AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00003
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A Randomised, Single-Blind, Placebo-Controlled, Single-Centre, Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics After Single Ascending Oral Doses of AZD1656 in Japanese Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 05 August 2008
Last healthy volunteer completed: 07 December 2008

Phase of development: Clinical pharmacology (1)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

This study was conducted at a single center in the United States of America. The first healthy volunteer was enrolled on 05 August 2008. The last volunteer completed the study on 07 December 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to study safety and tolerability after single ascending oral doses of AZD1656 given to Japanese healthy male volunteers.

The secondary objectives of this study were:

- To evaluate pharmacokinetics of AZD1656 after single ascending oral doses given to Japanese healthy male volunteers
- To evaluate the glucose lowering effect of AZD1656 and the effect on insulin secretion in Japanese healthy male volunteers during euglycemic clamp

An exploratory objective of this study was:

- To collect and store DNA for future exploratory research into genes that may influence response ie, distribution, safety, tolerability and efficacy of AZD1656 treatment

Study design

In this randomised, single-blind, placebo-controlled, single-centre phase I study the safety, tolerability, PK and PD were assessed after single ascending oral doses of AZD1656/placebo in male Japanese healthy volunteers. In total, 36 evaluable Japanese healthy male volunteers participated in the study. There were 6 different groups (Cohorts 1 to 6; 6 healthy volunteers per cohort). In each cohort, 6 healthy volunteers were randomised to AZD1656 or placebo in a ratio of 5:1 (AZD1656: placebo).

Target healthy volunteer population and sample size

Healthy Japanese male volunteers from 20 to 40 years of age were selected for this study.

Thirty-six, male subjects were enrolled; 5 subjects received AZD1656 at each dose level and 1 subject received placebo. All 36 subjects completed the study and were evaluated for safety, PK and PD data.

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

Single oral doses of 6, 18, 30, 50 100, and 180 mg AZD1656 or placebo were administered.

Table S-1 Identity of investigational product

Investigational product	Dosage form and strength	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
Placebo	Oral suspension	AstraZeneca R&D Mölndal	H 2002-01-01	H 2002-01-01-01

Duration of treatment

Each healthy volunteer received a single dose of AZD1656 or matching placebo. The duration of the study for each subject was approximately 32 days including up to 21 days for screening, a 4 day confinement period and a follow-up visit at 7 to 10 days post dose.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Pharmacokinetics: Assessment of the area under the plasma concentration versus time curve (AUC and AUC_{0-t}), the observed maximum plasma concentration (C_{max}), plasma elimination half-life ($t_{½}$), oral plasma clearance (CL/F) and the time to reach C_{max} (t_{max})

Pharmacodynamics: Evaluation of the glucose lowering effect of AZD1656, the effect on insulin secretion and c-peptide concentration and measurement of glucose infusion rate (GIR) during euglycemic clamp

Genetics: Blood samples for DNA extraction were taken and DNA samples were saved for potential future research into genes which may influence pharmacokinetic profile, drug disposition, efficacy, safety and tolerability of AZD1656.

Criteria for evaluation - safety (main variables)

Safety was evaluated through assessment of adverse events (AEs), vital signs, electrocardiogram (ECGs), physical examination and laboratory variables (clinical chemistry, haematology, urinalysis).

Statistical methods

The study data were evaluated using descriptive statistics and analysis of variance (ANOVA).

Subject population

The first healthy volunteer entered the study on 05 August 2008 and the last healthy volunteer finished the study on 07 December 2008. Thirty-six Japanese male healthy volunteers were planned and randomised into the study at a single study site; each volunteer received 1 administration of IP during the planned treatment visit. All healthy volunteers randomised to treatment completed the study.

There were no protocol deviations that led to exclusion of data from the PK, PD or safety analyses. The PK, PD and safety analyses included all randomised healthy volunteers.

Overall, the treatment groups were well balanced with regards to demographic and baseline characteristics. All of the subjects enrolled were male of Asian race and Japanese ethnicity.

Summary of pharmacokinetic results

Concentrations of AZD1656 increased quickly following administration of all dose levels. C_{max}, AUC_{0-t} and AUC steadily increased with each increasing dose level. Geometric mean C_{max} increased from 0.51 µmol/L (6 mg) to 7.52 µmol/L (180 mg), across the dose levels. Geometric mean AUC_{0-t} and AUC parameter values were essentially the same within each dose level and ranged from 1.4 µmol*h/L (6 mg) to 43.3 µmol*h/L (180 mg) across the dose levels.

Median t_{max} was 20 min for the 6 and 50 mg dose levels, 30 min for the 18 and 30 mg dose levels, 1.0 h for the 180 mg dose level, and 1.5 h for the 100 mg dose level.

Geometric mean $t_{½}$ and CL/F were consistent across dose levels; range 2.4 h to 2.9 h for $t_{½}$ and 7.3 L/h to 11.4 L/h for CL/F.

The predefined maximum exposure limits for this study were AUC = 70.7 µmol*h/L and C_{max} = 43.3 µmol/L. One subject (Ecode 0001055) administered the 180 mg dose level had an AUC of 75.5 µmol*h/L; however, C_{max} for this subject was 12.3 µmol/L, which was well under the exposure limit.

After administration of AZD1656, concentrations of AZ12555623 appeared quickly for all dose levels. C_{max} and AUC_{0-t} steadily increased with each increasing dose level. Geometric mean C_{max} increased from 0.041 µmol/L (6 mg) to 0.870 µmol/L (180 mg), across the dose levels. Geometric mean AUC_{0-t} ranged from 0.205 µmol*h/L (6 mg) to 9.67 µmol*h/L (180 mg). Median t_{max} was 20 min for the 6 and 50 mg dose levels, 30 min for the 18 mg dose level, 40 min for the 30 mg dose level and 1.5 h for the 100 and 180 mg dose levels.

It was not possible to calculate AZ12555623 $t_{½}$ and AUC for all subjects due to the profile of the concentration-time curves; therefore, the results should be interpreted with caution.

AZD1656 systemic exposure (AUC and C_{max}) was assessed for dose proportionality. For the dose range of 6 to 180 mg, AZD1656 AUC increases appear dose proportional and C_{max} increases were slightly less than dose proportional. The relationships were well described by a

power model, predicting a 1.7 fold increase in C_{max} and a 2.0–fold increase in AUC, with a 2-fold increase in dose.

The assessment of dose proportionality for AZ12555623 showed that for the AZD1656 dose range of 6 to 180 mg, AUC_{0-t} increases appear dose proportional and C_{max} increases appear less than dose-proportional. The relationships predicted a 1.8 fold increase in C_{max} and a 2.2 fold increase in AUC_{0-t} with a 2-fold increase in AZD1656 dose. However, the data for AZ12555623 show considerable variability.

Summary of pharmacodynamic results

AZD1656 had a marked glucose lowering effect, which was shown indirectly by a dose-dependent need for an increase in GIR in order to maintain euglycemia. Plasma glucose was maintained at approximately 5.6 mmol/L during euglycemic clamp. There was a dose-dependent increase in GIR in order to maintain euglycemia.

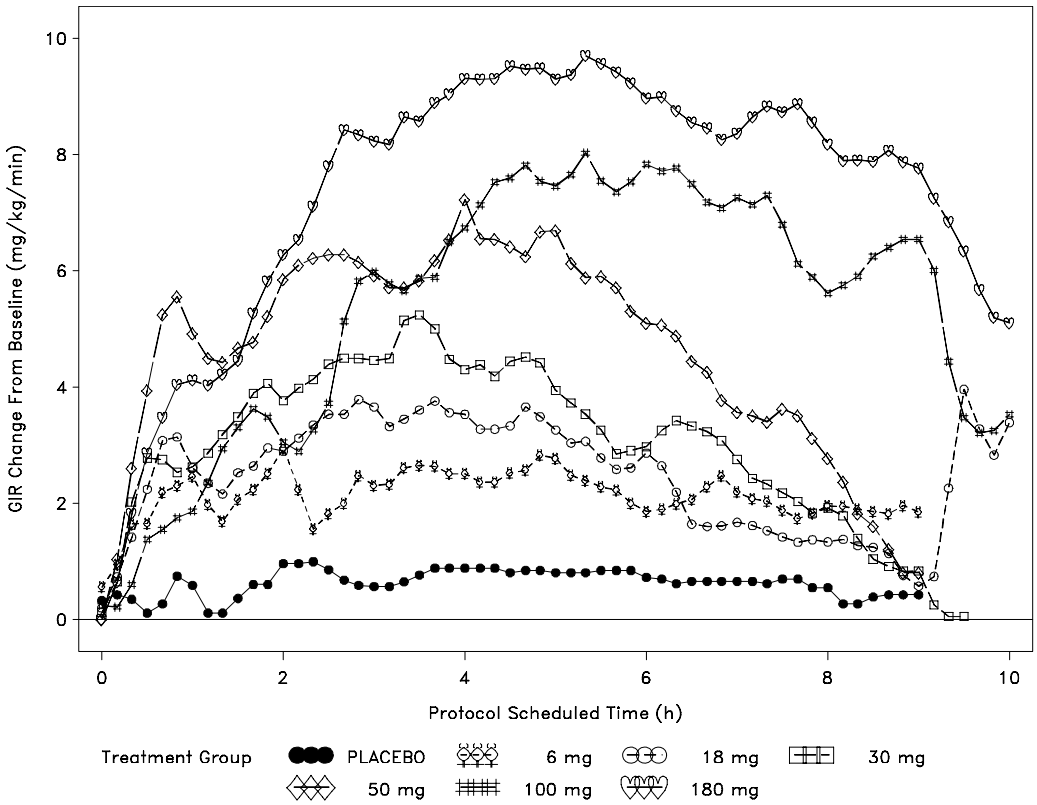
The mean GIR_{max} change from baseline data showed a dose-dependent increase with each escalating dose, ranging from 3.6 to 10.6 mg/kg/min over the 6 to 180 mg dose range. The placebo GIR_{max} change from baseline was 1.5 mg/kg/min.

The median $tGIR_{max}$ was variable across the 6 to 180 mg dose range. Median $tGIR_{max}$ increased over the 6 to 30 mg dose range (112 to 202 min) but varied at the 50, 100, and 180 mg doses (132, 324, and 272 min, respectively). The median $tGIR_{max}$ was 123 min in the placebo group.

The mean GIR AUC_{0-9} change from baseline showed a dose-dependent increase with each escalating dose, ranging from 1155 to 4034 mg/kg over the 6 to 180 mg dose range. The mean placebo GIR AUC_{0-9} change from baseline was 343 mg/kg.

Following escalating doses of AZD1656, both s-insulin and c-peptide concentrations increased over baseline. S-insulin and c-peptide increased from baseline beginning 2 h after dosing with the low AZD1656 doses (6, 18, 30, and 50 mg) and returned to near baseline by 8 h post-dose. A second increase in s-insulin and c-peptide was evident at 12 h post dose for the placebo, 6, 18, 30 and 50 mg treatment groups. An increase was seen for s-insulin and c-peptide from approximately 2 to 12 h post dose for the 100 and 180 mg dose levels. S-insulin and c-peptide returned to baseline levels by 24 h post dose for all treatment groups.

Figure S-1 Mean change from baseline GIR (mg/kg/min) versus time (9h) by treatment



Summary of pharmacokinetic/pharmacodynamic relationships

Visual inspection of the AZD1656 exposure (AUC and C_{max}) versus AZD1656 effect (GIR AUC_{0-9} and s-insulin AUC_{0-8}) figures showed a positive relationship between AZD1656 exposure and drug effect. Increased exposure results in an increased GIR_{0-9} and increased s-insulin.

There was a positive relationship between s-insulin and GIR. Increased s-insulin AUC_{0-8} change from baseline was associated with an increased GIR_{0-9} change from baseline.

Summary of safety results

No safety concerns were raised for the dose range studied (6 to 180 mg) during euglycemic clamp in this study. There were no SAEs, OAEs, study discontinuations due to AEs, or deaths in the study.

AZD1656 was well tolerated when given as single ascending oral administration up to a maximum dose of 180 mg in Japanese healthy subjects. There were 4 AEs of mild intensity reported in 4 subjects (vessel puncture site pain and headache in the placebo group, dizziness after AZD1656 30 mg, and back pain after AZD1656 50 mg). Only 2 AEs (headache in placebo group and dizziness in AZD1656 30 mg group) were considered by the Investigator to

have a reasonable possibility of a causal relationship with study treatment. Both events were mild and resolved without medical intervention.

There were no AEs reported for the lowest (6 and 18 mg) and highest (100 and 180 mg) dose levels.

There were no clinically significant clinical laboratory parameters, vital sign measurements, ECG measurements or physical exam findings following any dose of AZD1656 or placebo.