AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6714
Study Code	D1920C00001
Edition Number	1
Date	17 March 2010

A Randomised, Single-Blind, Placebo-Controlled, Single-Centre, Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Food Interaction after Single Ascending Oral Doses of AZD6714 in Healthy Male volunteers and Male Type II Diabetic Patients

Study dates: First healthy volunteer enrolled: 14 April 2009
Last healthy volunteer last visit: 29 September 2009
Date of early termination: 9 October 2009

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.

The dose escalation in Part A (Healthy Volunteers) was stopped due to a pre-defined stopping criterion, which was based on the expected pharmacological effect of GKA on glucose metabolism. The dose-escalation scheme in Part A (Healthy Volunteers) could not be explored to the extent necessary to establish relevant doses for use in Part B (Type 2 Diabetic Patients). Given the risk of limited information from Part B it was thus decided not to proceed.

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Study centre(s)

The study was conducted at 1 centre:

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 study safety and tolerability after single* oral doses of AZD6714 by assessment of adverse events (AEs) occurring during the study, blood pressure (BP), pulse, safety laboratory variables and electrocardiogram (ECG) and to estimate the maximum tolerated dose (MTD) * In Part B of the study the total daily dose could be divided in two doses depending on the pharmacokinetics (PK) of AZD6714.	Adverse events, Safety laboratory variables, Vital signs: BP, Pulse, ECG	Safety
Secondary	**Secondary**	
To characterise the PK of AZD6714 and assess the dose proportionality of the PK in healthy volunteers and T2DM patients following administration of single ascending doses (SADs) of AZD6714	AUC, AUC_{0-t}, AUC_{0-24}, C_{max}, t_{max}, $t_{1/2}$, CL/F AUC and C_{max} were evaluated for dose proportionality	PK
To evaluate PK of AZD6714 after single ascending oral doses in healthy volunteers and T2DM patients by calculation of area under the plasma-concentration curve (AUC), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), elimination half-life ($t_{1/2}$) and apparent oral clearance (CL/F)	AUC, AUC_{0-t}, AUC_{0-24}, C_{max}, t_{max}, $t_{1/2}$, CL/F	PK

Objectives	Outcome variables	Type
For subjects participating in Part A only: To evaluate the glucose lowering effect of AZD6714 and the effect on insulin secretion in healthy volunteers during euglycaemic clamp by assessment of glucose infusion rate (GIR), plasma (P-)glucose[a], serum (S-)insulin and S-C-peptide	GIR, P-glucose[a], S-C-peptide, S-insulin	PD (Part A only)
For subjects participating in Part A only: To evaluate the PK of AZD6714 under fed and fasted conditions by calculation of AUC, C_{max} and t_{max}	AUC, C_{max}, t_{max}	PK (Part A only)
For subjects participating in Part B only: To evaluate plasma glucose levels and insulin secretion in T2DM patients after administration of single oral doses of AZD6714 by assessment of P-glucose, S-insulin and S-C-peptide	P-glucose, S-C-peptide, S-insulin	PD (Part B only)
Exploratory[b]	**Exploratory[b]**	
To collect and store Deoxyribonucleic acid (DNA) for future exploratory research into genes that may influence drug response ie, distribution (PK profile), safety, tolerability and efficacy of AZD6714 treatment.	Pharmacogenetic biomarkers	PGx

PGx=Pharmacogenetics, PD=Pharmacodynamics, PK=Pharmacokinetics, T2DM=Type 2 Diabetes Mellitus

a P-glucose was measured in order to maintain euglycaemia, aiming at a P-glucose level of 5.6 mmol/L during the clamp.

b Results from any genetic research, if performed, will be reported separately from this report.

Study design

This was a first-time-in-man single ascending dose study designed as a single-blind, randomised, placebo-controlled, single-centre study to be conducted in male healthy volunteers (Part A) and Type 2 Diabetes Mellitus (T2DM) patients (Part B). The dose levels and the dosing frequency (once or twice daily) in Part B were to be based on the results from Part A.

Dose escalation in Part A of the study was stopped due to verified hypoglycaemia that was difficult to treat, ie, a predefined stopping criterion, which was based on the expected pharmacological effect of GKA on glucose metabolism. The dose-escalation scheme in Part A (healthy volunteers) could not be explored to the extent necessary to establish relevant doses for use in Part B (T2DM patients). Given the risk of limited information from Part B it was thus decided not to proceed.

Single oral doses of a suspension of AZD6714 or placebo were administered in 4 dose steps (1 mg, 5 mg, 15 mg and 30 mg) during euglycaemic clamp. Each healthy volunteer participated in 2 study sessions, either with AZD6714 (3 healthy volunteers in each cohort) or with placebo (1 healthy volunteer in each cohort), with the exception of the 30 mg dose group where the healthy volunteers participated in 1 study session. The 15 mg dose was administered in the same healthy volunteers during 2 study sessions, once with the investigational product (IP) given alone and once in combination with a standardised breakfast.

Target subject population and sample size

Twenty (20) evaluable male healthy volunteers, ≥20 and ≤40 years of age, were planned for the study. Since dose escalation was stopped, only 12 healthy volunteers were randomised, 3 to AZD6714 and 1 to placebo in each cohort. The sample size was primarily based on experience from previous similar studies with other compounds, and it was determined without formal statistical considerations or formal power calculation.

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

The details of the IP are given in Table S2.

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Formulation number	Batch number
AZD6714	Oral suspension 20 mg/mL	AstraZeneca R&D	D0900081	09-001233AZ
Placebo	Oral suspension	AstraZeneca R&D	D0900066	09-001039AZ

Duration of treatment

Single dose.

Statistical methods

The data were summarised using descriptive statistics. The influence of food was analysed with a mixed-effect analysis of variance (ANOVA) model using the logarithm of AUC (and C_{max}) as the response variable, food condition (fed or fasting) as an explanatory fixed factor, and subject as a random factor. Dose proportionality was analysed by fitting a mixed-effect model using the logarithm of AUC (and C_{max}) as the response variable, the logarithm of the dose as an exploratory continuous variable, and subject as a random factor.

Subject population

Forty-nine (49) male healthy volunteers were enrolled and 12 White male healthy volunteers, 21 to 36 years of age, were randomised, 9 to AZD6714 and 3 to placebo, at 1 study site. All of the 12 randomised healthy volunteers completed the study according to protocol.

The healthy volunteers in the AZD6714 group were younger and heavier compared to the placebo group. However, for the purpose of the study, the treatment groups were appropriately balanced with regards to demographic and baseline characteristics.

Summary of pharmacokinetic results

AZD6714 was generally rapidly absorbed as well as eliminated in all doses studied. The predefined maximum exposure limit for AUC (31 μmol*h/L) and C_{max} (3.7 μmol/L) was not reached, since the dose escalation was stopped due to another predefined stopping criterion. The mean peak plasma concentrations of AZD6714 occurred at 30 minutes, and the mean apparent elimination half-life ($t_{1/2}$) was 8.7 h. The mean oral plasma clearance (CL/F) was 5.85 L/h. Food seemed to have no effect on AUC, while C_{max} was decreased, and t_{max} was delayed with food. In fasted healthy volunteers, the exposure in terms of AUC and C_{max} seemed to increase in proportion to the increase in dose in the dose range studied (1 mg to 30 mg).

Summary of pharmacodynamic results

A plasma glucose lowering effect with AZD6714 was demonstrated indirectly. During euglycaemic clamp, a dose-dependent need of increased glucose infusion rate (GIR) to maintain the P-glucose level at 5.6 mmol/L was seen. An increase in secretion of S-insulin and S-C-peptide was seen with increased AZD6714 exposure. A mean increase in AUC for GIR, S-C-peptide and S-insulin levels was seen for AZD6714 15 mg when administered in combination with food compared to when given without food.

Summary of pharmacokinetic/pharmacodynamic relationships

An AZD6714 exposure dependent (AUC and C_{max}) increase in AUC for GIR, S-insulin and S-C-peptide was observed.

Summary of safety results

Dose escalation in Part A of the study was stopped, since 1 of the predefined stopping criteria for further dose escalation was met while exploring AZD6714 15 mg together with food - a hypoglycaemic episode which was classified as “difficult to treat”. Overall, there was no difference between AZD6714 treated and placebo treated healthy volunteers regarding frequency of AEs. Except for 2 hypoglycaemic events in the AZD6714 treatment group, the type of AEs in the 2 treatment groups was similar. One (1) healthy volunteer experienced an SAE, acute appendicitis, in the wash-out period after receiving AZD6714 15 mg. There were no deaths, discontinuations from the study due to AE, or any other significant adverse event (OAEs) during the study. The most common AE was headache. Most of the AEs were of mild/moderate intensity. Except for asymptomatic hyperglycaemia in 2 healthy volunteers, there were no clinically relevant treatment-related changes or trends in any laboratory

variables, blood pressure, pulse rate or ECG in healthy volunteers exposed to AZD6714. However, a trend to an increase in QTcF was observed at the higher doses (15 mg and 30 mg). Due to the low number of healthy volunteers in each treatment group, conclusions regarding possible QT effects cannot be drawn. There were no abnormalities in physical findings (except for a scar following surgery due to appendicitis) at follow-up compared to baseline.