AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00002
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A Randomised, Single-Blind, Placebo-Controlled, Single-Centre, Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics after Multiple Ascending Oral Doses of AZD1656 in T2DM Subjects

Study dates: First healthy volunteer/patient enrolled: 18 August 2008
Last healthy volunteer/patient completed: 14 April 2009

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: Profil Institute for Clinical Research Inc. California USA.

Publications

None at the time of writing this report.

Objectives

The primary objective was:

To study safety and tolerability after oral repeated doses of AZD1656 in T2DM subjects by assessment of adverse events (AEs) occurring during the study, blood pressure (BP), pulse, safety laboratory variables and electrocardiography (ECG)

The secondary objectives were:

To evaluate pharmacokinetics (PK) of AZD1656 after repeated oral doses in T2DM subjects by calculation of area under the plasma-concentration versus time curve (AUC), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), elimination halflife ($t_{1/2}$), apparent oral clearance (CL/F), amount of drug excreted in urine (A_e) and renal clearance (CL_R)

To evaluate plasma glucose, S-insulin and C-peptide levels after administration of repeated oral doses of AZD1656 in T2DM subjects

Exploratory objectives:

To collect and store DNA for future exploratory research into genes that may influence response ie distribution, safety, tolerability and efficacy of AZD1656 treatment and/or susceptibility or prognosis of T2DM.

To evaluate effect on incretin plasma levels in terms of GLP1 and Gastric inhibitor peptide (GIP) levels after standardised meal.

Study design

This was a randomised, single-blind, placebo-controlled, multi-centre phase I study. The safety, tolerability, PKs and pharmacodynamics were assessed after repeated ascending oral doses of AZD1656/placebo in 52 T2DM subjects (naïve or treated with one or two oral antidiabetic drugs). The study consisted of 2 parts, A and B. Part A included 8 days randomised treatment with escalating doses (including a short titration procedure) in 4 groups of T2DM patients with 8 patients in each group and Part B included an evaluation of a short titration procedure and continued treatment for 25 days in 20 T2DM out-patients.

Target population and sample size

Male and females with T2DM (naive or treated with one or two oral anti-diabetic drugs).

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

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

Table S 1 Details of investigational product and other study treatments

Investigational product or test drug	Part	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD1656	A	Oral suspension 25 mg/ml	AstraZeneca R&D	H 2001-01-01	H 2001-01-01-02
AZD1656	A	Oral suspension 2 mg/ml	AstraZeneca R&D	H 2000-01-01	H 2000-01-01-02
AZD1656	A	Oral suspension Placebo	AstraZeneca R&D	H 2002-01-01	H 2002-01-01-01
AZD1656	B	Oral suspension 0.38 mg/ml[a]	AstraZeneca R&D	H 2071-01-02	H 2071-01-02-01
AZD1656	B	Oral suspension 0.19 mg/ml[a]	AstraZeneca R&D	H 2072-01-02	H 2072-01-02-01
AZD1656	B	Oral suspension 0.75 mg/ml[a]	AstraZeneca R&D	H 2073-01-02	H 2073-01-02-01
AZD1656	B	Oral suspension Placebo[a]	AstraZeneca R&D	H 2053-01-02	H 2053-01-03-01

a Plastic bottles of 45 ml containing 20 ml

Duration of treatment

Part A; on each dose step the starting dose was half the target dose (7 mg/2 bd, 20 mg/2 bd, 40 mg/2 bd and 80 mg/2 bd). The dose was then titrated up to the target dose and the target dose was then administered for 6 days, ie 7 days on target dose (if tolerated) in total. Those who did not tolerate the target dose remained on 1/2 target dose.

Part B; the dose was titrated during 3 days to a tolerable dose (15 mg bd or to a top dose of 45 mg bd) and subjects were thereafter treated with this dose for 24 days, ie 25 days on target dose in total. The subjects were hospitalised during dose titration days and during the first 2 days on maintenance dose, thereafter outpatient conditions followed (ie subjects left the clinic on day 6). During the outpatient part, the subjects returned two times per week for measurements. Subjects took the study drug at home on those study days when they were not visiting the clinic. The IP was administered twice daily.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (main variables)

- Pharmacokinetic variables:

AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, A_e and CL_R

- Pharmacodynamic variables:

Plasma (P)-glucose, S-C-peptide, S-insulin, GIP and GLP-1.

Criteria for evaluation - safety (main variables)

AE, BP, pulse, plasma glucose, laboratory variables and ECG.

Statistical methods

The study data was evaluated mainly using descriptive statistics and analysis of variance.

Subject population

The first subject entered the study on 18 August 2008 and the last subject finished the study on 14 April 2009. In total, 52 male and non-fertile female subjects were randomised into the study at 1 study site, whereof 24 and 15 subjects were exposed to AZD1656 during part A and part B. 1 subject (randomised to part B) discontinued the treatment at day 2 due to voluntary discontinuation. The treatment groups were well balanced with regards to demographic and baseline characteristics.

Summary of pharmacokinetic results

AZD1656 was generally rapidly absorbed in all dose groups. The formed metabolite, AZ12555623, had a slower terminal elimination rate compared to AZD1656. Pharmacokinetic steady state of AZD1656 and AZ12555623 was reached for all subjects. There was a linear relationship between AUC_{0-24} of AZD1656 versus dose in T2DM subjects receiving increasing doses of AZD1656. For the tested doses, there was no or a small accumulation of AZD1656 and approximately 50% accumulation of AZ12555623 at steady state, which is in agreement with the short half-life of AZD1656 and an effective half-life of AZ12555623 of 8-12 hours. Small amounts of AZD1656 and AZ12555623 were found in urine. These data indicate that renal function is not likely to influence the PK of AZD1656 and AZ12555623.

Summary of pharmacodynamic results

AZD1656 had a significant P-glucose lowering effect in T2DM subjects. The majority of the patients had ongoing oral anti diabetic treatment before entering the study. The treatment was withdrawn 1 week before dosing and consequently the plasma glucose levels were expected to increase during the study. This was demonstrated by the increase in glucose levels over time in the placebo subjects. The decrease in P-glucose was up to 24% lower compared to placebo after 8 days of treatment (part A) and 28% after 28 days of treatment (part B). There were no obvious trends or changes in S-insulin and S-C-peptide over time following administration of AZD1656.

Summary of safety results

This first study including subjects from the target population, subjects with T2DM, did not identify any tolerability or safety concerns during repeated dosing of GKA AZD1656 up to the highest dose of 80 mg bd. Overall, there was no apparent difference between AZD1656-treated and placebo-treated subjects regarding AEs. The most commonly reported AE during the study was headache.

There were no clinically relevant treatment-related changes or trends in any safety laboratory variable, vital signs or ECG observations. Individual changes in ECG were observed however these changes are not uncommon for a population with diabetes.