Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130C00067
Edition Number	1
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A Randomised, Double-Blind, Placebo Controlled, Crossover, Single Centre Phase I Study to Assess the Effect of Ticagrelor on Adenosine-Induced Coronary Blood Flow Velocity in Healthy Male Subjects

Study dates: First subject enrolled: 2 December 2010
Last subject last visit: 6 April 2011

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
Primary	**Primary**
To assess the effect of Ticagrelor compared to placebo on the adenosine induced coronary blood flow velocity response by estimating the change in area under the adenosine dose response curve before and after study drug.	Area under the curve of coronary blood flow velocity
Secondary	**Secondary**
To assess the effect of Ticagrelor compared to placebo on the adenosine induced coronary blood flow velocity response by estimating the change in area under the adenosine dose response curve before and after infusion of theophylline	Area under the curve of coronary blood flow velocity
To assess the difference in basal blood flow (in the absence of adenosine) between Ticagrelor and placebo conditions before and after infusion of theophylline	Coronary blood flow velocity
Safety	
To assess the safety and tolerability of a single 180 mg dose of Ticagrelor in healthy subjects in the presence of adenosine and theophylline.	Adverse events, laboratory data, electrocardiogram, vital signs and physical examinations
Exploratory	
To assess the respiratory function of healthy subjects after administration of a single 180 mg dose of Ticagrelor compared to placebo in combination with adenosine, before and after infusion with theophylline, by means of dyspnoea assessment via the Borg scale and a qualitative questionnaire[a]	Dyspnoea assessment via the Borg scale, a qualitative questionnaire

a As planned in the Clinical Study Protocol, results will be reported separately from this report.

Study design

This was a randomised, double-blind, placebo controlled, crossover, single centre phase I study.

Each subject was administered a single oral dose of Ticagrelor or placebo during the treatment periods. The treatment periods were separated by a washout period of 6 to 21 days (between

dosing on Visit 2 and Visit 3). In addition, adenosine (at 5 different doses) and theophylline were administered during the treatment periods.

Target subject population and sample size

The target population was healthy male subjects aged between 18 and 40 years inclusive. With 32 evaluable subjects completing both study periods, the study had 80% power to detect a difference of 17% between the treatment groups on a 5% significance level using a two sided test for the primary variable. Forty (40) subjects were randomised and 38 were analysed for the efficacy variables (19 subjects in each of the treatment-sequence groups [placebo-Ticagrelor and Ticagrelor-placebo]).

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

Ticagrelor, oral tablet 90 mg (AstraZeneca, batch no 10-005647AZ), administered as a single dose of 180 mg (2 x 90 mg)

Placebo, oral tablet (AstraZeneca, batch no 10-005788AZ), administered as a single dose

Duration of treatment

During each treatment period a single dose of Ticagrelor/placebo was administrered. The 2 treatment periods were separated by a wash-out period of 6 to 21 days. The study duration for each subject was up to 9 weeks.

Statistical methods

For the primary objective, the change in area under the curve of coronary blood flow velocity was analysed using a mixed model analysis of variance with log AUC as response variable, pre-dose AUC as a covariate, treatment, period and sequence as fixed effects and a random effect for subject within sequence. Estimates of the mean difference (Ticagrelor-placebo) were calculated with 95% confidence intervals. The result was transformed back to the original scale in order to give an estimate of the true ratios and 95% CIs for these ratios.

For the first secondary objective, the effect of Ticagrelor before and after theophylline was estimated using a similar model as for the primary objective.

For the second secondary objective, the change in coronary blood flow velocity for the 0 μg/kg/min adenosine dose was analysed using a similar model as for the primary objective.

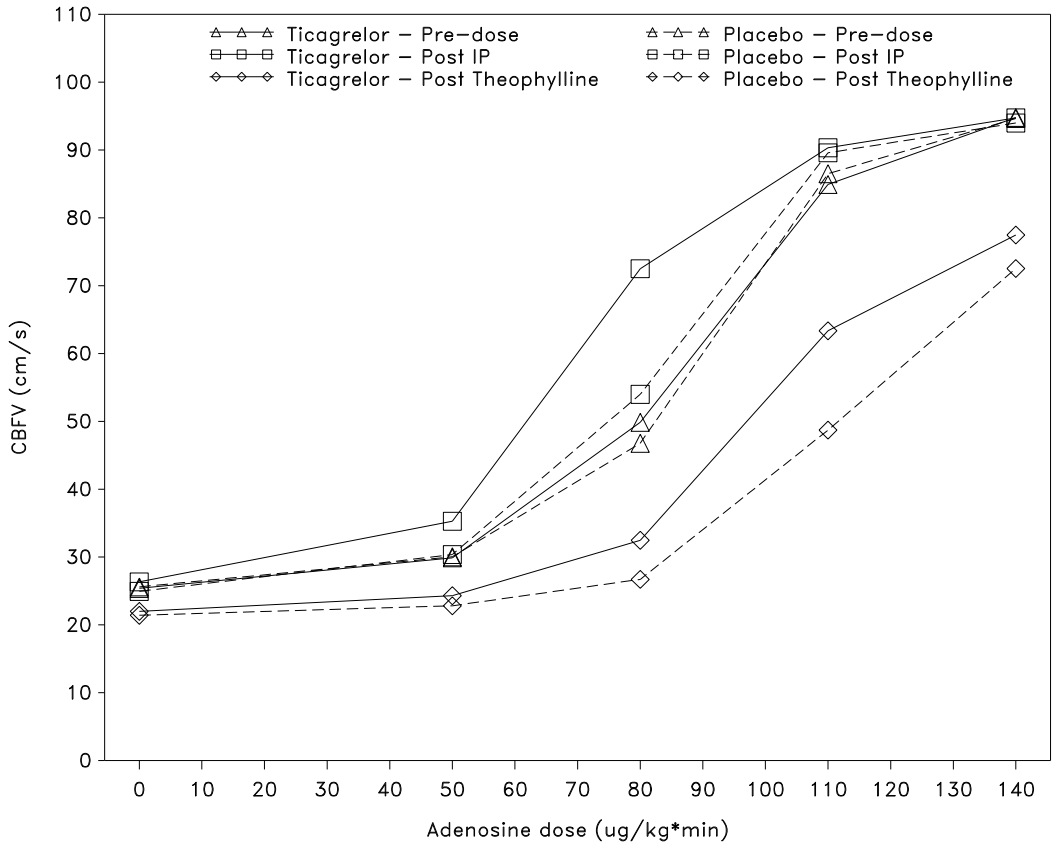
Subject population

A total of 55 male subjects were enrolled in the study. Forty (40) subjects, aged 20 to 31 years, were randomised. Their mean (±standard deviation) weight and body mass index were 76.1 (±7.9) kg and 23.05 (±2.09) kg/m^2, respectively. The treatment-sequence groups were well balanced in terms of demographics and baseline charachteristics. All subjects but 1 (randomised to placebo-Ticagrelor) completed the study.

Summary of efficacy results

Mean coronary blood flow velocity are presented versus adenosine dose for each treatment in the figure below.

Figure S1 Mean CBFV (cm/s) versus adenosine dose (Efficacy analysis set)



Predose curves appear in the center of Figure S1 (triangles): Ticagrelor (solid line) and placebo (dashed line) curves are virtually identical, confirming acceptable reproducibility of the adenosine flow dose response. After IP administration (squares), placebo resulted in a response similar to the pre-dose situation. In contrast, CBFV increased following Ticagrelor, an effect most evident at submaximal doses of adenosine. Finally, theophylline administration (diamonds) blunted, but did not eliminate, the adenosine flow response in a similar fashion after both treatments. Since theophylline is an adenosine receptor antagonist, this supports the hypothesis that the observed flow promoting effect of Ticagrelor is mediated via an adenosine mechanism.

Adenosine dose-dependently increased coronary blood flow velocity during all dose ladders. Ticagrelor significantly enhanced the adenosine-induced coronary blood flow velocity responses compared to placebo as the area under the coronary blood flow velocity versus adenosine dose curve increased significantly, 15% (95% CI: 9%, 21%) versus 4% (95% CI: -1%, 10%); p=0.008).

There was no statistically significant difference between treatment with Ticagrelor and placebo on the adenosine induced CBFV response before and after infusion of theophylline. Theophylline inhibited the adenosine-induced vasodilatory responses in a similar way in both groups, indicating the augmented response after Ticagrelor dosing was mediated via the adenosine receptors and not through a unique pathway.

There was no statistically significant difference in basal blood flow (in the absence of adenosine) between Ticagrelor and placebo conditions before and after infusion of theophylline. Following infusion of theophylline, coronary blood flow velocity decreased in both the Ticagrelor and the placebo group to similar values (from 26.3±7.0 cm/s to 22.0±5.5 cm/s and 24.9±5.5 cm/s to 21.4±5.0 cm/s for Ticagrelor and placebo, respectively (mean (±standard deviation) are given)).

Summary of safety results

There were no serious adverse events, no other significant adverse events and no discontinuations of investigational product due to an adverse event in the study. The majority of adverse events were reported as casually related to adenosine as assessed by the investigator. There were no AEs of severe intensity.

There were no clinically relevant findings in ECG, physical examination or weight during the study. There were no clinically relevant changes in vital signs between treatments (predose, post IP and post theophylline for Ticagrelor/placebo).