Clinical Study Report Synopsis

Drug Substance AZD4017

Study Code D2060M00001

Edition Number 1

A randomised, single-blind, placebo-controlled, single-centre, Phase I study in abdominally obese healthy volunteers to evaluate methods to assess 11-βHSD1 activity in adipose tissue and related downstream biomarkers after single and repeated oral doses of AZD4017 for 10 days

Study dates: First subject enrolled: 15 March 2010
Last subject last visit: 24 May 2010

Phase of development: Clinical pharmacology (I)

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

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 effect of single and repeated doses of AZD4017 and placebo on 11-βHSD1 activity in human adipose tissue in terms of cortisone to cortisol conversion assessed with *ex vivo* method in abdominally obese subjects	% ^{3}H cortisone to 3^{H} cortisol conversion/100 mg tissue	PD
Secondary	**Secondary**	
To investigate the safety and tolerability of repeated doses of AZD4017	Adverse events, ECG, BP, pulse, vital signs, laboratory variables (clinical chemistry, haematology, urinalysis)	Safety
Exploratory[a]	**Exploratory**[a]	
To investigate the effect of single and repeated doses of AZD4017 and placebo on 11-βHSD1 activity in human adipose tissue in terms of cortisone and cortisol levels assessed with mass spectrometry method	Cortisol and cortisone levels in adipocytes measured by MS (expressed in relation to K and as ratio between cortisol and cortisone) in fmol/100 mg adipose tissue	PD
To investigate the effect of single and repeated doses of AZD4017 and placebo on 11-βHSD1 activity in human adipose tissue in terms of expression of the glucocorticoid regulated genes in adipose tissue	mRNA levels of glucocorticoid regulated genes in adipose tissue	PD
To investigate the effect of single and repeated doses of AZD4017 and placebo on lipolysis by assessment of plasma and interstitial (measured by microdialysis) glycerol levels.	Plasma and interstitial glycerol levels	PD
To investigate the effect of single[b] and repeated doses of AZD4017 and placebo on plasma/serum levels of glucose, insulin, lipid variables and biomarkers of insulin sensitivity	Glucose, insulin, triglycerides (TG), cholesterol, LDL, HDL, glycerol, FFA, adiponectin, leptin and HOMA index	PD
To assess the relationship between AZD4017 plasma concentrations and PD variables	% conversion of 3H cortisone to 3H cortisol versus plasma concentrations of AZD4017	PD
To investigate the effect of single[b] and repeated doses of AZD4017 and placebo on body composition assessed by body weight, BMI, waist circumference and body fat (using bioimpedance)	Body weight, Waist circumference, Body fat mass	PD

[a] Not reported in the CSR.
[b] The variables were not measured after single dose apart from adiponectin.

Study design

This was a randomised, single-blind, placebo-controlled, single-centre, Phase I study performed in abdominally obese healthy volunteers to evaluate methods to assess 11-βHSD1 activity in adipose tissue and related downstream biomarkers after single and repeated oral once daily (od) 1200 mg doses of AZD4017 for 10 days.

The study consisted of 13 visits to the clinic. Following a 30-day screening period (starting with Visit 1), a baseline visit (Visit 2) was performed, which was to take place 3 days before the start of the 10-days repeated dosing period (Visits 3 to12). The repeated dosing period was followed by a post study follow up visit that was to take place 10 to14 days after the last dose.

Target subject population and sample size

Healthy volunteers participating in the study were males aged 18 to 65 years, who had a body mass index (BMI) between 27 and 35 kg/m^2 and a waist circumference of >102 cm. They were to be suitable for abdominal adipose tissue biopsy and have suitable veins for cannulation or repeated vein puncture.

Due to the exploratory nature of the study the sample size was not based on formal statistical considerations. The sample size was based on experience from previous similar Phase I studies with other compounds. The study was planned to include 16 healthy volunteers aged 18 to 65 years, who were to receive either AZD4017 or placebo, randomised 10:6. A total of 15 healthy volunteers aged 24 to 65 years were randomised and completed the study. They received either AZD4017 or placebo, randomised 9:6.

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

The following investigational products (IP) were administered:

- AZD4017, 20 mg/mL oral suspension, formulation numbers: P7823, P7821, batch numbers: 09-000882AZ, 09-000884AZ

- Placebo, 0 mg/mL oral suspension, formulation number: P7817, batch number: 09-000878AZ

Duration of treatment

Each healthy volunteer received repeated oral doses of 1200 mg AZD4017 or placebo once daily for 10 days. Each dose was administered with 250 mL of water and was given at the clinic after an overnight fast of at least 10 h.

Statistical methods

Given the exploratory nature of this study, no formal statistical hypothesis testing was performed. Data were summarised using descriptive statistics. P-values were calculated for the

primary variable but these should be regarded as descriptive measures and not as the result of statistical tests.

Subject population

Thirty healthy volunteers were enrolled into the study, by 1 center, whereof 15 were randomised to treatment. Nine of the randomised healthy volunteers received 1200 mg AZD4017 and 6 received placebo. All subjects completed the study. The first subject entered the study on the 15 March 2010 and the last subject completed on the 24 May 2010. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of pharmacodynamic results

Mean conversion in % of ^{3}H cortisone to ^{3}H cortisol/100 mg adipose tissue were measured after 1, 4 and 9 days of repeated dosing of AZD4017 or placebo.

There was a decrease from baseline in conversion of cortisone to cortisol after 1 and 4 days. The data does not suggest a sustained effect, as the conversion at day 9 was similar to the conversion at baseline. However, *ex vivo* analyses suggest the possibility to obtain an inhibition also after repeated dosing at high AZD4017 concentrations.

Summary of safety results

There were no serious adverse events, discontinuation of IP due to adverse events (DAEs) or other significant adverse events (OAEs) reported during the study. All AEs were of mild intensity and the most common AEs in the study were haematoma after biopsy and headache. The frequency of reported AEs were similar in the treatment groups.

One healthy volunteer on 1200 mg AZD4017 had a TSH value that was >3 x ULN but returned towards normal at follow-up. One healthy volunteer on 1200 mg AZD4017 had ALT and AST ≈ 1.5 x ULN, returning to normal at follow-up. No other consistent effects by AZD4017 were observed for other safety laboratory parameters or vital signs.

An activation of the HPA-axis was demonstrated by an increase in ACTH and a tendency towards an increase in DHEA-s levels after treatment with AZD4017. However, s-cortisol and testosterone levels were not consistently changed.