AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00007
Edition Number	1
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A Phase I, Multi-center, Open-label, Single Dose Study, to Assess the Pharmacokinetics of AZD1656 and its Metabolite AZD 5658 in Type 2 Diabetes Mellitus Patients With or Without Renal Impairment

Study dates: First subject enrolled: 17 March 2010
Last subject last visit: 22 October 2010

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)

The study was a multi-center study conducted at 3 centers in the United States (New Orleans Center for Clinical Research/Volunteer Research Group, Knoxville, Tennessee; Orlando Clinical Research Center, Orlando, Florida; and DaVita Clinical Research, Minneapolis, Minnesota) with a minimum of 28 and maximum of 36 patients (7 to 9 patients per renal category).

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	**Primary**	
To assess the pharmacokinetics of AZD1656, and its active metabolite AZD5658, in type 2 diabetes mellitus patients with varying degrees of renal impairment and to compare the results with those in patients with normal renal function	C_{max}, t_{max}, $t_{1/2}$, λ_z, $AUC_{(0-t)}$, AUC, $AUC_{(0-12)}$, CL/F, V_z/F, urine A_e, and CL_r	Pharmacokinetic
Secondary	**Secondary**	
To evaluate the safety of AZD1656 in type 2 diabetes mellitus patients with varying degrees of renal impairment	Adverse events, blood pressure, pulse rate, safety laboratory variables (including glucose), and Investigator's interpretation of electrocardiogram	Safety
To describe the pharmacodynamics of AZD1656 in type 2 diabetes mellitus patients with varying degrees of renal impairment by assessment of a 24-hour glucose profile.	$AUC_{(0-24)}$, C_{avg}, C_{min}, and baseline-adjusted glucose concentrations	Pharmacodynamic
Exploratory[a]	**Exploratory**	
To determine the unbound concentrations of AZD1656 and AZD5658 in patients with varying degrees of renal impairment and to compare the results with those in patients with normal renal function	f_u, $C_{u,\,max}$, $AUC_{u,\,(0-t)}$, AUC_u, and CL_u/F	Pharmacokinetic
To collect and store deoxyribose nucleic acid samples for potential future research into genes, which may influence pharmacokinetic profile, drug disposition, efficacy, safety, and tolerability of AZD1656	Not applicable	Pharmacogenetics

C_{max} maximum concentration in the plasma; t_{max} time to C_{max}; $t_{1/2}$ apparent terminal half-life; λ_z apparent terminal rate constant; $AUC_{(0-t)}$ area under the plasma concentration-time curve from zero to the time of the last measurable concentration; AUC area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-12)}$ area under the plasma concentration-time curve from zero to 12 hours postdose; CL/F apparent oral clearance; V_zF apparent volume of

distribution; Ae amount of analyte excreted in the urine; Cl_r renal clearance; C_{avg} average plasma glucose concentration; C_{min} minimum glucose concentration in the plasma over the given 24-hour sampling period

[a] Results from any genetic research, if performed, will be reported separately from this clinical study report.

Study design

This was a multi-center, Phase I, open-label, single-dose study to assess the pharmacokinetics of AZD1656 and its metabolite AZD5658 in type-2 diabetes mellitus patients with or without renal impairment.

Target subject population and sample size

Male and female patients of nonchildbearing potential with a clinical diagnosis of type-2 diabetes mellitus and treated with insulin and/or oral antidiabetic drugs aged 18 years or more, and having a body mass index of 19 to 42 kg/m^2, inclusive were divided into 4 groups based on renal function: normal (glomerular filtration rate greater than 80 mL/min), mild (glomerular filtration rate 50 to 80 mL/min), moderate (glomerular filtration rate 30 to less than 50 mL/min), and severe (glomerular filtration rate less than 30 mL/min).

Investigational product dosage, mode of administration, and batch numbers

The investigational product was AZD1656 50 mg single-dose oral tablet, lot number 10-000044AZ, manufactured by AstraZeneca.

Duration of treatment

The total duration of each patient's participation was approximately 40 days with a 28-day screening period, a 3-day treatment period, and a 7- to 10-day follow-up period.

A single in-house stay in the clinic was required which included estimation of the glomerular filtration rate with iohexol and a treatment period with AZD1656. The in-house stay was 3 nights and 4 days.

Statistical methods

The relationships between renal impairment and the PK of AZD1656 and AZD5658 were assessed by regression of the PK parameters (C_{max}, AUC, CL/F, and CL_u/F) onto the glomerular filtration rate (calculated using the MDRD formula, Cockcroft and Gault formula, and estimated using the iohexol method).

Furthermore, an analysis of variance model using log-transformed pharmacokinetic parameters of AZD1656 and AZD5658 (except t_{max}) was used to estimate ratios of true geometric means together with confidence intervals (2-sided 90%) for the comparisons of severe versus normal, moderate versus normal, and mild versus normal.

Subject population

Sixty-four patients were enrolled into this study and 34 patients were randomized (7 normal, 9 each mild, moderate, and severe). The first patient was enrolled on 17 March 2010 and the last patient completed on 22 October 2010. All 34 patients completed the study and were analyzed for safety and the pharmacokinetics of AZD1656 and its metabolite AZD5658.

The study population consisted of 23 males and 11 females with type 2 diabetes mellitus, with a mean age of 61.4 years.

Summary of pharmacokinetic results

Following single-dose oral administration of AZD1656 in patients in the different renal function groups the AZD1656 or AZD5658 median t_{max} was similar (1.0 to 1.5 hours) across all the renal function groups. The mean AZD1656 terminal elimination half-life was slightly longer for the severe renal function group as compared to the other 3 groups. The renal clearance of AZD1656 was low (<0.1 L/h) in all the renal groups in comparison to the oral plasma clearance. The mean unbound fractions ranged from 4.2% to 4.8% for AZD1656 and 12.1% to 15.4% for AZD5658 in the different renal function groups.

Table S2 Relationship between glomerular filtration rate and key AZD1656 or AZD5658 pharmacokinetic Parameters

Analyte	Renal Function Marker	PK Parameter	GFR Coefficient			
			N	Estimate	95% CI	p-value
AZD1656	Iohexol-GFR	AUC (µmol*h/L)	34	-0.0009	(-0.00290, 0.000961)	0.3134
		$AUC_{(0-t)}$ (µmol*h/L)	34	-0.0009	(-0.00290, 0.000967)	0.3157
		C_{max} (µmol/L)	34	0.0010	(-0.00119, 0.00323)	0.3551
		CL/F (L/h)	34	0.0009	(-0.000910, 0.00818)	0.3192
		CL_u/F (L/h)	33	0.0017	(-0.000372, 0.00379)	0.1040
AZD5658	Iohexol-GFR	$AUC_{(0-t)}$ (µmol*h/L)	34	0.0005	(-0.00358, 0.00459)	0.8029
		C_{max} (µmol/L)	34	0.0024	(-0.00166, 0.00646)	0.2381

GFR glomerular filtration rate

There was no significant relationship between the renal function (measured iohexol glomerular filtration rate) and AZD1656 exposure parameters (C_{max}, AUC, $AUC_{(0-t)}$) or AZD1656 oral clearance (total or unbound).

There was no significant relationship between the renal function (measured iohexol glomerular filtration rate) and AZD5658 total or peak exposure.

The analysis of variance analysis indicated that there was no significant change in the AZD1656 or AZD5658 total plasma exposure (AUC[AZD1656 only] or $AUC_{(0-t)}$) or total oral clearance (AZD1656 only) in the renal impairment groups as compared to the normal renal group however; the unbound oral clearance of AZD1656 was 23% and 21%, respectively lower in the moderate and severe renal groups compared to the normal group. The total C_{max} of AZD1656 as well as AZD5658 decreased in the severe renal group as compared to the normal group.

Summary of pharmacodynamic results

The mean glucose profiles followed a similar pattern in all 4 renal groups. The glucose concentrations were higher on Day 2 as compared to Day 1 in all the groups.

There were no remarkable differences in the glucose pharmacodynamic parameters in patients with normal renal function or in patients with different degrees of renal impairment, although the mean average plasma concentration for glucose was higher (10.7 mmol/L versus 8.76 to 9.54 mmol/L on Day 1 and 11.5 mmol/L versus 9.84 to 10.4 mmol/L) in the severe renal group as compared to other groups.

Summary of safety results

A total of 14 adverse events were reported by 9 (26.5%) patients during the treatment period of the study. The number of patients reporting an adverse event was similar across the renal groups. One patient (normal renal group) reported an adverse event of ear canal injury during the follow-up period.

There was no single adverse event reported by more than 1 patient in the study. One patient in each of the normal, mild, and moderate renal groups reported an adverse event that was considered by the Investigator to be causally related to investigational product. No adverse events were considered severe in intensity. Moderate AEs (back pain and rash pruritic) were only reported in the moderate renal group (2 [22.2%]). No patients reported an adverse event in conjunction with a low glucose value.

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