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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

Sponsor: AstraZeneca

AstraZeneca Research and Development site representative

_____
Date

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1			

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1			
2			
3			

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PROTOCOL SYNOPSIS

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

Principal investigator

Study center(s) and number of subjects planned

This study will be conducted at 1 study center:
Up to 22 volunteers will be included to receive study drug in order to ensure 18 evaluable volunteers.

Study period	Phase of development
Estimated date of first subject enrolled	Clinical Pharmacology (I)
Estimated date of last subject completed	

Objectives

Primary objective

The primary objectives of this study are:

- To assess the effect of ticagrelor on the pharmacokinetics of venlafaxine by assessment of C_{max} and AUC_{τ} of venlafaxine and O-desmethylvenlafaxine
- To assess the effect of venlafaxine on the pharmacokinetics of ticagrelor by assessment of C_{max} and AUC of ticagrelor and AR-C124910XX

Secondary objective

The secondary objective of this study is to assess the tolerability of ticagrelor and venlafaxine when given alone and concomitantly by assessment of adverse events, safety laboratory variables, physical examination, electrocardiogram, and vital signs

Exploratory objective

The exploratory objective of this study is to collect blood or urine samples for possible biomarker research. (These data will not form part of the main report for this study, see Section 6.5 and Appendix E.)

Study design

This is an open label, one-sequence, crossover study in which the effect of ticagrelor on the pharmacokinetics of venlafaxine and vice versa will be evaluated in healthy volunteers. In addition, the safety and tolerability of ticagrelor and venlafaxine, when given alone and concomitantly, will be investigated. The study duration for each volunteer will be up to 7 weeks. The study will consist of 3 visits. Visit 1 is a preentry visit (screening), Visit 2 is a treatment visit, during which the volunteers will be confined to the clinic from Day -1 until Day 12, and Visit 3 is a follow-up visit occurring 7 to 10 days after discharge.

Each volunteer will be administered 1 single dose of 180-mg ticagrelor on Day 1, followed by a 48-hour pharmacokinetic blood sampling period. Venlafaxine will be administered in the morning and evening from Day 4 until Day 10. The dose will be titrated from 37.5 mg twice daily on Day 4 to the target dose of 75 mg twice daily on Day 5. In the morning of Day 9, a single dose of 180-mg ticagrelor will be coadministered with 75-mg venlafaxine. A 12-hour pharmacokinetic blood sampling period will follow the morning dose administration of venlafaxine on Day 8 and a 48-hour pharmacokinetic blood sampling period will follow the concomitant morning dose of venlafaxine and ticagrelor on Day 9. Safety will be assessed throughout the study. Provided that no medical concerns are identified by the Investigator, the volunteers will be 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

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 must agree to use effective means of contraception.

Investigational product, dosage, and mode of administration

Volunteers will be administered 180-mg single oral doses of immediate-release ticagrelor tablets on Day 1 and Day 9. Venlafaxine will be 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).

Comparator, dosage, and mode of administration

Not applicable.

Duration of treatment

The treatment visit, Visit 2 will constitute in total 13 days. Ticagrelor (180-mg single dose) will be administered on Day 1. Venlafaxine will be administered on Days 4 to 10 (37.5 mg

twice daily on Day 4 and 75 mg twice daily on Days 5 to 10). In the morning of Day 9, a single dose of ticagrelor (180 mg) will be coadministered with venlafaxine (75 mg).

Outcome variable(s):

- Pharmacokinetics

  Primary pharmacokinetic parameters

  Venlafaxine and O-desmethylvenlafaxine on Day 8 (after multiple dose administration of venlafaxine for 4 days) and Day 9 (after concomitant administration of venlafaxine and ticagrelor): area under the plasma concentration-time curve during a dosing interval (AUC_τ) and observed maximum plasma concentration (C_{max})

  Ticagrelor and AR-C124910XX on Day 1 (after single-dose administration of ticagrelor) and Day 9 (after concomitant administration of venlafaxine and ticagrelor): area under the plasma concentration-time curve from zero to infinity (AUC) and C_{max}

  Secondary PK parameters
  Venlafaxine and O-desmethylvenlafaxine on Days 8 and 9: time to C_{max} (t_{max})

  Ticagrelor and AR-C124910XX on Days 1 and 9: t_{max} and terminal half-life $t_{(½\lambda z)}$

- Safety

  Adverse events, safety laboratory variables, physical examination, 12-lead electrocardiogram, vital signs, and suicidal ideation (Columbia-Suicide Severity Rating Scale)

Statistical methods

Plasma concentrations and pharmacokinetic parameters will be 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) will be log-transformed (natural log) prior to analysis. The log-transformed C_{max} and AUC_τ data of venlafaxine and O-desmethylvenlafaxine will be 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 will be 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 will be 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 lies entirely within the prespecified range of 80% to 125% then it will be concluded

that ticagrelor has no effect on the pharmacokinetics of venlafaxine. The estimated C_{max} and AUC of ticagrelor and AR-C124910XX (Day 1 and Day 9) will be analyzed using the mixed effects model described above. The treatment effect and its corresponding 90% confidence intervals obtained from the mixed effects model will be retransformed using anti-logarithms to its original scale and reported as ratio of treatments in percent. If the 90% confidence intervals lies entirely within the prespecified range of 80% to 125% then it will be concluded that venlafaxine has no effect on the pharmacokinetics of ticagrelor.

Safety variables will be presented by descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
%AUCex	Percentage of AUC obtained by extrapolation
AUC_{0-24}	Area under the plasma concentration-time curve from zero to 24
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.3.1)
ASA	Acetylsalicylic acid
AUC	Area under the plasma concentration-time curve from zero to infinity
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
BLQ	Below lower limit of quantification
BMI	Body mass index
CI	Confidence interval
C_{last}	The last observed plasma concentration
C_{max}	Observed maximum plasma concentration
CPA	Clinical Pharmacology Alliance
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
C-SSRS	Columbia-suicide severity rating scale
CYP	Cytochrome P450
DAE	Discontinuation of Investigational product due to adverse event
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IP	Investigational product
IPA	Inhibition of platelet aggregation
IRB	Institutional Review Board
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini-international neuropsychiatric interview
NA	Not applicable
ND	Not determined
OAE	Other significant adverse event (see definition in Section 11.1.1)
ODV	O-desmethylvenlafaxine
OTC	Over-the-counter
PK	Pharmacokinetic(s)
Rsq	The coefficient of determination, R-Squared (goodness of fit statistic for calculation of λ_z)
QTcF	QT interval corrected for heart rate using Fredericia's formula
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SNRI	Serotonin norephinephrine reuptake inhibitor
STEMI	ST segment elevation myocardial infarction
SUSAR	Suspected unexpected serious adverse reactions
$t_{½\lambda z}$	Terminal half-life
$t_{½\lambda z, n}$	Number of data points included in the log-linear regression analysis
t_{max}	Time to C_{max}
UA	Unstable angina
λ_z	Terminal rate constant
$\lambda_{z, lower}$ $\lambda_{z, upper}$	The time interval of the log-linear regression used to determine $t_{½\lambda z}$

1. INTRODUCTION

1.1 Background

Atherosclerosis is a progressive disease of the large conduit arteries. It is a worldwide public health concern, primarily due to the death and disability caused through its clinical manifestations as coronary (eg, unstable angina [UA] and myocardial infarction) and cerebral thrombotic events (eg, stroke and transient ischaemic attack). The term "acute coronary syndromes" (ACS) encompasses a range of clinical conditions that includes UA, non ST segment elevation myocardial infarction (STEMI), and ST STEMI. The process central to ACS is disruption or erosion of an atherosclerotic plaque, ultimately leading to the promotion of platelet aggregation and a thrombus.

Adenosine diphosphate (ADP) is 1 of the primary mediators of platelet aggregation, and inhibition of ADP mediated platelet aggregation by clopidogrel in combination with acetylsalicylic acid (ASA) has been shown to provide improved efficacy over ASA therapy alone in ACS, with a favorable bleeding profile. However, clopidogrel has a slow onset of action, irreversibly binds to its receptor resulting in a slow offset of effect, and often has incomplete and variable inhibition of platelet aggregation (IPA) from patient to patient.

Ticagrelor is an oral, reversible ADP receptor antagonist acting via the $P2Y_{12}$ receptor, which has been developed for the prevention of thrombotic events in patients with ACS. The goal of the ticagrelor Phase III program was to demonstrate substantial improvements in clinical efficacy (ie, clinical thrombotic event reduction) with an acceptable safety profile compared with currently available antiplatelet therapies (ie, ASA and clopidogrel). Most patients took concomitant ASA with ticagrelor.

The focus of the clinical pharmacology program for ticagrelor, which included 41 studies in approximately 1000 subjects, has been to examine the exposure-response relationship, investigate safety, and characterize drug interactions. The pharmacokinetics (PK) of ticagrelor, as well as the metabolism of the compound, have been characterized in healthy volunteers and the patient population. The dose range of ticagrelor administered during these studies was 0.1 mg to 1260 mg, and 900 mg was established as the maximum tolerated dose in healthy volunteers.

Inhibition of platelet aggregation mediated by ticagrelor increases with increasing plasma concentrations of ticagrelor, and its active metabolite AR-C124910XX, until almost complete inhibition is obtained. Ticagrelor has a more rapid onset, higher and less variable interpatient IPA, and faster offset compared to clinical doses of clopidogrel. Ticagrelor has a number of drug-drug interactions that are of clinical relevance since it is a substrate and an inhibitor of cytochrome P450 (CYP) 3A, a potential activator of *CYP3A4* and a substrate and an inhibitor of the P glycoprotein transporter. In this study, the potential interaction between ticagrelor and the *CYP2D6* substrate venlafaxine will be investigated.

Refer to the Investigator's Brochure for further details on ticagrelor exposure, PK, and safety findings. These data support the further development of ticagrelor as an oral antiplatelet agent, which may be able to prevent more thrombotic events than clopidogrel by sustaining higher levels of $P2Y_{12}$ receptor blockade with an acceptable safety profile. For further details on venlafaxine, refer to the package insert.

1.2 Research hypothesis

The research hypothesis is that ticagrelor, as a weak inhibitor of *CYP2D6*, will have no clinically relevant effect on the PK of venlafaxine, a *CYP2D6* substrate.

If the confidence intervals (CIs) for the geometric mean ratios (in percent) of AUC_{τ} and C_{max} of venlafaxine and its metabolite O-desmethylvenlafaxine (ODV) following treatment with venlafaxine in combination with ticagrelor and alone are within 80% to 125% the research hypothesis will be confirmed.

1.3 Rationale for conducting this study

The in vitro CYP inhibition profile of ticagrelor indicates that it may be a weak inhibitor of *CYP2D6*. This study is designed to characterize the effect of ticagrelor on this important CYP isoenzyme. Since venlafaxine, a serotonin norephinephrine reuptake inhibitor (SNRI), is a *CYP2D6* substrate and undergoes limited to no metabolism through the other CYP pathways, it is chosen as the investigational 2D6 substrate drug for the study.

1.4 Benefit/risk and ethical assessment

There are no direct benefits for the volunteers participating in this study.

Ticagrelor, like other inhibitors of platelet aggregation, increases the risk of bleeding. Reported events in previous Phase II and Phase III studies have included bleeding in areas considered to be clinically important such as the lung, brain, eye, and joints. In previous studies in healthy volunteers, adverse events (AEs) associated with bleeding were infrequent and were generally considered to be mild. In this study, necessary measures will be taken to minimize this risk of bleeding by excluding volunteers at high risk of bleeding such as volunteers with history of hemophilia, von Willebrand's disease, lupus anticoagulant, or other diseases/syndromes that can either alter or increase the propensity for bleeding. Also volunteers with a history of a clinically significant nontraumatic bleed or clinically significant bleeding risk, as judged by the Investigator, will be excluded.

The risk of ticagrelor exposure to volunteers in this study is expected to be equivalent to the safety profile in volunteers observed in previous Phase I studies where similar doses have been administered. The most common AEs, with an incidence of at least 2%, reported to date in the Phase I studies with at least 3 days of ticagrelor dosing include headache, somnolence, dizziness, epistaxis, nausea, abdominal pain, back pain, dyspnea, ecchymosis, lethargy, pharyngolaryngeal pain, blurred vision, postural dizziness, pollakiuria (frequent urination), and increased tendency for bruising.

The most commonly reported side effects of venlafaxine in clinical studies are nausea, dry mouth, headache, and sweating. The venlafaxine dose will be titrated to enhance tolerability, starting with 37.5 mg twice daily on Day 4 and ending with the target dose of 75 mg twice daily on Day 5.

Selective serotonin reuptake inhibitors and SNRIs, including venlafaxine, may increase the risk of bleeding events. Concomitant use of ticagrelor may add to this risk. The concomitant dosing of ticagrelor and venlafaxine in this study is limited to 1 occasion.

Antidepressants such as venlafaxine, and a few other drug classes, have been associated with increased treatment-emergent suicidality reports compared to placebo. Prospective monitoring allows identification and treatment of such patients and secondly, allows regulatory authorities to collect data and better understand the population occurrence of such reports. According to the guidance on studies involving antidepressants (Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials), treatment-emergent suicidality has also been reported in short-term Phase I studies in healthy volunteers with several different antidepressants. Suicidality assessments should, therefore, be included even in single-dose trials. In accordance with the guidance a mini-international neuropsychiatric interview (MINI) will be conducted at screening to exclude volunteers with a history of previous or ongoing psychiatric disease/condition and suicidal ideation will be assessed through means of Columbia-Suicide Severity Rating Scale (C-SSRS).

2. STUDY OBJECTIVES

2.1 Primary objectives

The primary objectives of this study are:

- To assess the effect of ticagrelor on the PK of venlafaxine by assessment of C_{max} and AUC_{τ} of venlafaxine and ODV
- To assess the effect of venlafaxine on the PK of ticagrelor by assessment of C_{max} and AUC of ticagrelor and AR-C124910XX

2.2 Secondary objective

The secondary objective of this study is to assess the tolerability of ticagrelor and venlafaxine when given alone and concomitantly by assessment of AEs, safety laboratory variables, physical examination, electrocardiogram (ECG), and vital signs.

2.3 Exploratory objective

The exploratory objective of this study is to collect blood or urine samples for possible biomarker research. (These data will not form part of the main report for this study, see Section 6.5 and Appendix E).

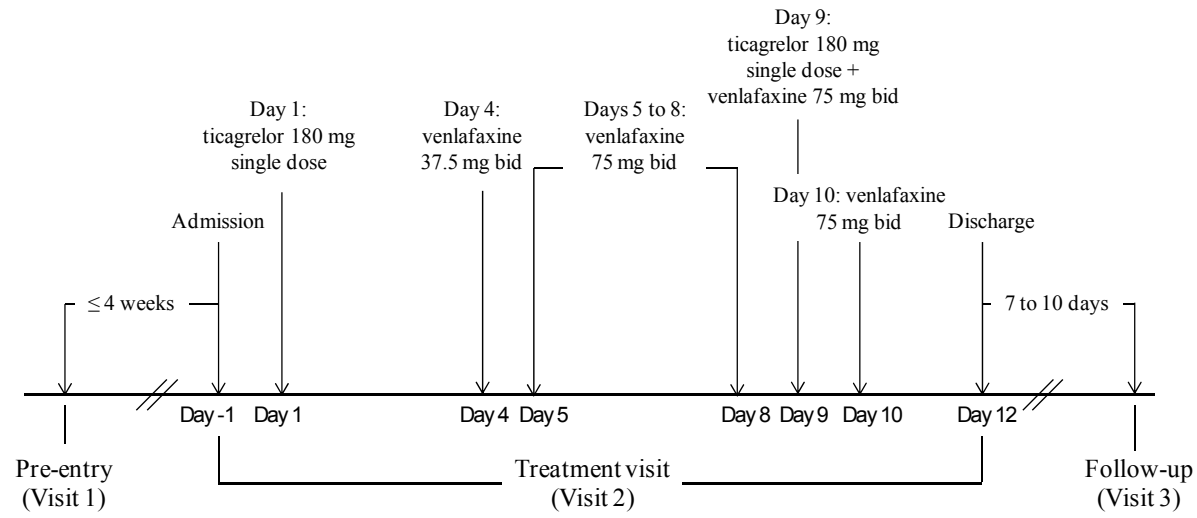
3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is an open label, one-sequence, crossover study in which the effect of ticagrelor on the PK of venlafaxine and vice versa will be evaluated in healthy volunteers. In addition, the safety and tolerability of ticagrelor and venlafaxine, when given alone and concomitantly, will be investigated. Up to 22 volunteers will be included to receive study drug in order to ensure 18 evaluable volunteers. The study will be conducted at a single center and will consist of 3 visits (See Figure 1). The study duration for each volunteer will be up to 7 weeks. Visit 1 is a preentry visit (screening), Visit 2 is a treatment visit during which the volunteers will be confined to the study unit from Day -1 until Day 12, and Visit 3 is a follow-up visit occurring 7 to 10 days after discharge.

Figure 1 Study flow chart



bid twice daily.

Visit 1 Preentry (screening)

Volunteers will be screened at the preentry visit (Visit 1), which will take place a maximum of 4 weeks before Day -1 of the treatment visit (Visit 2). Written informed consent will be obtained from all healthy volunteers prior to conducting any study-specific procedures. For details on preentry assessments, refer to Section 6.2.

A MINI will be performed by a physician to exclude volunteers with psychiatric disorder(s).

Visit 2 Treatment

At Visit 2, the treatment visit, the volunteers will come to the clinic on Day -1 (the day prior to the first administration of study drug) and will remain there until Day 12.

Each volunteer will be administered 1 single dose of 180 mg ticagrelor on Day 1, followed by a 48-hour PK sampling period. Venlafaxine will be administered to each volunteer in the morning and evening of Days 4 to 10. The dose will be titrated from 37.5 mg twice daily on Day 4 to the target dose of 75 mg twice daily on Day 5. In the morning of Day 9, a single dose of 180-mg ticagrelor will be coadministered with 75-mg venlafaxine. A 12-hour PK sampling period will follow the morning dose administration of venlafaxine on Day 8 and a 48-hour PK sampling period will follow the concomitant morning dose of venlafaxine and ticagrelor on Day 9. Provided that no medical concerns are identified by the Investigator, the volunteers will be 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.

A C-SSRS for assessment of suicidality will be performed by a physician or other certified staff delegate on Day -1 and Day 12.

Breakfast will be served 1 hour after morning dose intake, except on Days 1, 8, and 9, when the volunteers will fast at least 10 hours overnight and remain fasting until 4 hours post morning dose. Standardized meals will be served throughout the treatment visit.

Visit 3 Follow-up

A follow-up visit will be conducted 7 to 10 days after discharge from the clinic at Visit 2. For details on follow-up assessments, refer to Section 6.2.2.

The study assessments are outlined in Table 1 and a detailed time schedule for the assessments during the treatment visit (Visit 2) is shown in Table 2.

Table 1 Study assessments

Assessment	Visit 1	Visit 2							Visit 3
	Preentry visit (enrollment)	Treatment visit							Follow-up
	Day -28 to -2	Day -1	Day 1	Days 2-3	Days 4-8	Day 9	Day 10	Day 11	Day 12	7 to 10 days after discharge
Signed informed consent	X									
Optional informed consent for biomarker samples	X[a]	X[a]								
Assign subject number			X							
Inclusion & exclusion criteria	X	X								
Relevant medical & surgical history	X									
Body weight, height, and BMI	X									
Demographics	X									
Alcohol breath test	X	X								
Physical examination	X	X[b]							X[b]	X
MINI	X									
Optional biomarker blood or urine sampling		X[c]	X[c]							
Pulse rate, blood pressure, respiratory rate, and temperature	X	X	X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X
12-lead ECG	X	X							X	X
C-SSRS		X							X	
Administration of ticagrelor, 180 mg single dose			X			X				

Table 1 Study assessments

Assessment	Visit 1		Visit 2							Visit 3
	Preentry visit (enrollment)		Treatment visit							Follow-up
	Day -28 to -2	Day -1	Day 1	Days 2-3	Days 4-8	Day 9	Day 10	Day 11	Day 12	7 to 10 days after discharge
Administration of venlafaxine, 37.5 mg twice daily (Day 4) and 75 mg twice daily (Days 5 to 10)					X	X	X			
PK sampling ticagrelor + metabolite AR-C124910XX			X[e]	X[e]		X[e]	X[e]	X[e]		
PK sampling venlafaxine + metabolite ODV					X[f]	X[f]				
Clinical chemistry & hematology	X	X							X	X
Urinalysis	X	X							X	X
Screen for hepatitis and HIV	X									
Screen for drugs of abuse	X	X								
Pregnancy test (women only)[g]	X	X								X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
AEs			X[h]	X	X	X	X	X	X	X
SAEs	X	X	X[i]	X	X	X	X	X	X	X
Discharge from study unit									X[j]	

HIV human immunodeficiency virus; SAEs serious AEs.

[a] At the preentry visit (Visit 1) or on Day -1 of the treatment visit (Visit 2).

[b] A brief physical examination will be performed on Day -1 and before discharge on Day 12 and includes an assessment of the following: general appearance, cardiovascular, chest, abdomen, and skin.

[c] Predose on Day 1 or on Day -1.

[d] Predose each day of dosing days.

[e] Blood samples for the determination of ticagrelor and AR-C124910XX levels in plasma will be collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 hours postdose on Day 1 and Day 9.

[f] Blood samples for the determination of venlafaxine and ODV levels in plasma will be collected predose in the morning of Days 6 and 7; predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours postdose on Day 8; and predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours postdose on Day 9. Predose samples on Days 6, 7, 8, and 9, and 12 hours postdose samples on Days 8 and 9 (ie, samples predose evening dose of venlafaxine) should be taken within 15 minutes prior to dose.

[g] Serum pregnancy test will be performed at screening, Day -1, and follow-up.

[h] Adverse events will be collected from the start of dose until the end of the study.

[i] Serious AEs will be collected from the signing of the Informed Consent Form until the end of the study.

[j] Discharge provided that no safety concerns are identified by the Investigator.

Table 2 Time schedule of assessments for Visit 2

Day	Protocol time (hhmm)	PK blood sampling ticagrelor + AR-C124910XX	PK blood sampling venlafaxine + ODV	Other assessments/activities	Food/fasting requirements[a]
Day -1				Arrival at clinic Inclusion/exclusion criteria Alcohol breath test Brief physical examination Pulse rate, blood pressure, respiratory rate, and temperature 12-lead ECG C-SSRS Clinical chemistry and hematology Urinalysis including urine drug screen Serum pregnancy test for women Concomitant medications and SAE questioning Optional biomarker sampling (Day -1 or Day 1)	Fast (except for water) for 10 hours before dosing on Day 1
Day 1 morning	Predose	X		Assign subject number Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and SAE questioning Optional biomarker sampling (Day -1 or Day 1)	

Table 2 Time schedule of assessments for Visit 2

Day	Protocol time (hhmm)	PK blood sampling ticagrelor + AR-C124910XX	PK blood sampling venlafaxine + ODV	Other assessments/activities	Food/fasting requirements[a]
	0000			Administration of ticagrelor 180 mg Start of AE questioning	Fasting conditions
	0030	X			
	0100	X			
	0200	X			
	0300	X			
	0400	X			Lunch
	0600	X			Snack
	0800	X			
	0900				Dinner
	1000	X			
	1200	X			Evening snack
	1800	X			
Day 2 morning	2400	X		Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	
Day 2 evening	3600	X			

Table 2 Time schedule of assessments for Visit 2

Day	Protocol time (hhmm)	PK blood sampling ticagrelor + AR-C124910XX	PK blood sampling venlafaxine + ODV	Other assessments/activities	Food/fasting requirements[a]
Day 3 morning	4800	X		Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	
Day 4 morning	Predose			Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	
	0000			Administration of venlafaxine 37.5 mg	
Day 4 evening	1200			Administration of venlafaxine 37.5 mg	
Day 5 morning	Predose			Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	
	0000			Administration of venlafaxine 75 mg	
Day 5 evening	1200			Administration of venlafaxine 75 mg	
Day 6 morning	Predose		X[b]	Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	
	0000			Administration of venlafaxine 75 mg	
Day 6 evening	1200			Administration of venlafaxine 75 mg	

Table 2 Time schedule of assessments for Visit 2

Day	Protocol time (hhmm)	PK blood sampling ticagrelor + AR-C124910XX	PK blood sampling venlafaxine + ODV	Other assessments/activities	Food/fasting requirements[a]
Day 7 morning	Predose		X[b]	Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	
	0000			Administration of venlafaxine 75 mg	
Day 7 evening	1200			Administration of venlafaxine 75 mg	Fast (except for water) for 10 hours before dosing on Day 8
Day 8 morning	Predose		X[b]	Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	Fasting conditions
	0000			Administration of venlafaxine 75 mg	
	0030		X		
	0100		X		
	0200		X		
	0300		X		
	0400		X		Lunch
	0600		X		Snack
	0800		X		
	0900				Dinner

Table 2 Time schedule of assessments for Visit 2

Day	Protocol time (hhmm)	PK blood sampling ticagrelor + AR-C124910XX	PK blood sampling venlafaxine + ODV	Other assessments/activities	Food/fasting requirements[a]
	1000		X		
Day 8 evening	1200		X[c]	Administration of venlafaxine 75 mg	Evening snack Fast (except for water) for 10 hours before dosing on Day 9
Day 9 morning	Predose	X	X[b]	Pulse rate, blood pressure, respiratory rate, and temperature Concomitant medications and AE/SAE questioning	
	0000			Administration of ticagrelor 180 mg and venlafaxine 75 mg	Fasting conditions
	0030	X	X		
	0100	X	X		
	0200	X	X		
	0300	X	X		
	0400	X	X		Lunch
	0600	X	X		Snack
	0800	X	X		
	0900				Dinner
	1000	X	X		
Day 9 evening	1200	X	X[c]	Administration of venlafaxine 75 mg	Evening snack

Table 2 Time schedule of assessments for Visit 2

Day	Protocol time (hhmm)	PK blood sampling ticagrelor + AR-C124910XX	PK blood sampling venlafaxine + ODV	Other assessments/activities	Food/fasting requirements[a]
	1800	X			
Day 10 morning	Predose	X		Pulse rate, blood pressure, respiratory rate, and temperature	
				Concomitant medications and AE/SAE questioning	
	2400			Administration of venlafaxine 75 mg	
Day 10 evening	3600	X		Administration of venlafaxine 75 mg	
Day 11 morning	4800	X		Pulse rate, blood pressure, respiratory rate, and temperature	
				Concomitant medications and AE/SAE questioning	
Day 12				Pulse rate, blood pressure, respiratory rate, and temperature	
				Concomitant medications and AE/SAE questioning	
				Brief physical examination	
				12-lead ECG	
				C-SSRS	
				Clinical chemistry and hematology	
				Urinalysis	
				Discharge from study unit	

[a] Breakfast will be served 1 hour after morning dose intake, except on Days 1, 8, and 9 of the treatment visit, when the subjects will fast at least 10 hours overnight and remain fasting until 4 hours post morning dose. Standardized meals will be served throughout the treatment visit. Water is allowed until 1 hour before, and from 1 hour after, dosing. Water (up to 240 mL) needed for drug administration is allowed.

[b] The predose PK samples on Days 6, 7, 8, and 9 should be taken within 15 minutes prior to dose.

[c] The 12-hour PK samples on Day 8 and Day 9 should be taken within 15 minutes prior to the evening dose of venlafaxine dose.

3.2 Rationale for study design, doses, and control groups

An open label, one-sequence, crossover study design has been chosen in line with Food and Drug Administration (FDA) guidelines for in vivo drug-drug interaction studies (FDA Guidance for Industry, Drug Interaction Studies) and European Medicines Agency (EMA) guideline on the investigation of drug interactions (EMA Guideline on the Investigation of Drug Interactions). Open label is acceptable as no pharmacodynamic endpoints are critical to the assessment of the interaction.

The rationale for choosing healthy volunteers is to investigate the potential interaction of ticagrelor and venlafaxine without adding additional confounding factors, such as disease state or concomitant medications.

Since venlafaxine is given, suicidal ideation evaluation is included in accordance with guidance for studies involving antidepressants (Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials). For details on the rationale for using MINI and C-SSRS, see Section 1.4.

Ticagrelor will be administered as single doses (180 mg) on Day 1 and 9. The dose was selected since it is the recommended loading dose for patients and also the highest approved dose expected to be administered to patients. The PK of ticagrelor appeared linear and the C_{max} and AUC of ticagrelor and AR-C124910XX increased approximately in a dose-proportional manner over the dose range of 30 mg to 1260 mg. Since no time-dependent changes in ticagrelor PK over the course of multiple dosing were observed during its clinical development and mean accumulation ratios at 90 mg twice-daily dosing was approximately 1.8 for ticagrelor and AR-C124910XX, a 180 mg single dose would provide the exposure to ticagrelor and AR-C124910XX higher than those following multiple 90 mg twice-daily dosing. Thus, a single dose of 180 mg not only results in a simple study design, but also maximizes the potential impact of ticagrelor on the interaction drug (venlafaxine).

Venlafaxine will be administrated twice daily between Day 4 and Day 10. The venlafaxine dose will be titrated to enhance tolerability, starting at 37.5 mg twice daily on Day 4 and ending at the target dose of 75 mg twice daily on Day 5. The target dose was selected in accordance with clinical practice. The administration of venlafaxine on Day 10 (ie, 24 hours and 36 hours relative to the last dose of ticagrelor) will maintain the venlafaxine exposure at steady state during the entire ticagrelor PK sampling period. The coadministration is chosen so that ticagrelor and AR-C124910XX (t_{max}: 1.5 hours for ticagrelor and 2.5 hours for AR-C124910XX) and venlafaxine and ODV (t_{max}: 2 hours for venlafaxine and 3 hours for ODV) from the immediate-release tablet would reach their peak plasma concentrations at approximately the same time.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the volunteer screening log, of volunteers who entered prestudy screening.

Each volunteer should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study volunteers should fulfill the following criteria:

1. Provision of signed and dated written informed consent prior to any study specific procedures

2. Healthy male or female volunteers aged 18 to 45 years, inclusive, with suitable veins for cannulations or repeated vein venepuncture

3. Have a body mass index (BMI) between 18 and 30 kg/m^2, inclusive, and weigh at least 50 kg and no more than 100 kg

4. Women of childbearing potential must be using an adequate method of contraception (oral, implanted, or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods [diaphragm, condoms, or spermicides], the practice of true abstinence, or a sole partner who is sterile) to avoid pregnancy throughout the study and for up to 4 weeks after the study in such a manner that the risk of pregnancy is minimized. Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea greater than 12 consecutive months or women on hormone replacement therapy with documented serum follicle stimulating hormone [FSH] level in the laboratory postmenopausal range).

5. Women must have a negative serum pregnancy test at preentry (Visit 1) and on Day -1 (Visit 2).

6. Men participating in the study should also take precautions in line with inclusion criterion number 4 and use barrier contraception, ie, condoms in order to not father a baby while participating in the study and 4 weeks after the last dose of investigational product (IP). Even if a male volunteer has had a vasectomy, his partner should use proper birth control methods.

4.2 Exclusion criteria

Volunteers should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study or influence the results or the volunteer's ability to participate in the study

2. History or presence of gastrointestinal, hepatic, or renal disease or any other conditions known to interfere with absorption, distribution, metabolism, or excretion of drugs

3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IP

4. History of hemophilia, von Willebrand's disease, lupus anticoagulant, or other diseases/syndromes that can either alter or increase the propensity for bleeding

5. A personal history of vascular abnormalities including aneurysms; a personal history of severe hemorrhage, hematemesis, melena, hemoptysis, severe epistaxis, severe thrombocytopenia, intracranial hemorrhage; or rectal bleeding within 1 year prior to the preentry visit (Visit 1); or history suggestive of peptic ulcer disease; or at the discretion of the Investigator

6. History of a clinically significant nontraumatic bleed or clinically significant bleeding risk, as judged by the Investigator

7. History of previous or ongoing psychiatric disease/condition including psychosis, affective disorder, suicidality, anxiety disorder, borderline state, and personality disorder as assessed by using the MINI interview

8. Any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results as judged by the Investigator

9. Any positive result on enrollment for serum hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency virus (HIV)

10. Abnormal vital signs as judged by the Investigator

11. Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG as judged by the Investigator

12. Prolonged QTcF greater than 450 ms or shortened QTcF less than 340 ms or family history of long QT syndrome

13. Known or suspected history of drugs of abuse as judged by the Investigator

14. Smoking more than 7 cigarettes per week or consumption of more than 3 portions of snuff or equivalent per week

15. History of alcohol abuse or excessive intake of alcohol as judged by the Investigator

16. Positive screen for drugs of abuse and/or alcohol breath test at screening or on admission to the clinic (Day -1)

17. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity as judged by the Investigator

18. Excessive intake of caffeine-containing drinks, eg, coffee, tea, caffeine-containing energy drinks, and cola (more than 5 cups of coffee or equivalent per day)

19. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IP

20. Use of any prescribed or nonprescribed medication including antacids, analgesics other than paracetamol/acetaminophen, and herbal remedies during the 2 weeks prior to the first administration of the IP or longer if the medication has a long half-life. Vitamins and minerals must not be taken in doses above the manufacturer's recommendation. Occasional use of paracetamol/acetaminophen (up to 2 g per day) is allowed for minor pains and headache. Over-the-counter (OTC) saline nasal spray is allowed for relief of nasal congestion. Females are allowed to use hormonal contraception.

21. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of admission (Day -1)

22. Food containing poppy seeds within 7 days of admission (Day -1)

23. Plasma donation within 1 month of screening or any blood donation/blood loss greater than 500 mL during the 3 months prior to screening (Visit 1)

24. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 3 months of the first administration of IP in this study. The period of exclusion begins at the time of the last dose in the prior study. Note: volunteers consented and screened but not dosed in this study or a previous Phase I study, are not excluded.

25. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

26. Judgment by the Investigator that the volunteer should not participate in the study if they are considered unlikely to comply with study procedures, restrictions, and requirements.

Procedures for withdrawal of incorrectly enrolled volunteers (see Section 5.3).

5. STUDY CONDUCT

5.1 Restrictions during the study

Volunteers will be required to:

1. Fast (except for water) for at least 10 hours before dosing on Days 1, 8, and 9 of the treatment visit (Visit 2) and remain fasting until 4 hours post morning dose on these days. Water is allowed until 1 hour before and from 1 hour after dosing. Water (up to 240 mL) needed for drug administration is allowed.

2. Eat and drink only the standardized meals and drinks provided (apart from water) during the residential period in the clinic.

3. Abstain from consuming any of the following:

   - Alcohol from 72 hours prior to admission (Day -1), during the residential period, and for 72 hours before the follow-up visit

   - Energy drinks containing taurine or glucoronolactone eg, Red Bull, from 72 hours before admission (Day -1), during the residential period, and for 72 hours before the follow-up visit

   - Caffeine-containing drinks during the residential period apart from any provided as part of a standardized meal. Excessive intake of caffeine should be avoided between discharge from the unit and the study follow-up visit.

   - Poppy seeds found in specialty bread from 7 days prior to admission until Day 12 of the treatment period (Visit 2)

   - Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges and grapefruit from 7 days prior to admission (Day -1) until Day 12 of the treatment period (Visit 2)

   - Tobacco or nicotine-containing products and drugs of abuse from time of consent until after the final medical examination at the study follow-up

   - Any medication (prescribed or OTC products including St. John's Wort, herbal medications, and medicines purchased via the Internet) during the 2 weeks

prior to the first administration of IP (for St. John's Wort 3 weeks) until the follow-up visit, unless the Investigator has given prior consent. Vitamins and minerals in doses below the manufacturer's recommendations are allowed until Day -1 but disallowed during Visit 2. Occasional use of acetaminophen/paracetamol (up to 2 g per day) is allowed for minor pains and headache and OTC saline nasal spray is allowed for relief of nasal congestion. Hormonal contraceptives are allowed for women.

4. Refrain from strenuous physical activity, which is not within the volunteer's normal daily routine, from 72 hours prior to admission (Day -1), during the residential period, and for 72 hours prior to the follow-up visit.

5. Abstain from blood or plasma donation until 3 months after the last dose of IP.

6. Refrain from scheduling surgery, including dental surgery, at any time following the preentry visit (Visit 1), and throughout the study.

7. Stay at the clinic from Day -1 until Day 12. The stay might also be prolonged for safety reasons, if judged necessary by the Investigator.

8. Male volunteers should use a condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child until 4 weeks after the last administration of IP.

9. Women of childbearing potential must be using appropriate birth control during the entire study.

5.2 Volunteer enrollment and initiation of investigational product

The Investigator will:

1. Obtain signed informed consent from the potential volunteer before any study-specific procedures are performed

2. Assign the potential volunteer a unique enrollment number, beginning with 'E0001001'

3. Determine volunteer eligibility. See Sections 4.1 and 4.2.

4. Assign eligible volunteers a unique volunteer number, beginning with '101'

If a volunteer withdraws from participation in the study, then his/her enrollment/volunteer code cannot be reused. Criteria for replacement of volunteers are described in Section 5.8.

5.2.1 Procedures for randomization (not applicable)

This is a nonrandomized study.

5.3 Procedures for handling subjects incorrectly enrolled or initiated on investigational product

Volunteers who fail to meet the inclusion criteria or who meet any of the exclusion criteria should not, under any circumstances, be enrolled. There can be no exceptions to this rule.

Where volunteers who do not meet the selection criteria are incorrectly started on treatment, or where volunteers subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Clinical Pharmacology Alliance (CPA) Physician and the Investigator regarding whether to continue or discontinue the volunteer from treatment.

The AstraZeneca CPA Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the volunteer should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study (not applicable)

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
ticagrelor	90-mg oral, immediate-release tablets	AstraZeneca
venlafaxine	37.5-mg or 75-mg oral, immediate-release tablets	To be decided

Ticagrelor 90 mg will be manufactured in accordance with Good Manufacturing Practice (GMP) and provided by AstraZeneca to the study unit as a bulk.

Commercial bulk packages of venlafaxine will be supplied to the clinic on behalf of AstraZeneca. Details on venlafaxine tablets can be found in the package insert.

will repackage ticagrelor and venlafaxine.

5.5.2 Doses and treatment regimens

Each volunteer will receive the following treatments during the treatment visit (Visit 2):

Day 1: ticagrelor (180 mg single dose)

Day 4: venlafaxine (37.5 mg twice daily)

Days 5, 6, 7, and 8: venlafaxine (75 mg twice daily)

Day 9: ticagrelor (180 mg) coadministered with venlafaxine (75 mg) in the morning + venlafaxine (75 mg) in the evening

Day 10: venlafaxine (75 mg twice daily)

The tablets will be administered orally with 240 mL water. Breakfast will be served 1 hour after morning dose intake, except on Days 1, 8, and 9 of the treatment visit, when the volunteers will fast overnight (at least 10 hours) and remain fasting until 4 hours postdose morning dose.

5.5.3 Labeling

AstraZeneca will provide with dosing labels for ticagrelor and venlafaxine. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

5.5.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label specifies the appropriate storage.

5.6 Concomitant and poststudy treatment(s)

No concomitant medication or therapy will be allowed except for paracetamol/acetaminophen for pain relief and OTC saline nasal spray for relief of nasal congestion. Female volunteers may use hormonal contraceptives. No other OTC drugs are allowed as specified in exclusion criterion number 20 (Section 4.2) and restrictions (Section 5.1). The healthy volunteers must be instructed that no additional medication will be allowed without the prior consent of the Investigator.

Medication, which is considered necessary for the volunteer's safety and well-being, may be given at the discretion of the Investigator during the residential period. When any medication is required, it should be prescribed by the Investigator who should inform the AstraZeneca CPA Physician. Following consultation with the CPA Physician, the Investigator should determine whether or not the volunteer should continue in the study.

5.7 Treatment compliance

The administration of all study drugs (including IP[s]) should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

Compliance will be assured by supervised administration of IP by the study personnel.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the CSP.

The study personnel will account for all study drugs dispensed to and returned from the volunteer.

The study site personnel will account for all study drugs received at the site, unused study drugs, and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation from the study

Volunteers may be discontinued from IP and assessments at any time. Specific reasons for discontinuing a volunteer from this study are:

- Voluntary discontinuation by the volunteers, who are at any time free to discontinue his or her participation in the study without prejudice to further treatment
- Safety reasons as judged by the Investigator and/or AstraZeneca
- Severe noncompliance to the CSP as judged by the Investigator and/or AstraZeneca
- Incorrect enrollment (ie, the volunteer does not meet the required inclusion or exclusion criteria) or if the volunteer is not allocated study drug as described in the CSP.
- The volunteer is lost to follow-up

Volunteers who are withdrawn from the study by the Investigator due to AEs after dosing will not be replaced. Volunteers who withdraw for any reason before dosing or for reasons other than AEs after dosing may be replaced following a discussion between the Investigator and AstraZeneca.

5.8.1 Procedures for discontinuation of a subject from the study

Volunteers are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the Investigator. The follow-up procedures listed on Table 1 will be preformed, if possible. Adverse events will be followed up (See Sections 6.3.3 and 6.3.4).

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of these assessments are detailed in Table 1 and Table 2.

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1. Adverse events

2. Blood pressure, pulse rate, respiratory rate, and temperature

3. Pharmacokinetic blood sample

Predose assessments may be performed up to 1 hour prior to dosing except for the predose venlafaxine and ODV PK samples on Days 6, 7, 8, 9, and the venlafaxine and ODV 12 hours postdose PK samples on Days 8 and 9 (ie, samples predose evening dose of venlafaxine), which should be taken within 15 minutes prior to dosing. Acceptable deviations from scheduled assessment times of PK samples from 0.5 hour up to and including 48 hours will be ±5% or ±15 minute, whichever is the shortest. Acceptable deviations for postdose assessments other than PK at 24 and 48 hours postdose (Days 2, 3, 10, and 11) will be ±60 minute.

6.1 Recording of data

The Investigator ensures that all data are recorded in the eCRFs as specified in this CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.2 Data collection and enrollment and follow-up

6.2.1 Enrollment procedures

Each volunteer will undergo screening at Visit 1 within 4 weeks of Day -1 of Visit 2, to confirm eligibility. This will consist of the following:

- Obtaining written informed consent prior to conducting any study-specific procedures

- Obtaining optional informed consent for biomarker samples (may also be done on Day -1)

- Allocation of an enrollment code

- Review of inclusion and exclusion criteria with the volunteer
- Recording of demographic data (date of birth, sex, race, and ethnicity)
- Recording of weight and height and calculation of BMI
- Recording of significant medical and surgical history
- A complete physical examination (Section 6.3.6)
- Blood sampling for clinical chemistry and hematology (Section 6.3.5)
- Blood sampling to test for HBsAg, HCV antibody, and HIV (Section 6.3.5)
- Serum sampling for pregnancy test (women only) (Section 6.3.5)
- Urine sample for drugs-of-abuse and urinalsyis (Section 6.3.5)
- Vital signs: blood pressure, pulse rate, respiratory rate, and temperature after 10 minutes supine rest (Section 6.3.8.1)
- Recording of a resting 12-lead ECG after 10 minutes supine rest (Section 6.3.7.1)
- Review of concomitant medications
- Alcohol breath test
- Start of serious AE (SAE) recording (Section 6.3.3)
- Mini-international neuropsychiatric interview (Section 6.3.9)

6.2.2 Follow-up procedures

Volunteers will return to the clinic for a follow-up visit 7 to 10 days after discharge (Visit 2). The follow-up assessments will include a complete physical examination, measurements of vital signs (blood pressure, pulse rate, respiratory rate, and temperature), a recording of a resting 12-lead ECG, blood sampling for clinical chemistry and hematology analyses, serum pregnancy test (women only), urine sampling for urinalysis, and AE and concomitant medications questioning.

6.3 Safety

The Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea and chest pain), signs (eg, tachycardia and enlarged liver), or the abnormal results of an investigation (eg, laboratory findings and ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and nonserious AEs.

6.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, or follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the volunteer or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix B to the CSP.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from administration of the first dose of IP (Day 1), throughout the study, including the follow-up visit.

Serious AEs will be recorded from the time of informed consent, throughout the study, including the follow-up visit.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the volunteer's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any volunteer with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Intensity, rating according to the following scale:
  - Mild (awareness of sign of symptom, but easily tolerated)
  - Moderate (discomfort sufficient to cause interference with normal activities)
  - Severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality rating against the IP (ticagrelor and/or venlafaxine) (yes or no)
- Action taken with regard to IP
- Whether the AE caused volunteer's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The Investigator will assess causal relationship between IP (ticagrelor and/or venlafaxine) and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'.

For SAEs causal relationship will also be assessed for study procedures. Note, that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the volunteer or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from CSP-mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR). Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs, or ECG should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel must inform appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for ticagrelor and in the package insert for venlafaxine.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in Table 1. The date and time of collection of all laboratory tests will be recorded in the appropriate eCRF.

The safety laboratory variables are shown in Table 3.

Table 3 Safety laboratory variables

Clinical chemistry	**Hematology**
S-Alkaline phosphatase	B-Hemoglobin
S-Aspartate aminotransferase	B-Hematocrit
S-Alanine aminotransferase	B-Absolute leukocyte differential count
S-Total Bilirubin	B-Platelet count
S-Uric acid	B-Erythrocytes (Red blood cells)
S-Glucose	B-Total white blood cells
S-Albumin	**Urinalysis**
S-Calcium, total	U-Glucose
S-Creatinine	U-Hemoglobin
S-Potassium	U-Protein
S-FSH[a]	U-Specific gravity
S-Sodium	**Urine drug screen**[d]
S-Pregnancy test[b]	amphetamines
S-Total protein	benzodiazepines
S-Blood urea nitrogen	cannabinoids
S-Gamma-glutamyl transpeptidase	cocaine
Serology[c]	opiates
HBsAg	
HCV antibodies	
HIV antibodies	

B blood; HBsAG hepatitis B surface antigen; HCV hepatitis C virus; P plasma; S serum; U urine

[a] At the preentry visit (Visit 1), postmenopausal women only.

[b] At the preentry visit (Visit 1), on Day -1, and at follow-up (Visit 3), women only.

[c] At the preentry visit (Visit 1).

[d] At the preentry visit (Visit 1) and Day -1.

A screen for HBsAg, HCV, and HIV will be done at the preentry visit (Visit 1). Screen for drugs of abuse (amphetamines, benzodiazepines, cannabinoids, cocaine, and opiates) will be done at the preentry visit (Visit 1) and on Day -1 of the treatment visit (Visit 2). Pregnancy test (women) will be done at the preentry visit, Day -1, and at follow-up. If a volunteer tests positive to any of these tests he/she will be excluded from the study.

The safety laboratory samples will be analyzed using routine methods at

Follow-up testing for abnormal laboratory results will be performed by
according to instructions on the laboratory reports from the central laboratory or according to local practice.

For blood volume see Section 7.1.

6.3.6 Physical examination

A complete physical examination will be performed at the preentry visit and follow-up (Visit 1 and Visit 3, respectively) and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

A brief physical examination will be performed Day -1 and before discharge Day 12 and include an assessment of the following: general appearance, cardiovascular, chest, abdomen, and skin. Results will be recorded as an overall normal or abnormal with a listing of abnormalities.

6.3.7 ECG

6.3.7.1 Resting 12-lead ECG

Standard 12-lead ECGs will be recorded after a 10-minute supine rest at the preentry visit (Visit 1), on Day-1 of the treatment visit (Visit 2), before discharge, and at the follow-up visit (Table 1). All ECGs will be evaluated by the Investigator. Date and time of measurement and the Investigator's overall evaluation (normal or abnormal; if abnormal, clinically significant, or not clinically significant) will be recorded in the eCRF. Additional ECG assessments may be performed at the discretion of the Investigator.

For reporting of AEs based on examinations and tests, see Section 6.3.3.

6.3.8 Vital signs

6.3.8.1 Pulse rate, blood pressure, respiratory rate, and temperature

Supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature will be measured using noninvasive equipment after the volunteer has been at rest for 10 minutes. Measurements will be done at Visit 1, every day of the treatment visit (Visit 2, predose those days when study drug is given), and at the follow-up visit (Visit 3) as outlined in Table 1.

6.3.9 Other safety assessments

A MINI will be performed at enrollment (Visit 1) for assessment of psychiatric history or hereditary liability for psychotic disorder. For assessment of suicidal ideation, C-SSRS will be used on Day -1 and on Day 12 of Visit 2.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples for determination of ticagrelor and its metabolite AR-C124910XX (2 mL) and venlafaxine and its metabolite ODV (2 mL) in plasma will be taken at the times presented in Table 1 and Table 2.

The exact blood sampling date and time will be recorded in the eCRF. Samples will be collected, labeled, stored, and shipped as detailed in Laboratory Manual. The samples will be analyzed within the time frame after collection for which the stability in the samples has been validated and found acceptable. Samples stored longer will not be reported.

For total blood volume to be drawn from each volunteer, see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analyzed by on behalf of AstraZeneca, using appropriate bioanalytical methods which will be detailed in the Bioanalytical Report appended to the CSR. The lower limits of quantification (LLOQ) of ticagrelor and its metabolite in plasma are 1 ng/mL and 2.5 ng/mL, respectively. The LLOQ of venlafaxine and its metabolite ODV are aimed at 0.1 ng/mL, respectively.

6.5 Collection of biomarker samples

Study participants not on any concomitant medications will be offered the option to participate in biomarker research. After giving written consent for optional biomarker research, a blood or urine sample will be collected in accordance with the inclusion criteria and study schedule.

The blood or urine sample must be collected before administration of any IP, or study-specific noninvestigational products, according to the Table 1. Only 1 sample (blood or urine) should be collected per volunteer for biomarker research during the study. A 10-mL blood sample, or a 10-mL urine sample, will be collected. Samples will be collected, labeled, stored, and shipped as detailed in the Safety Biomarker Laboratory Manual.

Some of the data sets (eg, age, sex, race, body weight, height, BMI, and fasting state) from the main study may be duplicated within AstraZeneca for exploratory analyses in combination with the optional biomarker data. This information will be provided to AstraZeneca with the biomarker samples shipment. Neither the volunteers' names nor any other personal identifiers will be part of this data set. Optional biomarker data will not be reported in the CSR.

For total blood volume to be drawn from each volunteer, see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each volunteer in this study is as follows:

Table 4 Volume of blood to be drawn from each subject

Assessment[a]		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3.5	4	14
	Hematology	4	4	16
	Serology	3.5	1	3.5
Pharmacokinetics	Ticagrelor + AR-C124910XX	2	28	56
	Venlafaxine + ODV	2	22	44
Total				133.5

[a] If using an indwelling catheter, 2.0 mL of blood will be removed prior to sample collection.

The number of samples taken, as well as the volume required for each analysis, may be changed during the study (ie, if additional samples are drawn for repeated safety assessments). However, the maximum volume to be drawn from each volunteer will not exceed 450 mL, ie, the same volume as would be drawn during a regular blood donation.

An optional 10 mL biomarker blood sample may also be taken as described in Section 6.5.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Safety samples

Safety samples will be disposed after analysis.

7.2.2 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalized.

7.2.3 Biomarker samples

Biological samples for biomarker research can be retained on behalf of AstraZeneca for a maximum of 25 years following the last volunteer's last visit in the study. The results from future analysis will not be reported in the CSR but separately in a Scientific Report.

7.3 Labeling and shipment of biohazard samples

The Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the volunteer unless agreed with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The Investigator keeps full traceability of collected biological samples from the volunteers while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a volunteer withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the volunteer is withdrawn from further study participation. If a volunteer withdraws consent to the use of the optional biomarker sample, then the volunteer may remain in the study.

The Investigator:

- Ensures volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that volunteer, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented, and the signed document returned to the study site

- Ensures that the volunteer and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final study CSP, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the volunteers. The Investigator will ensure the distribution of these documents to the applicable IRB and to the clinic staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any volunteer into the study.

The IRB should approve all advertising used to recruit volunteers for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the IRB annually.

Before enrollment of any volunteer into the study, the final CSP, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, IRBs, and the Investigator with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

8.4 Informed consent

The Investigator will:

- Ensure each volunteer is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each volunteer is notified that they are free to discontinue from the study at any time
- Ensure that each volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each volunteer provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the volunteer
- Ensure that any incentives for volunteers who participate in the study, as well as any provisions for volunteers harmed as a consequence of study participation, are described in the Informed Consent Form that is approved by an IRB

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a study CSP amendment and where required in a new version of the study CSP (Revised CSP).

The amendment is to be approved by the relevant IRB and, if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised CSPs.

AstraZeneca will distribute any subsequent amendments and new versions of the CSP to the Investigator. For distribution to the IRB see Section 8.3.

If a CSP amendment requires a change to a center's Informed Consent Form, AstraZeneca and the center's IRB are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the CSP, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first volunteer is entered into the study, the Investigator or delegate will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures as appropriate.

9.2 Monitoring of the study

During the study, monitoring will be conducted on behalf of AstraZeneca. The monitoring activities will include regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the CSP, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability is being performed
- Perform source data verification (a comparison of the data in the eCRFs with the volunteer's source data documents when other than eCRF and other records relevant to the study) including verification of informed consent of participating volunteers. This will require direct access to all original records for each volunteer (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the volunteer's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the volunteer

The monitor will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct. Monitoring will be conducted in agreement with the Phase I Global CPA monitoring plan.

9.2.1 Source data

Refer to the Source Data Identification and Location Log for location of source data (eCRF or other source documents).

9.3 Study agreements

should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of volunteers and in all other respects, not relating to study conduct or treatment of volunteers, the terms of the CSA shall prevail.

Agreements between AstraZeneca and should be in place before any study-related procedures can take place or volunteers are enrolled.

9.3.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.4 Study timetable and end of study

The end of the study is defined as 'the last visit of the last volunteer undergoing the study'.

The study is expected to start in and to end by .

The study may be terminated if the study procedures are not being performed according to GCP or if recruitment is slow. AstraZeneca may also terminate the study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

10. DATA MANAGEMENT

Data management will be performed by

The data in this study will be collected using eCRFs. Safety lab data will be transferred electronically. Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Electronic CRF operations follow Standard Operating Procedures and data is processed in validated CFR 21 Part 11 compliant systems.

Screening failures (volunteers who signed consent to take part in the study but were not allocated a volunteer number) will not be entered into the clinical study database.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by

When all data have been coded and validated, a clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

Where appropriate, change-from-baseline variables will be calculated for the continuous variables as the post-treatment value minus the value at baseline.

Baseline will be defined as follows:

- Clinical chemistry and hematology: Day -1
- Vital signs: Day 1, predose

If a volunteer is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline evaluation exists then the baseline value will be treated as missing.

11.1.1 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuation of IP due to AEs (DAEs). Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the CPA Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

11.2 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at
Pharmacokinetic analysis will be conducted according to Standard Operating Procedures and Work Instructions for PK analysis.

The actual sampling times will be used in the PK calculations except for predose for which the time will be set to zero. Pharmacokinetic parameters will be determined using standard noncompartmental methods in WinNonlin Professional 5.2, or higher
Graphics may be prepared with WinNonlin Professional Version 5.2, or higher, SigmaPlot version 9.0 or higher, or SAS® Version 9.2, or higher. The following PK parameters will be determined:

Primary PK parameters
Venlafaxine and ODV on Days 8 and 9

- Area under the plasma concentration-time curve during a dosing interval (AUC_τ) calculated using linear-up/log-down methodology
- Observed maximum plasma concentration (C_{max})

Ticagrelor and AR-C124910XX on Day 1 (after single-dose administration of ticagrelor) and Day 9 (after concomitant administration of venlafaxine and ticagrelor)

- Area under the plasma concentration-time curve from zero to infinity (AUC), calculated by the area under the plasma-concentration time curve from zero to the time of the last quantifiable plasma concentration (calculated using linear-up/log-down methodology) + C_{last}/λ_z, where C_{last} is the last observed plasma concentration and λ_z is the terminal rate constant estimated from individual linear regression of the terminal part of the log plasma concentration-time curve
- C_{max}

Secondary PK parameters
Venlafaxine and ODV on Days 8 and 9

- Time to C_{max} (t_{max})

Ticagrelor and AR-C124910XX on Days 1 and 9

- t_{max}
- terminal half-life ($t_{½\lambda z}$)

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

$\lambda_{z, lower}$ $\lambda_{z, upper}$	The time interval of the log-linear regression used to determine $t_{½\lambda z}$
$t_{½\lambda z, n}$	Number of data points included in the log-linear regression analysis
Rsq	The coefficient of determination, R-Squared (goodness-of-fit statistic for calculation of λ_z). If Rsq is <0.80, then λ_z and related parameters will be listed but not included in summaries and statistical analyses.
%AUCex	Percentage of AUC obtained by extrapolation. If the extrapolated area is greater than 20% of AUC, then AUC and related parameters will be listed but not included in summaries and statistical analyses.

Additional PK parameters may be calculated if deemed appropriate.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Safety analysis set

All volunteers who receive at least 1 administration of IP will be included in the analysis of safety.

12.1.2 PK analysis set

The PK analysis set will be a subset of the safety analysis set and will include only volunteers who have at least 1 postdose plasma concentration measurement without important CSP deviations or violations thought to significantly affect the PK (eg, volunteer vomited at or before 2 times median t_{max}; wrong dose administered; prohibited concomitant medication, etc). A strategy for dealing with data affected by CSP violations and deviations will be specified prior to the analysis by pharmacokineticist and statistician.

Presentation of PK data will be handled as follows:

For all volunteers with available concentration data:

- Plasma concentration data of venlafaxine, ODV, ticagrelor, and AR-C124910XX will be listed for all volunteers for whom data are available.
- The PK parameters of venlafaxine, ODV, ticagrelor, and AR-C124910XX will be calculated and listed for all volunteers for whom sufficient data are available to perform such calculations.

For volunteers in the PK analysis set:

- Summaries of plasma concentration data, including figures such as mean plasma concentration-time profiles, will include all volunteers in the PK analysis set.

- Summaries of PK parameters, including line plots comparing PK parameters between periods, will include all volunteers in PK analysis set.

Data from volunteers excluded from the PK analysis set will be included in the data listings, but not in the summaries and statistical analyses. If volunteers have been excluded from the statistical analysis due to deviations, then additional summaries and statistical analyses including these volunteers may be performed, if appropriate.

12.2 Methods of statistical analyses

12.2.1 General principles

The statistical analyses will be performed using SAS®, version 9.2 or later.

Standard Operating Procedures and Work Instructions will be used as the default methodology if not otherwise specified.

Missing data will result in a reduced sample size for that parameter. No action will be taken to handle missing data.

No adjustment for multiplicity will be made.

A volunteer who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

All data will be included in the data listings. Any data excluded from the summaries and statistical analyses will be flagged accordingly.

12.2.2 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) in total. Categorical variables will be summarized in frequency tables (frequency and proportion) in total.

12.2.3 Safety and tolerability

All safety data will be listed in volunteer listings.

Continuous variables (hematology, clinical chemistry, and vital signs) will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) by treatment and/or each scheduled assessment point, both as absolute values, and as change from baseline. Categorical variables (urinalysis and ECG interpretation) will be summarized in frequency tables (frequency and proportion) by scheduled assessment point. Shift plots showing maximum values postdose versus baseline will be presented for the continuous safety variables. Laboratory values and vital signs outside extended reference limits are marked high

(H) and low (L), where appropriate. For laboratory data and vital signs assessments all repeat values will be included in the data listings. For calculation of descriptive statistics the following rules will be applied: For measurement time points before first dose the last valid repeat value will be used. For measurement time points after first dose the first valid value will be used. Retake of a predose value will not be used if taken after dose. Laboratory values beneath the detectable limit (<X) will be replaced by X when summarizing mean, SD, etc.

Abnormalities found in physical examinations should be listed.

All AEs will be collected for each volunteer from the time of first administration of IP (Day 1, Visit 2) throughout the study, including follow-up (Visit 3). Adverse events will be summarized by number of events and volunteer incidence as follows:

- ticagrelor: time of dosing of ticagrelor until time of first dosing of venlafaxine
- venlafaxine: time of first dosing of venlafaxine until time of dosing of ticagrelor+venlafaxine
- ticagrelor+venlafaxine: time of dosing of ticagrelor+venlafaxine until discharge
- follow-up: time from discharge until and including the follow-up visit

Adverse events will be summarized by preferred term and system organ class according to the latest version of the MedDRA. The number of volunteers who had any AEs, SAEs, DAEs, OAEs, AEs with severe intensity and AEs judged causally related to IP by the Investigator will be summarized. Any SAEs and DAEs will be listed separately.

Results from the C-SSRS will be listed in volunteer listings.

12.2.4 Pharmacokinetics

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Plasma concentrations and PK parameters will be summarized using appropriate descriptive statistics (ie, n, mean, SD, geometric mean, geometric coefficient of variation [CV], minimum, median, and maximum) by analyte and treatment. The geometric mean is calculated as the exponential of the mean calculated from data on a log scale. The CV is calculated as:

$$100 \cdot \sqrt{\left(\exp\left(s^2\right) - 1\right)}$$

where s is the SD of log transformed values.

Plasma concentrations will be reported with the same precision as the source data. For descriptive statistics, concentrations below the LLOQ will be handled as follows:

- At a time point where less than or equal to 50% of the values are below LLOQ (BLQ), all BLQ values will be set to LLOQ and all descriptive statistics will be calculated.

- At a time point where more than 50% of the values are BLQ, the mean, SD, geometric mean, and CV% will be set to not determined (ND). The maximum value will be reported from the individual data and the minimum and median will be set to BLQ.

- If all values are below BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, minimum, median, and maximum.

- The number of BLQ values (n below LLOQ) will be reported for each time point.

Pharmacokinetic parameters will be rounded for reporting purposes in the summary tables and volunteer listings, as per Standard Operating Procedures.

Graphical presentations will include mean (±SD) plasma concentration-time curves by treatment and individual volunteer plasma concentration-time curves over the PK sampling times on Days 1 to 3 and Days 9 to 11 for ticagrelor and AR-C124910XX and on Days 8 and 9 for venlafaxine and ODV. Individual and mean (±SD) plasma concentration-time curves of the predose concentrations of venlafaxine and ODV on Days 6, 7, 8, and 9 will also be presented. The PK parameters will be presented graphically by line plots comparing individual and mean PK parameters between treatments.

The statistical analysis for venlafaxine PK will be C_{max} and AUC_{τ} of venlafaxine and ODV estimated on Day 8 and Day 9. The PK parameters will be log-transformed (natural log) prior to analysis. The log-transformed C_{max} and AUC_{τ} data of venlafaxine will be 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 will be used to construct 90% CIs for the difference in means on the log scale between the 2 treatments. The treatment effect and its corresponding 90% CIs will be retransformed using anti-logarithms to its original scale and reported as ratio of treatments (venlafaxine + ticagrelor/venlafaxine alone) in percent. Geometric mean C_{max} and AUC_{τ} will also be presented by treatment along with the corresponding 2-sided 95% CIs. If the 90% CIs for the treatment ratio lies entirely within the prespecified range of 80% to 125% then it will be concluded that ticagrelor has no effect on the PK of venlafaxine. The ODV PK parameters will also be analyzed using the mixed effects model described above.

The statistical analysis for ticagrelor PK will be C_{max} and AUC of ticagrelor and AR-C124910XX estimated on Day 1 and Day 9. These parameters will be analyzed using the mixed effects model described above. The treatment effect and its corresponding 90% CIs obtained from the mixed effects model will be retransformed using anti-logarithms to its original scale and reported as ratio of treatments in percent. If the 90% CIs lies entirely within the prespecified range of 80.00% to 125.00% then it will be concluded that venlafaxine has no effect on the PK of ticagrelor.

12.3 Determination of sample size

In a previously published study, 18 healthy volunteers received oral venlafaxine twice daily (75 mg twice daily) (Troy et al 1995). The intervolunteer CV for C_{max} and $AUC_{(0-24)}$ for these healthy volunteers were estimated to be 28.6% and 38.5%, respectively. A sample size of 18 volunteers would provide approximately 90% power that the 90% CI for the ratios of interest [C_{max} or $AUC_{(0-24)}$] of venlafaxine to that of venlafaxine administered with ticagrelor would be completely contained within the prespecified equivalence range of 0.80 to 1.25. These calculations were based on a 2 one-sided testing procedure at an alpha level of 0.05, assuming a true ratio of 1.0. No adjustments for preplanned multiple comparisons were made.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4.**

In the case of a medical emergency the Investigator may contact the AstraZeneca CPA Physician. If the CPA Physician is not available, the CPA program director should be contacted at AstraZeneca Research and Development.

Name	Role in the study	Address & telephone number
	CPA Program Director	
	CPA Physician	
SAE reporting	24 hour emergency cover at central R&D site.	
	Investigator	
	Project Manager	

13.2 Overdose

There is currently no known antidote to reverse the effects of ticagrelor and ticagrelor is not expected to be dialyzable. Treatment of an overdose of ticagrelor should follow local standard medical practice. Bleeding is the expected pharmacologic effect of excessive ticagrelor dosing. If bleeding occurs, appropriate supportive measures should be taken.

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnea and ventricular pauses.

In the event of overdose, observation for these potential adverse effects should occur and ECG monitoring should be considered.

No specific antidotes for venlafaxine are known. Treatment of a venlafaxine overdose should consist of those general measures employed in the management of overdose with any antidepressant. Ensure there are adequate airway, oxygenation, and ventilation. Cardiac rhythm and vital signs should be monitored. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel must inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAEs, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a volunteer becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome

of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the volunteer was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform appropriate AstraZeneca representatives **within 1 day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, (see Section 6.3.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Male volunteers should refrain from fathering a child or donating sperm during the study and 4 weeks following the last dose of IP.

Pregnancy of a volunteer's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should, if possible, be followed up and documented.

14. LIST OF REFERENCES

EMA Guideline on the Investigation of Drug Interactions
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090112.pdf.

FDA Guidance for Industry, Drug Interaction Studies
Study Design, Data Analysis, and Implications for Dosing and Labeling (2006):
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf.

Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf.

Troy et al 1995
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Clinical Study Protocol Appendix B

Drug Substance Ticagrelor

Study Code D5130C00073

Edition Number 1.0

Date

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance Ticagrelor

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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Ticagrelor
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Appendix D
Pharmacogenetics Research (Not Applicable)

Clinical Study Protocol Appendix E

Drug Substance Ticagrelor

Study Code D5130C00073

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Appendix E
Optional Biomarker Research Samples

OPTIONAL BIOMARKER RESEARCH SYNOPSIS

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

The research activities described in this appendix (including the collection and storage of body fluid samples), are optional for study centres as well as for individual healthy subjects. These research activities will hereafter be referred to as "this research." The Clinical Study Protocol to which this document is appended will be referred to as "the main study." The term "sample" means:

Plasma, serum or urine

This research will be performed only after the appropriate Institutional Review Board has approved it. Informed consent for this research will be obtained using a separate Informed Consent Form from that used for the main study. All sections of the Clinical Study Protocol for the main study also apply to this research.

Study center(s) and number of subjects who may be enrolled in this biomarker research

It is the intent of AstraZeneca to collect serum, plasma or urine samples from all Clinical Pharmacology studies conducted by the Clinical Pharmacology Alliance (CPA) to further the goal of improving biochemical markers that can be used to monitor or predict drug-induced organ damage. The goal will be to collect approximately 3000 such samples.

Objectives

Objective	Outcome variables
To analyze biological samples (eg, human plasma) for circulating biomarkers from consenting subjects prior to drug treatment.	

Study design

It is proposed to collect a single serum, plasma or urine sample from each subject enrolled in the study as optional samples for biomarker analysis. The type of sample to be collected will be determined at the outset of the trial. Provision of these samples for analysis will be optional for all subjects entering the study, and acceptance of this procedure will not be a requirement for participation in the main study.

The samples and data for optional biomarker analysis in this research will be coded. Each sample will be labelled with the study number and subject enrolment number (E-code). Only the Investigator will be able to link the sample to the individual subject. The samples and data will not be labelled with personal details.

Target population

All consenting subjects participating in the main study.

Statistical methods

The number of subjects who will agree to participate in this research is unknown. It is therefore not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ALT	Alanine aminotransferase
CPA	Clinical Pharmacology Alliance
CSR	Clinical Study Report
eCRF	Electronic Case Report Form

1. BACKGROUND

As part of collaborative efforts with other pharmaceutical companies, diagnostic companies and academic institutions AstraZeneca is collecting samples to perform general research for variations in "safety" biomarker profiles. These biomarkers may be derived from proteins and/or metabolites. By using this information, the aim is to better understand drug effect on major organs in the human body and how circulating biomarkers can be used to better monitor organ function and thus improve safety of drugs.

To achieve this goal, a systematic collection of biological samples (urine, serum and/or blood plasma) will be undertaken as specified where appropriate.

1.1 Rationale for research

AstraZeneca may perform optional sampling determination for biomarker research in some of the studies for the clinical programs of new chemical entities under development. The objective of this research is to explore normal variations in biomarkers (protein or small molecule based) that occur in individuals enrolled in this trial **prior to drug treatment**. In particular, developing better biochemical markers to help assess potential deleterious drug is the primary goal of this research. A key aspect to understanding how to use these new markers is to assess the normal variation in these markers in healthy subjects so we will appropriately interpret how changes in these new biochemical markers are affected by drug treatment. Understanding this normal variation is part of a process known as qualification which attempts to establish sufficient evidence of changes in these biomarkers in relationship to organ damage that they are suitable for monitoring safety for clinical trials. Other recent studies have suggested that using proteomic and metabolomic platforms may help identify other new predictive biomarkers that help explain alanine aminotransferase (ALT) elevation (Andersson et al 2009).

The ability to acquire appropriate consent to collect biological samples to establish an archive and allow future meta-analysis of data derived from a number of studies is of the utmost importance. This research forms part of this strategy.

The benefits of being able to explore associations between biomarker variations and clinical outcomes are potentially many including the possibility to identify subjects early who may be at risk of adverse drug reaction or to explain potential adverse reactions related to drug exposure.

2. RESEARCH OBJECTIVES

Biomarker technologies enable the measurement of many different molecules, including proteins and metabolites, within a sample. The objective of this research is to determine if correlations exist between traditional biomarkers used to monitor organ function (such as

ALT and bilirubin for liver) and new biomarkers that may be more sensitive and/or specific indicators of drug induced organ damage.

2.1 Research plan

The subject will be asked to participate in this optional biomarker research during their enrollment or screening visit. If the subject agrees to participate the following samples will be requested:

A single 10 mL blood sample or a single urine sample of up to 15 mL.

2.2 Selection of optional biomarker research population

2.2.1 Study selection record

All subjects who take part in the study will be asked to participate in this optional biomarker research. Participation is voluntary and if a subject declines to participate in this optional biomarker research they will not be excluded from any aspect of the main study.

2.2.2 Withdrawal of healthy volunteers from this optional biomarker research

2.2.2.1 Criteria for withdrawal

Specific reasons for withdrawing a subject from this optional biomarker research are:

- Withdrawal of consent for optional biomarker research. Subjects may withdraw from this optional biomarker research at any time, independent of any decision concerning participation in other aspects of the main study. Subject withdrawal will not prejudice further treatment.

2.2.2.2 Procedures for withdrawal

Subjects who withdraw from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this optional biomarker research. It must be established whether the subject:

- Agrees to the optional biomarker samples and any preparations derived from the sample being kept for research in the future

- Withdraws consent for the samples to be kept for optional biomarker research in the future and wishes the samples to be destroyed. Destruction of the samples (or the preparations derived from the samples) will only be possible so long as the particular samples are traceable. In the event that optional biomarker research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The Principal Investigator is responsible for providing written notification to AstraZeneca of any subject who has withdrawn consent for the use of the sample taken for optional biomarker

research. AstraZeneca will provide written confirmation to the Investigator of the actions taken with the sample, which must be filed in the Investigator's Study File.

3. MEASUREMENTS AND CO-VARIABLES

3.1 Summary of objectives and analysis

The purpose of this research is to generate data that will help interpret results from future clinical trials. The results of this research will not form part of the Clinical Study Report (CSR) for the main study. The results may be pooled with data from other studies generate hypotheses to be tested in future studies.

3.2 Collection of samples for optional biomarker research

AstraZeneca or its designee will act as the central laboratory for sample logistics. Details of sample collection, processing, shipping, and storage will be described in the Laboratory Manual.

The samples and data for analysis in this research will be coded and will not be labelled with any personal details. Each sample will be identified with the study number and subject enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled. However, only the Investigator will be able to link the biomarker sample to the individual subject.

The coded samples may be made available to groups or organizations working with AstraZeneca on this research or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give samples, sample derivatives or data derived from the samples to any other parties, except as required by law.

3.2.1 Biomarker analysis

The precise details of the biomarker analysis will be established by AstraZeneca scientists. However, in some cases, samples may be sent to commercial or academic partners for specialized analyses.

In addition to studies to identify new candidate biomarkers, samples may also be used to measure existing candidate biomarkers by methods that will depend on the specific biomarker.

4. MANAGEMENT OF RESEARCH DATA

Some of the dataset from the main study may be duplicated within AstraZeneca for exploratory analyses in combination with the optional biomarker data. Neither the subject's name nor any other personal identifiers will be part of this dataset. Optional biomarker data will not be reported in the CSR. Only the date the subject gave consent to participation in the

research and the date and time the biological sample(s) (if applicable) was taken from the subject will be recorded in the electronic Case Report Form (eCRF) and database.

AstraZeneca will not provide optional biomarker research results to subjects, their family members, any insurance company, an employer, Investigator, general physician or any other third party, unless required to do so by law. The subject's samples will not be used for any purpose other than optional biomarker research.

Individual subjects will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the subject's name nor any other personal identifiers will appear in any publication or report.

5. STATISTICAL METHODS

One of the primary goals of these exploratory studies is to establish a large sample cohort that will help us understand the variability of new biomarkers in a general population. The samples that compose this cohort will come from multiple different studies and a statistical analysis plan will be prepared for analyses of each new biomarker. This analysis will help us determine how many subjects will be needed for future trials. However, neither the results of this biomarker work nor the statistical analysis will be included in CSR for the trials from which these samples have been collected.

5.1 Monitoring

During the study, monitors will have regular contacts with the investigational centers. One of the purposes of these visits will be to perform source verification of the informed consent of the participating subject and to ensure that the investigational team are adhering to the specific requirements of this optional biomarker research.

5.2 Training of staff

Before the first subject is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of samples and optional biomarker research with a representative of AstraZeneca. The requirements for the collections of the subject's sample will also be made clear.

5.3 Changes to the protocol

Any changes to the optional biomarker research will comply with the principles described in Section 8.5 of the main body of the Clinical Study Protocol.

5.4 Study agreements

The Principal Investigator at each study center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this research. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the

Clinical Study Protocol shall prevail. Specific reference to requirements relating to this optional biomarker research will be included in the study agreement(s).

6. ETHICS

6.1 Ethics review

In addition to documenting Institutional Review Board approval of the main study, approval must be obtained for this optional biomarker research and the associated informed consent from the relevant Institutional Review Board. It must be clearly stated in the approval that this optional biomarker research is approved. The Investigator must submit written approval to AstraZeneca before any subject participates in this optional biomarker research.

6.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

6.3 Informed consent

The biomarker component of this research is optional and the subject may participate in other components of the study without participating in the optional biomarker component. To participate in the optional biomarker component of the study, the subject must sign and date both the consent form for the main study and the consent form for the optional biomarker component of the study. Copies of both signed and dated consent forms must be given to the subject and the originals filed at the study center in the Investigator's Study File. The Principal Investigator is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the optional biomarker aspect of the study at any time.

6.4 Volunteer data protection

All data protection and confidentiality principles, described in the main Clinical Study Protocol, are applicable to this optional biomarker research.

Due to the exploratory nature of this optional biomarker research, there will be no routine communication of results to subjects. AstraZeneca will not provide individual results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

7. REFERENCES

Andersson et al 2009
Andersson U, Lindberg J, Wang S, Balasubramanian R, Marcusson-Ståhl M, Hannula M. A systems biology approach to understanding elevated serum alanine transaminase levels in a clinical trial with ximelagatran. Biomarkers. 2009 Sep 25. [Epub ahead of print]