using the logarithm of AUC (and C_{max}) as the response variable and sequence, period and treatment as fixed effects, and patient within sequence as random effect. The analysis was performed for AZD1656 and the metabolite AZD5658.

The influence of food was analyzed utilizing data from treatment with Tablet B administered prior to food as reference and after food as test. Estimates from the above model were used to perform this comparison. The analyses were performed for AZD1656 and the metabolite AZD5658.

The comparison of treatments listed above were performed for t_{max}. Nonparametric methods were used to compute medians on t_{max} for each treatment and median differences, and associated 90% confidence interval differences for t_{max} between the treatments. The data were analyzed by a Wilcoxon Signed-Rank Test. The 90% confidence intervals were calculated using the method of Hahn and Meeker. The analyses were performed for AZD1656 and the metabolite AZD5658.

Analysis of the pharmacodynamic variables was performed by fitting a linear mixed-effect analysis of covariance model, using the logarithm of AUC [ie, $AUC_{(0-4)}$ and $AUC_{(0-24)}$ for plasma glucose, $AUC_{(0-4)}$ for serum insulin and baseline-adjusted parameters) as the response variable, the logarithm of the predose plasma glucose measurement (or serum insulin) in each treatment period as a covariate (continuous variable), treatment, sequence, and period as fixed effects, and patient within sequence as a random effect.

All safety variables were presented descriptively.

Subject population

Of the 53 patients screened in this study, 16 patients were randomly assigned to treatment and received treatment, and 14 (87.5%) patients completed the study. The first patient was enrolled on 28 September 2010 and the last patient completed the study on 10 February 2011. Sixteen patients were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

Summary of pharmacokinetic results

The table below shows comparison of key pharmacokinetic parameters forAZD1656 and AZD5658 for treatments where AZD1656 was administered prior to breakfast (Treatments A, B, and C).

Table S2 Comparison of key PK parameters for Treatments A, B, and C

						Pairwise Comparisons		
Analyte	Parameter (unit)	Trt [a]	N	Geometric LS Mean	Geometric LS Mean 95% CI	Pair	Ratio (%)	90% CI
AZD1656	AUC (µmol•h/L)	A	15	22.86	(19.26, 27.14)			
		B	14	21.89	(18.43, 26.00)	B/A	95.75	(92.37, 99.26)
		C	15	22.25	(18.74, 26.42)	C/A	97.34	(93.98, 100.83)
	C_{max} (µmol/L)	A	15	3.788	(3.156, 4.545)			
		B	15	4.037	(3.364, 4.844)	B/A	106.57	(91.00, 124.81)
		C	15	3.031	(2.526, 3.637)	C/A	80.02	(68.33, 93.72)
AZD5658	AUC (µmol•h/L)	A	10	2.907	(2.319, 3.644)			
		B	12	2.963	(2.368, 3.707)	B/A	101.94	(92.99, 111.75)
		C	10	2.784	(2.219, 3.492)	C/A	95.77	(87.07, 105.34)
	C_{max} (µmol/L)	A	15	0.233	(0.1738, 0.3126)			
		B	15	0.2911	(0.2170, 0.3904)	B/A	124.9	(109.37, 142.64)
		C	15	0.2022	(0.1508, 0.2712)	C/A	86.77	(75.99, 99.09)

LS Least-squares

[a] Treatment A Tablet A, AZD1656 film-coated tablets, 2 x 50 mg prior to food; Treatment B Tablet B, AZD1656 film-coated tablet, 100 mg prior to food; Treatment C Tablet C, AZD1656 film-coated tablet variant, 100 mg prior to food; Treatment D Tablet B, AZD1656 film-coated tablet, 100 mg after food.

The AUC comparisons for both analytes and test formulations met bioequivalence criteria since the geometric mean ratios for all comparisons were within the 80 to 125% bioequivalence bounds.

With exception of the AZD1656 C_{max} comparison of Treatment B compared to Treatment A, which met bioequivalence criteria, the observed differences in the C_{max} values were shown to be somewhat larger: AZD1656 C_{max} in Treatment C was lower (by 20%); AZD5658 C_{max}

was higher (by about 25%) for Treatment B and lower (by about 13%) for Treatment C relative to Treatment A.

The table for comparison of Treatment B and D exposures is shown below:

Table S3 Comparison of key PK parameters for Treatments B and D

						Comparison of Fed to Fasted		
Analyte	**Parameter (unit)**	**Trt [a]**	**N**	**Geometric LS Mean**	**Geometric LS Mean 95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AZD1656	AUC (µmol•h/L)	B	14	21.89	(18.43, 26.00)	D/B	103.79	(100.12, 107.61)
		D	16	22.72	(19.14, 26.97)			
	C_{max} (µmol/L)	B	15	4.037	(3.364, 4.844)	D/B	88.63	(75.77, 103.68)
		D	16	3.578	(2.996, 4.272)			
AZD5658	AUC (µmol•h/L)	B	12	2.963	(2.368, 3.707)	D/B	102.81	(94.19, 112.22)
		D	13	3.047	(2.438, 3.806)			
	C_{max} (µmol/L)	B	15	0.2911	(0.2170, 0.3904)	D/B	83.19	(72.87, 94.99)
		D	16	0.2422	(0.1809, 0.3241)			

LS Least-squares

[a] Treatment A Tablet A, AZD1656 film-coated tablets, 2 x 50 mg prior to food; Treatment B Tablet B, AZD1656 film-coated tablet, 100 mg prior to food; Treatment C Tablet C, AZD1656 film-coated tablet variant, 100 mg prior to food; Treatment D Tablet B, AZD1656 film-coated tablet, 100 mg after food.

Dose administration at 20 minutes after start of a meal did not affect total exposure for both AZD1656 and AZD5658 as the the 90% CI of the geometric mean ratios were fully contained within the 80 to 125% boundaries. The C_{max} however were lower for Treatment D for both analytes (by about 11 and 17% for AZD1656 and AZD5658, respectively)

When t_{max} was compared across treatments, for both AZD1656 and AZD5658, time to maximum concentration was the same for Treatments B and A and similar (0.75 to 1 hour later) for Treatment C.

For both AZD1656 and AZD5658, time to maximum exposure was significantly delayed by 2.5 and 2 hours respectively, for Treatment D relative to Treatment B.

The PK parameters half-life and CL/F for AZD1656 were similar across all treatments and similarly, the half-life of AZD5658 was similar across all treatments.

Summary of pharmacodynamic results

Following administration of AZD1656, plasma glucose decreased and serum insulin increased for all treatments. For both S-insulin and P-glucose, AUCs were similar (within ± 6% of reference) for both treatments B and C relative to treatment A. While the pairwise comparison for insulin had wider confidence interval indicating higher variability in the results, the 90% CI for all glucose pairwise comparisons fell within the 80 to 125% bounds. This indicates a lack of treatment difference between the three AZD1656 formulations for glucose response.

Summary of safety results

A total of 65 adverse events were reported by 15 patients during the treatment period of the study. The number of patients reporting an adverse event was similar across the treatments.

Patient E0001032 (sequence DCBA) discontinued from the study due to an AE of mild headache, occurring approximately 21 hours postdose, on Day 2 of Treatment D. The Investigator assessed the AE as causally related to study drug, and the subject recovered without sequela. The patient had experienced 4 moderate AEs (headache, hypoglycemia, nausea, and vomiting) and 1 mild AE (tremor), each on Day 1.

Patient E0001013 completed only Treatment D (Period 1), subsequent to which the patient withdrew from the study due to subject decision on Day 21. This patient had 2 mild AEs of diarrhea and nausea, both on Day 13.

All other adverse events in the study were of mild intensity. The most frequently reported adverse events were headache, tremor, hypoglycemia, ecchymosis, and nausea. Five (31.3%) patients had 8 adverse events of hypoglycaemia (7 mild and 1 moderate).

Patient E0001028 had 3 AEs of mild hypoglycemia on Day 1 of Treatment A, Day 20 of Treatment C, and Day 27 of Treatment D. Patient E0001032 had an AE of moderate hypoglycaemia on Day 1 of Treatment D. Patient E0001044 had an AE of mild hypoglycemia on Day 7 of Treatment A. Patient E0001051 had an AE of mild hypoglycemia on Day 1 of Treatment A. Patient E0001052 had 2 mild AEs of hypoglycemia on Day 14 of Treatment B and Day 21 of Treatment A. None of these AEs required treatment.

There were no significant changes in laboratory, electrocardiogram, vital sign (blood pressure and pulse), weight, and physical examination findings.