AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5658
Study Code	D2920C00001
Edition Number	1
Date	8 September 2011

A Randomized, Single-blind, Placebo-controlled, Single-center, Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and the Effect of Fasting after Single Ascending Oral Doses of AZD5658 in Type 2 Diabetes Mellitus Patients

Study dates:	First subject enrolled: 16 July 2010 Last subject last visit: 11 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)

The study was conducted at a single center: Profil Institute for Clinical Research Inc, Chula Vista, California, United States.

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 investigate the safety and tolerability of AZD5658 following oral administration of single ascending doses and to estimate the maximum tolerated dose, if within the predefined exposure and dose limits	Adverse events, blood pressure, pulse rate, safety laboratory variables (including glucose), and digital electrocardiograms	Safety
Secondary	**Secondary**	
To investigate the pharmacokinetics of AZD5658 after single ascending oral doses in type 2 diabetes mellitus patients	C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, λz, $t_{1/2,\lambda z}$, CL/F, V_zF	Pharmacokinetic
To investigate glucose levels and insulin secretions in type 2 diabetes mellitus patients after administration of single oral doses of AZD5658	$sAUC_{(0-4)}$, $sAUC_{(9-12)}$, $sAUC_{(0-24)}$	Pharmacodynamic
To investigate the effect of fasting on the pharmacokinetics and explore the pharmacodynamics of AZD5658	Not applicable	Pharmacokinetic

Study design

This was a Phase I randomized single-blind placebo-controlled single-center study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of AZD5658 following single ascending oral dose administration to type 2 diabetes mellitus patients. There were 6 dose levels with 8 patients in each cohort, 6 receiving AZD5658 and 2 receiving placebo. The effect of fasting on the pharmacokinetics of AZD5658 was also studied for 2 dose levels.

Target subject population and sample size

Male and female (of nonchildbearing potential) Type 2 diabetes mellitus patients treated with metformin, 20 to 65 years of age with body mass index between 19 and 40 kg/m^2 participated in the study. Patients were treated with metformin and had HbA1c at enrollment between 7.5% to 10%.

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

AZD5658 was administered orally as a suspension in escalating doses between 3 mg and up to 400 mg (Batch number: 10-002541AZ). Before proceeding to the next dose level, safety, tolerability, and pharmacokinetic data from the previous dose level(s) were evaluated by a Safety Review Committee. The dose-escalation portion of the study included doses of 3, 10, 30, 100, 200, and 400 mg AZD5658. Doses of 30 and 200 mg AZD5658 under fasted conditions were administered in the fasting-effect portion of the study.

Comparator was an oral suspension of placebo to match AZD5658 (Batch number: P8243).

Duration of treatment

Each patient treated with metformin received a maximum of 2 single oral suspension doses (1 on a low dose of AZD5658/placebo and 1 on a high dose of AZD5658/placebo under fed conditions), except for patients participating in the evaluation of the effect of fasting, who received a maximum of 3 single oral suspension doses. For each patient the study included a pre-entry visit (Visit 1), 2 or 3 clinic-based treatment visits (Visit 2, 3, and 4) and a follow-up visit (Visit 5). Hence, the total duration of the study for each patient was approximately 2.5 months, assuming 3 weeks between dose levels.

Statistical methods

No formal statistical hypothesis testing was performed. All variables were presented with descriptive statistics within treatment group (AZD5658 and placebo) and within dose. This was done separately for fed/fasting patients. The potential relationship between pharmacodynamic variables and dose was explored graphically. Descriptive statistics and frequency counts were provided for safety variables, as applicable.

Pharmacokinetics

Assessment of dose proportionality of AZD5658 was assessed graphically and analyzed using the power model approach utilizing random coefficients and random intercepts. To investigate the effect of fasting on pharmacokinetic parameters AUC and C_{max} of AZD5658, an analysis of variance was performed on the log-transformed pharmacokinetic parameters of AZD5658. Additionally, the effect of fasting across dose levels on pharmacokinetic parameters AUC and C_{max} of AZD5658, an analysis of variance on the dose-normalized, log-transformed pharmacokinetic parameters of AZD5658 was performed.

Pharmacodynamics

Exploratory analyses of the fed pharmacodynamic variables (glucose or insulin) was performed by fitting a linear mixed-effects analysis of covariance model. Similar analyses were also performed for fasted pharmacodynamics by fitting a linear effects analysis of covariance. Exploratory analyses of the effect of dose level on pharmacodynamic variables [$sAUC_{(0-4)}$, $sAUC_{(9-12)}$, and $sAUC_{(0-24)}$] was assessed graphically and analyzed using the power model approach. To investigate the effect of fasting on pharmacodynamic parameters, an

analysis of covariance was performed for the change in logarithm of sAUC [log($sAUC_{(0-4)}$, $sAUC_{(9-12)}$, or $sAUC_{(0-24)}$ at Day 1) – log ($sAUC_{(0-4)}$, $sAUC_{(9-12)}$, or $sAUC_{(0-24)}$ at Day -1)].

Subject population

There were 28 study participants with 23 patients who completed the study and 5 patients who discontinued the study. Two patients withdrew at their discretion and 3 patients were withdrawn for other reasons including 2 patients who no longer met the liver function test criteria and 1 patient who had poor venous access. All 28 patients were included in the safety and pharmacodynamic analysis sets; all patients receiving AZD5658 were included in the pharmacokinetic analysis set.

All patients had a history of type 2 diabetes mellitus (mean duration of 7.9 ±5.4 years) and continued the use of metformin therapy during the study. There were 9 patients with ongoing hypertension treated with medication; otherwise, study participants were without significant ongoing medical conditions. The 21 (75.0%) men and 7 (25.0%) women who were enrolled in the study had an average age of 51.4 ±7.1 years and average HbA1c of 8.73 ±0.80%. No meaningful differences in demographics or baseline characteristics among the dose groups were noted.

Summary of pharmacokinetic results

The predefined maximum exposure limit for AZD5658 AUC (31 µmol·h/L) was reached in 2 patients, whereas the predefined maximum exposure limit for AZD5658 C_{max} (7.4 µmol/L) was reached in 1 patient at the 400 mg dose level; hence, further dose escalation was stopped.

The summary of key pharmacokinetic parameters of AZD5658 is presented in Table S2.

Table S2 Geometric mean (%CV) of key pharmacokinetic parameters of AZD5658

Variable	AZD5658 Dose (mg)/fed- fasted state							
	3 mg/fed	10 mg/fed	30 mg/fed	100 mg/fed	200 mg/fed	400mg/ fed	30 mg/ fasted	200 mg/ fasted
AUC (h·µmol/L)	ND	ND	(n=4) 1.18 (62.9)	(n=4) 4.14 (53.8)	(n=6) 8.99(44.9)	(n=6) 19.4 (48.9)	(n=3) 1.21 (56.8)	(n=6) 7.42 (38.9)
$AUC_{(0-t)}$ (h·µmol/L)	(n=6) 0.0246 (81.7)	(n=6) 0.232 (73.6)	(n=9) 0.812 (74.1)	(n=6) 3.61 (43.0)	(n=6) 8.43 (45.2)	(n=6) 19.2 (50.6)	(n=6) 1.15 (48.5)	(n=6) 7.18 (39.5)
C_{max} (µmol/L)	(n=6) 0.0207 (28.0)	(n=6) 0.0923 (72.0)	(n=9) 0.305 (76.9)	(n=6) 1.13 (46.5)	(n=6) 2.58 (58.5)	(n=6) 5.98 (28.0)	(n=6) 0.448 (54.9)	(n=6) 3.04 (49.1)
t_{max} (h)[a]	(n=6) 0.50 (0.25-1.00)	(n=6) 0.50 0.25-0.75)	(n=9) 0.50 (0.25-0.52)	(n=6) 0.50 (0.25-0.75)	(n=6) 0.38 (0.25-0.75)	(n=6) 0.50 (0.50-0.75)	(n=6) 0.50 (0.25-1.00)	(n=6) 0.50 (0.50-1.50)
$t_{1/2}$ (h)	ND	ND	(n=5) 14.0 (65.8)	(n=4) 13.9 (58.3)	(n=6) 16.7 (67.4)	(n=4) 15.8 (43.6)	(n=3) 13.2 (64.4)	(n=6) 11.8 (58.0)

Table S2 Geometric mean (%CV) of key pharmacokinetic parameters of AZD5658

Variable	AZD5658 Dose (mg)/fed- fasted state							
	3 mg/fed	10 mg/fed	30 mg/fed	100 mg/fed	200 mg/fed	400mg/ fed	30 mg/ fasted	200 mg/ fasted
CL/F (L/h)	ND	ND	(n=4) 54.5 (62.8)	(n=4) 51.9 (53.7)	(n=6) 47.9 (45.0)	(n=4) 44.4 (49.0)	(n=3) 53.5 (56.5)	(n=6) 58.0 (39.0)
V_Z/F (L)	ND	ND	(n=4) 1060 (25.9)	(n=4) 1040 (36.0)	(n=6) 1160 (57.2)	(n=4) 1010 (51.8)	(n=3) 1020 (79.6)	(n=6) 991 (82.2)

ND not determined.
[a] Presented as median (range).

The AZD5658 t_{max} as well as $t_{1/2}$ were dose independent and similar in the fasted and fed states.

Based on the visual observation of the exposure data, and estimates of slope, the peak and total exposure of AZD5658 appears to be dose proportional in the 3 to 400 mg dose range [for C_{max} and $AUC_{(0-t)}$; 30 to 400 mg dose range for AUC] although the 90% confidence intervals are wide for the total exposure [AUC and $AUC_{(0-t)}$] and the 90% confidence interval for C_{max} was slightly above unity (1.07, 1.16).

Based on the statistical analysis of dose-normalized AZD5658 exposure parameters, the total exposure [AUC and $AUC_{(0-t)}$] of AZD5658 appears to be similar in the fed and the fasted states though the confidence intervals for AUC are wide. The peak exposure of AZD5658 is about 21% lower in the fed state as compared to the fasted state and total exposure was 15% higher.

Summary of pharmacodynamic results

In the fed state, the mean plasma glucose concentrations were lower than placebo at several time points, particularly for the 10 to 400 mg AZD5658 doses. The effect was most pronounced for the first 4 hours after dosing. In the fasted state, the plasma glucose concentrations were lower at most of the time points following administration of 30 or 200 mg AZD5658 when compared to placebo.

In the fed state, the insulin concentrations were higher than placebo for the 100 to 400 mg AZD5658 dose groups at several time points in the first 4 hours after dosing. There was no clear dose dependency in the insulin concentrations with AZD5658 doses.

There was a significant negative relationship between the AZD5658 dose and the glucose sAUC in the 0 to 4, 9 to 12, and 0 to 24 hour intervals. There was a significant positive relationship between insulin sAUC and AZD5658 dose for the 0 to 4 hour interval but not for the 9 to 12 and 0 to 24 hour intervals.

Summary of pharmacokinetic/pharmacodynamic relationships

A decrease in change-in-glucose sAUC was seen with increase in AZD5658 $AUC_{(0-t)}$ over the 0 to 4, 9 to 12, and 0 to 24 hour time periods. The decline appeared to be steeper for the 0 to 4 hour glucose sAUC. The response seem to level off at AZD5658 $AUC_{(0-t)}$ of about 8 μmol·h/L.

An increase in change-in-insulin sAUC was seen with increase in AZD5658 $AUC_{(0-t)}$ for the 0 to 4 and 0 to 24 hour time periods. However, the effect tended to level off at higher $AUC_{(0-t)}$ values (8 to 10 μmol·h/L). For insulin $sAUC_{(9-12)}$, no obvious trend was seen in the relationship with AZD5658 $AUC_{(0-t)}$.

Similar results were seen for the relationship between change in glucose or insulin sAUC and AZD5658 C_{max}.

Summary of safety results

There were no deaths, serious adverse events, discontinuations due to adverse events, or adverse events of severe intensity during the study. Overall, there were 13 (61.9%) AZD5658-treated patients with adverse events compared to 2 (28.6%) patients who received placebo. There were no trends noted with increasing dose in the number of adverse events overall or within any preferred term. The most frequently occurring adverse events were hypoglycemia and diarrhea, each occurring in 3 AZD5658-treated patients. One adverse event of ear pain (30 mg AZD5658 fed) was assessed by the Investigator as moderate in intensity; all other adverse events were of mild intensity. Five adverse events in AZD5658-treated patients were assessed by the Investigator as causally related to investigational product, including hypoglycemia in 3 patients (100 mg, 200 mg fasted, and 400 mg AZD5658), diarrhea in 1 patient (200 mg AZD5658 fasted), and headache in 1 patient (30 mg AZD5658). No adverse events in placebo-treated patients were assessed as causally related to investigational product. The 3 patients who experienced hypoglycemia adverse events were treated with intake of food or orange juice and the episodes resolved in less than 1 hour.

No clinically meaningful trends were noted in clinical laboratory parameters, vital signs, or electrocardiograms following each treatment or with increasing dose.