AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6482
Study Code	D1700C00004
Edition Number	1.0
Date	29 October 2009

A Randomised, Open-label, Single-Centre, Phase I, Crossover Study to Evaluate the Effect of AZD6482, Compared with Clopidogrel, on Bleeding Time in Healthy Volunteers Receiving Low-Dose ASA

Study dates: First healthy volunteer enrolled: 24 February 2009
Last healthy volunteer completed: 15 July 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

The study was conducted at a single centre, the Clinical Pharmacology Unit in Lund, Sweden.

Publications

None at the time of writing this report.

Objectives

Primary Objective: The primary objective of the study is to evaluate the effect of AZD6482 and clopidogrel on bleeding time when taken together with low-dose ASA.

Secondary Objectives:

1. To evaluate the effect of low-dose ASA on bleeding time.

2. To evaluate the effect of AZD6482, clopidogrel and low-dose ASA on platelet function markers by using the following methods: optical aggregometry (ADP-induced*), Impact-R© (shear-induced), Multiplate© (AA, ADP and CD9 antibody-induced*) and Verify*Now*© $P2Y_{12}$.

3. To evaluate the plasma levels of AZD6482 after a single dose, by assessment of C_{ss}.

4. To evaluate the safety and tolerability of AZD6482 when taken with low-dose ASA.

Explorative Objective: To potentially collect blood samples for exploratory in vitro research of platelet function, eg, thrombogenecity by use of perfusion chamber and VASP (Vasodilator Stimulated Phosphoprotein) assay.

The results of the explorative analysis are not presented in the study report.

Study design

The study was conducted as a single-centre, open-label, randomised, phase I, crossover study. The study consisted of two treatment periods, A and B. In each treatment period the subjects received ASA 75 mg once daily on top of which either AZD6482 or clopidogrel was administered.

Target healthy volunteer population and sample size

The study was done in healthy subjects to aid compliance with complex study procedures and to avoid interference with the results from disease processes and other drugs. The inclusion and exclusion criteria are defined such that subjects who are known to be free from any illness

* Additional agonists may be explored

Additional agonists may be explored

were selected. To minimize the influence of other medications, the use of allowed concomitant medications was restricted. Since data on reproductive and developmental toxicity is not available for AZD6482, only male subjects participated in the study.

Assuming that the standard deviation for the variable associated with the primary objective, δ_W, is of the same magnitude as observed in a previous study (D5130C05261) comparing AZD6140 with clopidogrel on top of low-dose ASA. A study with 24 completing subjects will then be able to, with 80% statistical power, detect a 75% difference (ie, a mean ratio of 1.75) between treatments on a 5% significance level, using a Student's t-test. To ensure 24 completing subjects 29 subjects were randomised.

Investigational product and comparators: dosage, mode of administration and batch numbers´

For details of investigational product and comparators see Table S 1.

Table S 1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number
AZD6482	Conc. solution, 3.0 mg/mL, one dose 0.68 mg/min for max 5 hours (max dose 204 mg), intravenous infusion	AstraZeneca R&D Mölndal, Sweden	H 1993-01-01-02
Acetylsalicylic acid (Trombyl®)	Tablets, 75 mg, 75 mg od for 2 x 7 days, orally	Pfizer	H 1063-05-01-02
Clopidogrel (Plavix®)	Tablets, 75 mg, one loading dose 300 mg followed by 75 mg od for 6 days, orally	Bristol-Meyers Squibb	H 1487-04-01-01

Duration of treatment

Treatment A: The subjects received 75 mg ASA orally od for 6 days followed by 75 mg ASA and AZD6482, given as an intravenous infusion (0.68 mg/min, aiming at a predicted steady state concentration of 1μM) for a maximum of 5 hours (maximum dose 204 mg), on day 7.

Treatment B: The subjects received 75 mg ASA orally od for 7 days together with oral doses of clopidogrel, given as a 300 mg loading dose on day 1 (four 75 mg tablets) followed by 75 mg od for 6 days.

The 2 treatment periods were separated by a washout period of at least 21 days.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary pharmacodynamic variable: Capillary bleeding time (CBT).

Secondary pharmacodynamic variable: Inhibition of platelet aggregation (IPA)

Secondary pharmacology variable: Steady state drug concentration in plasma during constant rate infusion (C_{ss}).

Criteria for evaluation - safety (main variables)

Secondary safety variables: Adverse events (AEs), safety laboratory variables, electrocardiogram (ECG), and vital signs.

Statistical methods

Results are presented by treatment. For treatment A results are presented for Day 6 (ASA) and for Day 7 (ASA + AZD6482). For treatment B results are presented for Day 7 (ASA + clopidogrel).

Pharmacodynamics: The primary objective, to evaluate the effect of AZD6482 and clopidogrel on bleeding time when taken together with low-dose ASA, was addressed in a random effects Analysis of Variance (ANOVA) model with treatment (ASA + AZD6482 or ASA + clopidogrel) and study period as fixed effects and subject as random effect. Results are presented as geometric mean change from baseline within treatment with 95% confidence intervals and geometric mean change ratio between treatments with 95% confidence intervals (CIs).

One of the secondary objectives, to evaluate the effect of ASA on bleeding time was addressed by estimating the geometric mean change from baseline with 95% CI using Student's t-distribution.

Interaction with ASA with respect to change from baseline in CBT was assessed using a 95% confidence interval from a paired samples t-test, relating ASA + AZD6482 to ASA alone.

In the event of a truncated CBT sample at 3 hours and 45 minutes in a subject on AZD6482 and low-dose ASA, 3 hours and 45 minutes was used as the truncation time for all CBT samples, regardless of treatment, where the actual CBT is longer than 3 hours and 45 minutes. This is done to avoid sampling bias in the statistical analysis caused by the study design where different sampling times for CBT was decided for the two treatments.

Effect on IPA between treatments was assessed using a one-way ANOVA model controlling for treatment (ASA, ASA+AZD6482 or ASA + Clopidogrel) as fixed effect. Results are presented as mean within treatment with 95% confidence intervals and mean difference between treatments with 95% confidence intervals.

Pharmacokinetics and Safety: PK and safety variables are presented descriptively.

Adverse events starting after administration of study drug until 23:59 the day after the last administration of study drug are reported as having onset during the treatment period.

Subject population

Healthy male volunteers fulfilling the exclusion and inclusion criteria were recruited and were considered to be representative of the intended study population. 29 healthy volunteers were randomised in order to have at least 24 evaluable subjects completing the study. 27 healthy volunteers completed the study.

29 healthy volunteers received at least one dose of investigational product and was included in the Safety population. Two healthy volunteers were excluded from the Per Protocol analysis set because of study discontinuation and one healthy volunteer was excluded due to important protocol deviation (use of ibuprofen (Ibumetin ®) during treatment A) since it may potentially affect the PD measurements. 26 healthy volunteers were thus included in the Per Protocol analysis set.

Summary of pharmacokinetic results

Mean plasma concentration of AZD6482 versus time since start of infusion of AZD6482 is presented in Table S 2. A mean steady state AZD6482 concentration in plasma in the desired concentration range was obtained. The plasma concentration of AZD6482 was considered to be at steady state at the time for CBT measurement.

Table S 2 Descriptive presentation of plasma concentration (µmol/L) of AZD6482 by protocol time. Per Protocol population

Protocol time [a]	n	# <LOQ	Mean	SD	Min	Median	Max
-00:05	0	26					
01:10	26	0	1.202	0.22	0.731	1.14	1.82
At end of infusion [b]	26	0	1.384	0.23	1.05	1.325	1.96
30 min after end of infusion	26	0	0.245	0.07	0.138	0.235	0.437
3 hours after end of infusion	26	0	0.027	0.02	0.007	0.021	0.066
6 hours after end of infusion	25	0	0.012	0	0.005	0.012	0.023

a In relation to start of infusion of AZD6482
b The infusion time varied between subjects
D1700C00004_Cp

Summary of pharmacodynamic results

Treatment with low-dose ASA alone increased bleeding time 2-fold as compared to baseline (see Table S 3).

When taken together with low-dose ASA both AZD6482 and clopidogrel significantly prolonged bleeding time. The bleeding time was increased both as compared to baseline and as compared to low-dose ASA alone (see Table S 3 and Table S 4).

The increase in bleeding time with the combination of clopidogrel and low-dose ASA was significantly higher, a redoubling in bleeding time, than the increase seen with the combination of AZD6482 and low-dose ASA (see Table S 3 and Table S 4).

Table S 3 Geometric mean change from baseline in CBT within treatment with 95% CIs. Per Protocol population

Treatment	Comparison	Geom. Mean (95% CI)
ASA	Day 6/Baseline	1.8 (1.5 ; 2.2)
ASA + AZD6482	Day 7/Baseline	6.6 (4.4 ; 9.8)
ASA + Clopidogrel	Day 7/Baseline	14.9 (10 ; 22.1)

D1700C00004_CBT ANOVA change from baseline

Table S 4 Geometric mean change ratio in CBT between treatments with 95% CIs. Per Protocol population

Comparison	Mean Ratio (95% CI)
ASA+AZD6482 / ASA+Clopidogrel	0.44 (0.25 ; 0.77)
ASA+AZD6482 / ASA	3.6 (2.29 ; 5.64)
ASA+Clopidogrel / ASA	8.12 (5.41 ; 12.18)

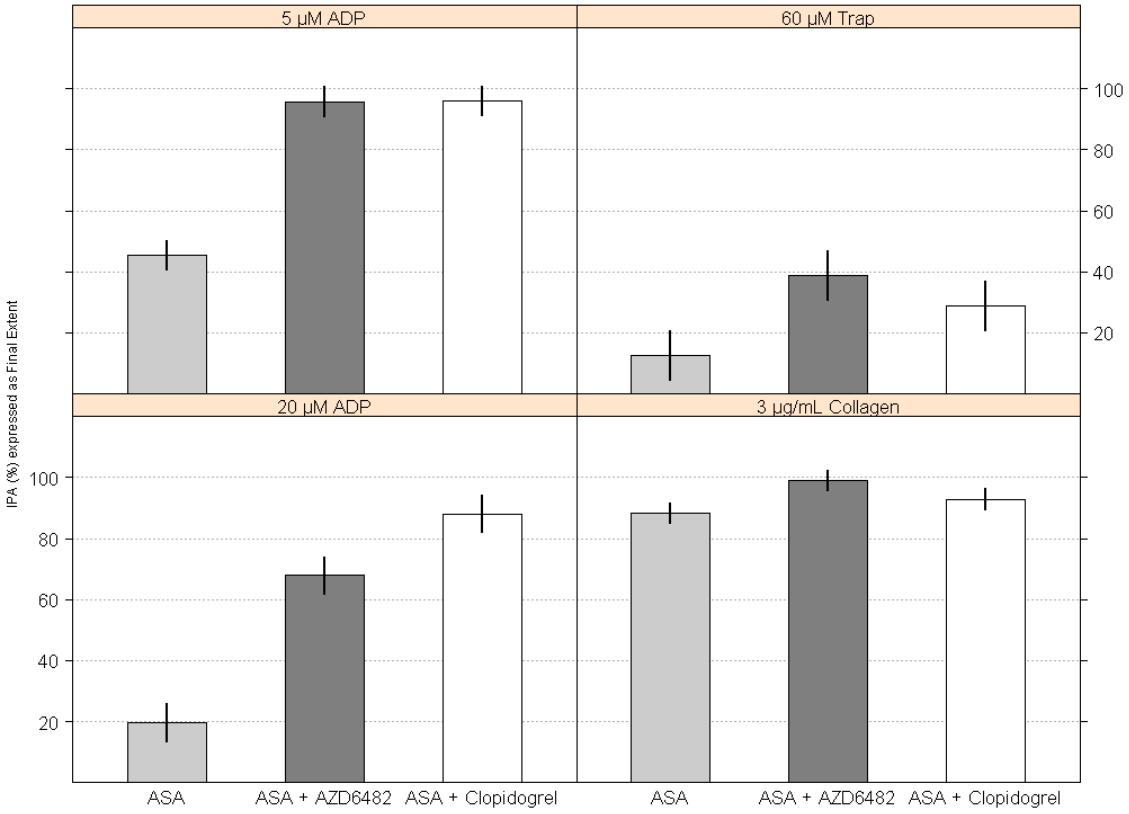
Change ratio for ASA+AZD6482 and ASA+Clopidogrel: Day7/Baseline.
Change ratio for ASA: Day6/Baseline.
D1700C00004_CBT ANOVA changefrom baseline

The relative efficacy of AZD6482 + low-dose ASA and clopidogrel + low-dose ASA on IPA varied depending on agonist, agonist concentration and method. When taken together with low-dose ASA the effect of AZD6482 and clopidogrel on overall platelet inhibition were similar or slightly better with AZD6482 (see Figure S 1).

Low-dose ASA alone had an expected effect on platelet inhibition as is shown with collagen and Arachidonic acid (AA) as agonists (see Figure S 1).

Both the combination of AZD6482 and low-dose ASA and the combination of clopidogrel and low-dose ASA resulted in a significantly higher effect as compared to low-dose ASA alone (see Figure S 1).

Figure S 1 IPA (%) determined by Optical Aggregometry. Effect on Final Extent of aggregation. Mean and 95% CI by agonist and treatment



Summary of safety results

There were few adverse events (AEs) in the study and more AEs were reported during low-dose ASA and clopidogrel treatment than during low-dose ASA and AZD6482 treatment. The majority of the AEs were of mild intensity. A few mild, non-treatment related AEs were still present at follow-up. No SAEs were reported during the study. One AE (viral gastroenteritis) leading to discontinuation of treatment was reported during treatment A before AZD6482 administration. Two AEs with possible relationship to investigational product were reported: one AE (nose bleeding) during low-dose ASA and AZD6482 treatment and one AE (bruise) during low-dose ASA and clopidogrel treatment.