AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6482
Study Code	D1700C00001
Edition Number	1
Date	18 September 2008

A randomized, double-blind, placebo-controlled Phase I study to assess the tolerability, safety, pharmacokinetic and pharmacodynamic properties of AZD6482 alone and co-administered with ASA, after single dose, ascending intravenous doses to healthy male subjects.

Study dates: First healthy volunteer enrolled: 8 January 2008
Last healthy volunteer completed: 1 April 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)

The study was conducted in Sweden.

Study dates: First healthy volunteer enrolled: 8 January 2008 and last healthy volunteer completed: 1 April 2008

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was:

To assess the tolerability and safety of AZD6482 following escalating single intravenous dosing in healthy subjects by assessment of adverse events, physical examination, vital signs, electrocardiographic (ECG) parameters, and laboratory variables.

The secondary objectives of the study were:

- To evaluate the pharmacokinetic properties of AZD6482 following escalating single intravenous doses of AZD6482 to healthy subjects by assessment of total area under the plasma concentration vs. time curve (AUC), area under the plasma concentration vs. time curve from zero to time t, (AUC0-t), maximum plasma concentration (Cmax), elimination half-life (t1/2), volume of distribution at steady state (Vss), total body clearance of drug from plasma (CL), cumulative amount of unchanged drug excreted into urine (Ae), and renal clearance of drug from plasma (CLR)

- To characterise the dose-response of AZD6482 on platelet function following escalating single intravenous doses to healthy subjects by using the following methods; optical aggregometry (ADP-induced), Impact-R© (shear-induced) and Multiplate© (ADP and CD9 antibody-induced)

- To characterise the effect of AZD6482 on bleeding time by using the Surgicutt technique

- To characterise the effect of AZD6482 on insulin and glucose homeostasis as assessed by the HOMA index.

- Potentially to study the effect of co-administration of AZD6482 and ASA on: tolerability and safety, platelet function and bleeding time.

Study design

AZD6482 is an anti-thrombotic agent, acting as an inhibitor of the enzymatic activity of recombinant human PI3Kβ, and thereby has the potential to inhibit human platelet function *in*

vivo. In total 49 subjects were randomized to Part A (comprising 8 dose-escalation steps) and Part B (co-administration of AZD6482 with ASA). In Part A subjects were divided into 4 groups of 9 subjects each (in each group, 6 subjects received a 3-hour infusion of AZD6482 and 3 subjects received placebo.

Target healthy volunteer population and sample size

Healthy male subjects between 18 and 45 years, with body mass index between 19.0 to 30.0 kg/m2 and body weight between 50.0 to 100.0 kg were enrolled in the study. In total, 78 Caucasian male healthy subjects were enrolled in the study, 49 were randomised to treatment and included in safety set and 48 in a per protocol analysis set.

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

Part A comprised 8 dose-escalation steps of AZD6482: 0.9 mg, 4.5 mg, 13.5 mg, 40.5 mg, 121.5 mg, 364.5 mg, 455.8 and 364.5 mg. Following batch numbers of AZD6482 were used in the study: H 1992-01-01-01, H 1993-01-01-01 and H 1994-01-01-01. Investigational product was administered as an intravenous infusion over 3 hours. In part B, 121.5 mg of AZD6482 was chosen and administered with 650 mg ASA (batch number: H 1917-01-01-01).

Duration of treatment

Each subject group participated in two dose steps, ie, each subject received two single doses of AZD6482 or placebo. In each group, 6 subjects received a 3-hour infusion of AZD6482 on both occasions and 3 subjects received a 3-hour infusion of placebo on both occasions. The washout period between doses for each subject in Part A was at least 5 half-lives for AZD6482.

Criteria for evaluation - efficacy and pharmacokinetics

See Objectives.

Statistical methods

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. The safety analysis set included all healthy volunteers who received study treatment and had data collected post-dose.

The data are summarized using descriptive statistics: number of values, mean values, standard deviation, minimum, median and maximum values both for the actual values and for change from baseline (where applicable). For laboratory variables also the number of values above ULN and below LLN are presented.

Plasma concentration values below Lower Limit Of Quantification (LLOQ) are set to LLOQ/2, values measured before first dose that are below LLOQ are set to zero. All confidence intervals presented are 95% and two-sided. Log-transformation was used when

constructing confidence intervals for AUC, Cmax, inhibition of platelet aggregation (IPA) and prolongation of capillary bleeding time (CBT). Dose proportionality was analysed by using the power model approach. Adverse events starting the day after any administration of study drug were reported as having onset during the treatment period.

Subject population

In total 49 subjects were randomized to study Part A and B. This included 14 subjects randomized to placebo treatment group and 26 to AZD6482 group, in Part A. Additional 9 subjects were randomized to treatment with AZD6482 + ASA in study Part B. One subject was discontinued from study treatment due to AE and 2 subjects discontinued the study due to AE. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of safety results (primary objective)

AZD6482 demonstrated an acceptable safety and tolerability profile after single ascending doses of 0.9 to 455.8 mg of AZD6482 in healthy male volunteers. Generally, adverse events were infrequent, the majority was of mild intensity and all AEs were reversible. No clinically significant changes in the blood pressure, pulse rate, laboratory parameters or ECG, which might be attributed to the exposure to study drug, were found. Tolerability and safety of AZD6482 was not influenced by co-administration with ASA.

Summary of pharmacodynamic results

There was a clear significant and increasing relationship between dose as well as plasma concentration of AZD6482 and the level of platelet inhibition. The effect was rapidly reversible as it declined in parallel with the exposure of AZD6482 after end of infusion.

Bleeding time was significantly prolonged versus predose only in the two highest doses of AZD6482. However there was a significant and increasing relationship between plasma concentration of AZD6482 and the level of bleeding time prolongation. Bleeding time was prolonged 2.5 fold with ASA versus predose and the combination of AZD6482 and ASA further prolonged bleeding ≥2.1 fold versus ASA alone. The dose of AZD6482 which was given in the combination (121.5 mg) showed no prolongation of bleeding time when given alone.

A small but statistically significant dose-dependent increase in HoMa-index was observed but no single dose showed a significant increase versus placebo. The effect seen was rapidly reversible as it was normalised after end of infusion.

Summary of pharmacokinetic results

The $AUC_{0-\infty}$ (area under plasma concentration-time curve from zero to time t) and the plateau plasma concentration at the end of infusion (3 hour sample) (C_{ss}) increased in a dose proportional manner. The starting dose (0.9 mg) resulted in a mean C_{ss} of 0.012 µmol/L and the highest dose (455.8 mg) resulted in a mean C_{ss} of 5.7 µmol/L.

The clearance of AZD6482 was high, approximately 70 L/h and the mean effective half-life was short, approximately 20 minutes. AZD6482 was most likely immediately converted to its acyl glucuronide conjugate and eliminated via the urine. The kidney does not seem to be important in the elimination of the mother compound (AZD6482) since CL_R contributed to less than 1% of the total clearance of the study drug.

The shape of the log plasma concentration versus time profile was tri-phasic. An initial rapid decline (a minor amount of AZD6482 eliminated during this phase) was followed by the effective elimination rate of importance for the time to plateau and elimination of AZD6482 from the body. Last, a slow elimination at low concentrations, again with minor amount of AZD6482 eliminated.