AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130C00073
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A Sequential, Open Label Study to Compare the Pharmacokinetics, Safety, and Tolerability of Ticagrelor and Venlafaxine Given Concomitantly in Healthy Subjects Aged 18 to 45 Years

Study dates: First subject enrolled: 06 January 2012
Last subject last visit: 15 March 2012

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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To assess the effect of ticagrelor on the pharmacokinetics of venlafaxine by assessment of C_{max} and AUC_{τ} of venlafaxine and O-desmethylvenlafaxine	Primary Variables: C_{max} and AUC_{τ} of venlafaxine and ODV Secondary Variables: t_{max} of venlafaxine and ODV
	Pharmacokinetics	To assess the effect of venlafaxine on the pharmacokinetics of ticagrelor by assessment of C_{max} and AUC of ticagrelor and AR-C124910XX	Primary Variables: C_{max} and AUC of ticagrelor and AR-C124910XX Secondary Variables: t_{max} and $t_{1/2}$ of of ticagrelor and AR-C124910XX
Secondary	Safety	To assess the safety and tolerability of ticagrelor and venlafaxine when given alone and concomitantly by assessment of adverse events, safety laboratory variables, physical examination, electrocardiogram, and vital signs	Adverse events, safety laboratory variables, physical examinations, electrocardiograms, and vital signs
Exploratory	Pharmacogenetic	To collect blood or urine samples for possible biomarker research [a]	Biomarker

AEs adverse events; AUC Area under the plasma concentration-time curve from zero to infinity; AUCτ Area under the plasma concentration-time curve during a dosing interval;C_{max}: Observed maximum plasma concentration ; CSP Clinical study protocol; ECG electrocardiograms; ODV desmethylvenlafaxine; PK pharmacokinetic; $t_{1/2}$ terminal half-life and t_{max} Time to C_{max}.
[a] These data are not included in this clinical study report.

Study design

This was an open-label, one-sequence, crossover study in which the effect of ticagrelor on the pharmacokinetics of venlafaxine and vice versa was evaluated in healthy volunteers. In addition, the safety and tolerability of ticagrelor and venlafaxine, when given alone and concomitantly, was investigated. The study duration for each volunteer was up to 7 weeks and included 1 period of treatment confinement of 13 days (from Day -1 to Day 12).

Each volunteer was administered 1 single dose of 180-mg ticagrelor on Day 1, followed by a 48-hour pharmacokinetic blood sampling period. Venlafaxine was administered in the morning and evening from Day 4 until Day 10. The dose was titrated from 37.5 mg twice daily on Day 4 to the target dose of 75 mg twice daily on Days 5 through 10. In the morning

of Day 9, a single dose of 180-mg ticagrelor was coadministered with 75-mg venlafaxine. A 12-hour pharmacokinetic blood sampling period followed the morning dose administration of venlafaxine on Day 8 and a 48-hour pharmacokinetic blood sampling period followed the concomitant morning dose of venlafaxine and ticagrelor on Day 9. Safety was assessed throughout the study. Provided that no medical concerns were identified by the Investigator, the volunteers were free to leave the clinic on Day 12, 72 hours after the last dose of ticagrelor and 36 hours after the last dose of venlafaxine.

Target subject population and sample size

Healthy male and female volunteers aged 18 to 45 years (inclusive) with a body mass index between 18 and 30 kg/m^2 (inclusive). Women of childbearing potential agreed to use effective means of contraception. There were 25 volunteers enrolled and treated in the study.

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

The study medication consisted of:

- ticagrelor, supplied as 90-mg oral, immediate-release tablets, manufactured by AzstraZeneca, batch number 11-0010009AZ

- venlafaxine, 37.5- and 75-mg oral, immediate-release tables, manufactured by ZyGenerics, batch number ML8048

In this open-label study, volunteers were administered 180-mg single oral doses of immediate-release ticagrelor tablets on Day 1. Venlafaxine was administered as oral immediate-release tablets to each volunteer on Days 4 to 10 (37.5 mg twice daily on Day 4 and 75 mg twice daily from Day 5 until Day 10). On Day 9, a single oral dose of immediate-release 180-mg ticagrelor was coadministered with a single oral dose of immediate-release 75 mg of venlafaxine.

There was no comparator.

Duration of treatment

The duration of volunteer participation was approximately 7 weeks, consisting of 3 visits: a screening visit (Visit 1) of up to -28 days, a treatment visit (Visit 2) during which the volunteers were confined to the clinic from Day -1 until Day 12, and a follow-up visit (Visit 3) occurring 7 to 10 days after discharge.

Statistical methods

Plasma concentrations and pharmacokinetic parameters were summarized using appropriate descriptive statistics by analyte and treatment.

The estimated C_{max} and AUC_{τ} of venlafaxine and O-desmethylvenlafaxine (Day 8 and Day 9) were log-transformed (natural log) prior to analysis. The log-transformed C_{max} and AUC_{τ} data

of venlafaxine and O-desmethylvenlafaxine were analyzed separately using a mixed-effects model with terms for treatment as fixed effect and volunteer as random effect. The estimated least-squares means and intravolunteer variability from the mixed-effects model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments. The treatment effect and its corresponding 90% confidence intervals were retransformed using anti-logarithms to its original scale and reported as ratio of treatments (venlafaxine + ticagrelor/venlafaxine alone) in percent. If the 90% confidence intervals are entirely within the prespecified range of 80% to 125% then it was concluded that ticagrelor had no effect on the pharmacokinetics of venlafaxine. The estimated C_{max} and AUC of ticagrelor and AR-C124910XX (Day 1 and Day 9) were analyzed using the mixed effects model described above. The treatment effect and its corresponding 90% confidence intervals obtained from the mixed-effects model were retransformed using anti-logarithms to its original scale and reported as ratio of treatments in percent. If the 90% confidence intervals were entirely contained within the prespecified range of 80% to 125% then it was concluded that venlafaxine had no effect on the pharmacokinetics of ticagrelor.

Safety variables were presented by descriptive statistics.

Subject population

There were 25 volunteers enrolled and treated in this study. Of these, 3 (12%) volunteers did not complete treatment due to volunteer decision (E0001016 withdrew on Day 3; E0001007 withdrew on Day 5; E0001039 withdrew on Day 7), and 1 (4%) volunteer (E0001075) completed all of the treatments but was lost to follow-up on Day 15. All volunteers were included in the safety analysis. For PK, 25 volunteers were included in the Day 1 PK analysis and 22 volunteers were included in the Day 8 and Day 9 PK analysis as there was no PK data available for subjects who withdrew before Day 8.

Healthy male and female volunteers between the ages of 18 to 45 year, inclusive, were screened for enrollment in this study. Of the 25 volunteers enrolled, 19 (76%) were male, 6 (24%) were female, 14 (56%) were white, 10 (40%) were black, and 1 (4%) was Asian. The mean age of all volunteers was 26±5.6 years (range from 18 to 43 years); mean height was 176±8.7 cm; mean weight was 75.2±10.7 kg; and mean body mass index was 24.3±2.9 kg/m^2.

Summary of pharmacokinetic results

Inferential analysis indicated that venlafaxine had no statistically significant effect on the exposure of ticagrelor as the 90% confidence intervals for both AUC (82.78, 97.14%) and C_{max} (85.03, 109.61%) for the estimated geometric mean ratios for ticagrelor in combination with venlafaxine versus ticagrelor alone were entirely contained within the interval 80% to 125%. Similarly, for AR-C124910XX, the 90% confidence intervals for both AUC (97.28, 116.21) and C_{max} (96.10, 117.78%) for the estimated geometric mean ratios for ticagrelor in combination with venlafaxine versus ticagrelor alone were entirely contained within the interval 80% to 125% indicating that venlafaxine had no significant effect on the exposure of AR-C124910XX.

Ticagrelor had no statistically significant effect on the overall exposure (AUC_τ) of venlafaxine, as the 90% confidence intervals for AUC_τ (106.27, 114.52%) for the estimated geometric mean ratio for ticagrelor in combination with venlafaxine versus venlafaxine alone was entirely contained within the interval 80% to 125%. However, C_{max} of venlafaxine was 22% higher when venlafaxine was administered along with ticagrelor in comparison to when venlafaxine was given alone. The upper bound of the 90% confidence interval for C_{max} (111.80, 132.75%) was above 125%, indicating that ticagrelor had a statistically significant effect on the C_{max} of venlafaxine. Ticagrelor had no statistically significant effect on the exposure of O-desmethylvenlafaxine, as the 90% confidence intervals for both AUC_τ (96.61, 100.85%) and C_{max} (98.34, 104.65%) for the estimated geometric mean ratios for ticagrelor in combination with venlafaxine versus venlafaxine alone were entirely contained within the interval 80% to 125%.

The median time to maximum concentration (t_{max}) and $t_{1/2}$ for ticagrelor and its metabolite AR-C124910XX was similar between both treatments. The median time to maximum concentration (t_{max}) for venlafaxine and its metabolite O-desmethylvenlafaxine was similar between both treatments.

Summary of safety results

There were no deaths, serious adverse events, adverse events of severe intensity, or adverse events that led to discontinuation reported during the study. Overall, there were 21 (84%) volunteers who reported at least 1 adverse event during the study. There were twice as many volunteers who had at least one adverse event during the single-day treatment with ticagrelor plus venlafaxine (10 volunteers [45%]), than during the single-day treatment with ticagrelor alone (5 volunteers [20%]). There were 18 volunteers (75%) who reported at least 1 adverse event during the 4-day treatment period of venlafaxine alone, and there were 4 (17%) volunteers who reported an adverse event during the follow-up period.

Overall, there were 3 adverse events of moderate intensity (2 events of nausea and 1 event of neuropraxia of the shoulder) and the remaining events were all of mild intensity. Overall, there were 19 (76%) of 25 volunteers who had adverse events that were assessed by the Investigator as related to study treatment.

The most commonly reported adverse events across all treatments, in decreasing order of frequency, were: nausea, decreased appetite, headache, vomiting, mydirasis, and muscle twitching. There were no safety concerns or differences between treatments identified in clinical laboratory tests, vital signs, electrocardiograms, physical examinations, or the Columbia-Suicide Severity Rating Scale.