AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00001
Edition Number	1
Date	8 January 2009

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 AZD1656 in Healthy Male Subjects

Study dates: First healthy volunteer enrolled: 3 July 2008
Last healthy volunteer completed: 25 September 2008

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 1 centre: AstraZeneca Clinical Pharmacology Unit, Philadelphia, USA.

Publications

None at the time of writing this report.

Objectives

The primary objective was to assess safety and tolerability after single oral doses of AZD1656 by assessment of adverse events (AEs) occurring during the study, blood pressure (BP), pulse, safety laboratory variables and electrocardiography (ECG).

The secondary objectives of the study were:

To evaluate pharmacokinetics of AZD1656 after single ascending oral doses in healthy subjects 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) in healthy subjects.

To evaluate the glucose lowering effect of AZD1656 and the effect on insulin secretion in healthy subjects during euglycaemic clamp by assessment of glucose infusion rate (GIR), P-glucose and S-insulin.

To evaluate the pharmacokinetics of AZD1656 under fed and fasted conditions by calculation of AUC, C_{max}, $t_{max,}$ CL/F and $t_{1/2}$.

Exploratory objective:

To collect and store Deoxyribonucleic acid (DNA) samples for potential future research into genes which may influence PK profile, drug disposition, efficacy, safety and tolerability of AZD1656.

Study design

This was a first-time-in-man study designed as a single-blind, randomised, placebo-controlled, single-centre study. Gradually increasing single oral doses of a suspension of AZD1656 or placebo were administered in 7 dose-steps (2 mg to 180 mg) during euglycaemic clamp. Each subject participated in 1 study session, either with AZD1656 (3 subjects in each group) or with placebo (1 subject in each group), with the exception of those in the 30 mg and 50 mg dose groups. These subjects participated on 2 study sessions, once with study drug given alone and once with study drug in combination with a standardized breakfast.

Target healthy volunteer population and sample size

Healthy male subjects aged between 20-45 years.

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

The details of the investigational products are given in Table 1.

Table 1 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Formulation number	Batch number
AZD1656	Oral suspension 25 mg/ml	AstraZeneca R&D Mölndal	H 2001-01-01	H 2001-01-01-01
AZD1656	Oral suspension 2 mg/ml	AstraZeneca R&D Mölndal	H 2000-01-01	H 2000-01-01-01
AZD1656	Oral suspension Placebo	AstraZeneca R&D Mölndal	H 2002-01-01	H 2002-01-01-01

Duration of treatment

Single dose.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

AUC, C_{max} and t_{max} of GIR and AUC of S-Insulin.

AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, AUC_{0-t} of AZD1656.

Criteria for evaluation - safety (main variables)

Adverse events occurring during the study, blood pressure, pulse, safety laboratory variables and electrocardiography.

Statistical methods

All variables are presented with descriptive statistics within treatment group (AZD1656 and placebo) and within dose. Dose-proportionality and the influence of food were analysed with mixed-effect analyses of variance models.

Subject population

28 healthy male volunteers were randomised and 28 were analysed. In each dose step, 4 subjects participated with 3 randomised to AZD1656 and 1 to placebo. 1 subject randomised to the food interaction part of the study was discontinued from participating in the study between the 2 study sessions due to positive urine drug screen. The AZD1656-treated and placebo-treated subjects were well balanced with regards to demographic characteristics.

Summary of pharmacokinetic results

AZD1656 was generally rapidly absorbed as well as eliminated in all dose groups, median t_{max} was 30 minutes and mean oral plasma clearance (CL/F) was approximately 12.3 L/h. The mean terminal $t_{1/2}$ was 2.87 hours. AZD1656 was metabolised to an active metabolite, AZ12555623, which peaked at the same time as AZD1656. The initial AZ12555623 decline was virtually parallel to the decline in AZD1656 but a slower terminal elimination phase was evident. The mean exposure to the metabolite was lower than the exposure to AZD1656.

Summary of pharmacodynamic results

A blood glucose lowering effect with AZD1656 was demonstrated indirectly. During euglycaemic clamp, a dose-dependent need of increased glucose infusion rate (GIR) to maintain blood glucose level at 5.6 mmol/L was seen. There was an indication also of a dose-dependent increase in S-insulin levels.

Summary of pharmacokinetic/pharmacodynamic relationships

An AZD1656 exposure dependent increase in both GIR_{AUC} and $S\text{-}Insulin_{AUC}$ was observed**.**

Summary of safety results

No safety and tolerability concerns were identified in this study up to the highest dose given (180 mg). The dose escalation was stopped at 180 mg due to the predefined stopping criteria: “glucose infusion is needed for more than 24 hours from dose intake in more than one subject”.