AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1175
Study Code	D1740C00001
Edition Number	1
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A Single-Blind, Randomized, Placebo Controlled Phase I Study to Investigate the Effect of Single Oral Doses of AZD1175 With and Without Food on Safety, Tolerability and Pharmacokinetics

Study dates: First healthy volunteer enrolled: 01 August 2006
Last healthy volunteer completed: 29 January 2007

Phase of development: Clinical Pharmacology (1)

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

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Study centre(s)

AstraZeneca Clinical Pharmacology Unit (CPU), Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden

Publications

None at the time of writing this report.

Objectives

The primary objective of the study is to investigate the safety and tolerability of single oral doses of AZD1175 by assessment of adverse events (AEs), blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory variables.

Secondary objectives

1. to investigate the pharmacokinetics of AZD1175 after administration of single oral doses of AZD1175 by assessment of AUC, C_{max}, $t_{1/2}$, CL/F, t_{max}

2. to investigate the effect of food on AUC, C_{max}, $t_{1/2}$, CL/F, t_{max} after administration of single oral doses of AZD1175

3. to collect DNA samples from healthy volunteers who consent to participate in optional genetics research

Study design

This was a single-blind, randomized, placebo controlled phase I study conducted at 1 centre. The study included an 8-step dose-escalation part, in which 2 of the doses also were studied together with food. However, dose-escalation was stopped after the seventh dose, since a stopping criterion regarding AUC (>13 µmol*h/L) was met. In addition, the study included a crossover part where ECG was investigated after the highest tolerated dose of AZD1175 (18 mg) and placebo.

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 52, 8 on each dose (6 on AZD1175 and 2 on placebo) in the dose-escalation part and 12 in the ECG crossover part, which was considered sufficient to evaluate tolerability and safety.

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

Oral suspension 5 mg/mL batch number: H 1853-01-01-01, Oral placebo suspension for AZD1175 batch number: H 1854-01-01-01, Oral placebo solution for AZD1175 batch

number: H 1855-01-01-01. The same solution as the placebo solution was used as dilution media.

Duration of treatment

Each subject received 2 single doses of AZD1175 or placebo with a washout period of at least 3 weeks.

Criteria for evaluation - 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 healthy volunteers who received study treatment and had data collected post-dose. Descriptive statistics are provided for all safety variables, and the analyses were performed according to actual exposure, regardless of randomization. No formal comparison was performed. Geometric means together with confidence intervals were calculated for AUC, C_{max} and $t_{1/2}$. The influence of food on AZD1175 single-dose pharmacokinetics and dose proportionality were analysed with mixed-effect analysis of variance (ANOVA) models. A population specific correction of QT interval was done and a mixed-effect ANOVA model was used for analysis.

Subject population

In total, 52 male healthy volunteers (51 Caucasians and 1 Black) were randomized into the study, 8 on each dose (6 on AZD1175 and 2 on placebo) in the dose-escalation part and 12 in the ECG crossover part. Forty-eight (48) healthy volunteers randomized to treatment completed the study. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of pharmacokinetic results

AZD1175 was generally rapidly absorbed in all dose groups (median t_{max} = 1 hour). The mean terminal $t_{1/2}$ was 62 hours. There was a less than dose proportional increase in AUC and C_{max}. However, at the lower doses the increase in exposure was approximately dose proportional. The plasma concentration time profile, following administration of AZD1175 oral suspension (1 and 8 mg) after standardized high fat, high calorie breakfast, was characterised by a later (median t_{max} = 3.5 hours) compared to when given during fasting conditions. Exposure was not substantially affected when given together with food, but there was a 24% increase of AUC at the higher dose level (8 mg) and a 33% decrease of C_{max} at the lower dose (1 mg).

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 doses up to 18 mg of AZD1175. Overall, there was no apparent difference between AZD1175 treated and placebo treated subjects regarding adverse events (AEs). The most commonly collected AEs were nasopharyngitis and headache. There were no clinically relevant treatment-related changes or trends in any laboratory variable or vital sign measured during the study in healthy volunteers exposed to AZD1175. 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.