AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2207
Study Code	D3180C00002
Edition Number	1
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A Phase I, randomized, single-blind, placebo-controlled, single-centre study in healthy male subjects and obese subjects to assess the safety, tolerability, pharmacokinetics and pharmacodynamics after repeated oral doses of AZD2207

Study dates:

First healthy volunteer/patient enrolled: 23 July 2007
Last healthy volunteer/patient completed: 20 December 2007
End of study (defined as database lock): 04 February 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)

AstraZeneca Clinical Pharmacology Unit (CPU) Lund, Sweden

Publications

None at the time of writing this report.

Objectives

Primary objective

The primary objective of the study was to study the safety and tolerability after repeated oral doses of AZD2207 by assessment of adverse events (AE), blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory variables

Secondary objectives

The secondary objectives of the study were:

1. To study the pharmacokinetics of AZD2207 after multiple oral doses of AZD2207

2. To study the effect on PD variables such as glucose, insulin, HOMA index, high molecule weight (HMW) adiponectin, lipid variables (ApoA1, ApoB, ApoB/ApoA1 ratio, FFA, HDL-C, non-HDL-C, LDL-C, TG, tot Cholesterol), inflammatory variables (IL-6, TNF_{α}, hs-CRP), ghrelin (active and total), GLP-1 and leptin after multiple oral doses of AZD2207

3. To study the change in weight and waist circumference after multiple oral doses of AZD2207

4. To study the effect on eating behaviour after repeated doses of AZD2207

5. To collect and store DNA samples for potential future research into genes which may influence PK profile, drug disposition, efficacy, safety and tolerability of AZD2207

Study design

This multiple ascending dose, randomized, single-blind, placebo-controlled and single-centre phase I study evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics after repeated oral administration of AZD2207 in healthy male subjects and obese subjects. The study was a dose escalation study where subjects were given repeated doses of AZD2207 or placebo during 10 days. The starting dose of AZD2207 was 2 mg and the maximum dose 300 mg. Before the start of repeated dosing, single dose pharmacokinetics were evaluated for 5 days.

Target healthy volunteer population and sample size

The study was to be conducted in healthy male volunteers aged between 20 and 40 years. The inclusion and exclusion criteria were defined such that healthy volunteers who are known to be free from any significant illness was to be selected. The study was restricted to male

healthy volunteers, since reproduction toxicology data in animals were not yet available. The planned number of healthy male volunteers randomized in this study was 56 (40 of normal weight and 16 obese), 8 in each cohort (6 on AZD2207 and 2 on placebo), which was considered sufficient to evaluate tolerability and safety.

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

Oral capsules of AZD2207 0.5 mg, AZD2207 5 mg, AZD2207 50 mg and corresponding oral capsules of placebo were used in this study. Individual batch numbers are included in the CSR.

Duration of treatment

Single dose pharmacokinetics of AZD2207 was evaluated in each subject for 5 days before the following 10 days of repeated dosing started.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

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

Criteria for evaluation - safety (main variables)

AEs, BP, pulse, ECG and laboratory variables

Statistical methods

The full analysis set included all subjects who received study treatment and had data collected post-dose. All subjects with available data were included in the PK and PD analyses. Descriptive statistics are provided for all safety variables. All PK and PD variables are presented using appropriate descriptive statistics within the dose of AZD2207 and study day. Geometric means together with confidence intervals were calculated for AUC, C_{max} and $t_{1/2}$. Potential time dependency was investigated by comparison of AUC and AUC_{τ}. The accumulation of AZD2207 after repeated dosing, dose proportionality and change (from baseline to end of treatment) in PD variables during study were analysed with mixed-effect analysis of variance (ANOVA) models. The potential relationships between PK and PD variables were investigated graphically. A population specific correction of QT interval was done and a mixed-effect ANOVA model was used for analysis.

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.

Subject population

This study included both healthy normal weight and obese subjects. In total, 56 White male subjects were randomized into the study at 1 study site. Fifty-two (52) subjects randomized to treatment completed the study. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of efficacy results

A weight reduction of 2% (AZD2207 100 mg) and a waist circumference reduction of 3 to 5% (AZD2207 100 and 10mg) compared to placebo were seen in obese subjects. No conclusions regarding eating behaviour after 10 days repeated once daily doses of AZD2207 can be made based on subject reports of hunger satiety on Visual Analogue Scale (VAS), but there appears to be a tendency to increased satiety in obese subjects on AZD2207 100 mg.

Summary of pharmacokinetic results

Pharmacokinetics has been evaluated following single and multiple oral doses of AZD2207 capsules in fasting subjects involving a total of 42 healthy male subjects (30 normal weight and 12 obese) on active treatment. AZD2207 was rapidly absorbed in all dose groups. The median t_{max} was 2 h day 1 and 1.5 h day 15. In general, there was little difference in the concentration-time curves between normal weight and obese subjects. However, obese subjects had approximately 2 times as long terminal half-life in comparison to normal weight subjects. Following once daily administration of AZD2207, steady state was reached for all doses at the last full PK profile (study day 15) after 10 days repeated dosing. The ratio AUC_{τ}/AUC was >1 for all doses, except for the obese subjects given the 100 mg dose. However, the ratio was only statistically significantly different from 1 for the 10 mg group. Thus, there was a tendency to non-linear increase in exposure with time. Dose proportionality of AUC and C_{max} was evaluated by fitting a power model to the data. According to the applied power model there was a less than dose proportional increase in AUC and C_{max}. However, the exposure appears approximately proportional to dose for the lower doses.

Summary of pharmacodynamic results

No clinically relevant PD effects on lipid biomarkers or inflammation biomarkers were seen. An increase of >10% from baseline and of approximately 40% compared to placebo was seen for both S-Insulin and HOMA index in obese subjects (AZD2207 10 and 100 mg).

Summary of pharmacokinetic/pharmacodynamic relationships

No formal statistical comparison was made for PD markers or efficacy vs. dose or exposure. However, a tendency to a dose response was seen when the change in body weight vs. dose was plotted for explorative purposes.

Summary of pharmacogenetic results

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

Summary of safety results

No safety or tolerability concerns were identified in this study after single and 10 days repeated doses of AZD2207 up to 300 mg in healthy normal weight subjects, and up to 100 mg in obese subjects. Overall, there was no apparent difference between AZD2207 treated and placebo treated subjects regarding adverse events (AEs), except for Gastrointestinal Disorders, including Nausea, Diarrhoea and Flatulence, that were reported

more frequently in AZD2207 dose groups than in placebo groups. The single most commonly collected AE was headache. Other commonly reported AEs were Nausea, Diarrhoea, Flatulence and Nasopharyngitis (by descending order during active treatment). There were no clinically relevant treatment-related changes or trends in any laboratory variable or vital sign measured during the study in subjects exposed to AZD2207. An increase in variables related to liver function was seen in the second dose panel but was not repeated in panels with higher doses, and is thus considered a finding at random. All digital ECGs were evaluated as within physiologic range for the studied population. No clinically relevant trends over time or between dose groups were observed. No clinically significant individual interval data were observed, nor judged as any clinically relevant substance effect.