Clinical Study Protocol

Drug Substance	Esomeprazole 20 mg/ASA 81 mg
Study Code	D961FC00010
Edition Number	1
Date	

An Open-label, Randomized, Single-center, 2-way Cross-over Interaction Study, Evaluating the Effect of Esomeprazole 20 mg/Acetylsalicylic acid 81 mg on the Pharmacodynamics and the Pharmacokinetics of Clopidogrel on Days 1 and 9 in Healthy Volunteers

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

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

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

An Open-label, Randomized, Single-center, 2-way Cross-over Interaction Study, Evaluating the Effect of Esomeprazole 20 mg/Acetylsalicylic acid 81 mg on the Pharmacodynamics and the Pharmacokinetics of Clopidogrel on Days 1 and 9 in Healthy Volunteers

Principal Investigator

Study center(s) and number of subjects planned

This is a single-center study. Fifty-nine (59) healthy male and female volunteers will be enrolled and randomized to treatment.

Study period		Phase of development
Estimated date of first healthy volunteer enrolled	Q1 2011	Phase I
Estimated date of last healthy volunteer completed	Q3 2011	

Objectives

Primary objective

To assess the effect of esomeprazole 20 mg/acetylsalicylic acid 81 mg on the pharmacodynamics of clopidogrel by assessing maximal inhibition of platelet aggregation after 9 days of clopidogrel treatment relative to baseline

Secondary objectives

- To assess the effect of esomeprazole 20 mg/acetylsalicylic acid 81 mg on the pharmacokinetics of the active metabolite of clopidogrel by assessing AUC, $AUC_{0\text{-last}}$ and $C_{ss,max}$ of the active metabolite of clopidogrel on Day 9

- To assess the safety and tolerability of clopidogrel given alone and concomitantly with esomeprazole 20 mg/acetylsalicylic acid 81 mg by assessing adverse events, vital signs, laboratory variables, electrocardiogram and physical examination

Exploratory objective

To summarize the pharmacodynamic and pharmacokinetic variables in relation to CYP2C19 genotype

Study design

This is a single-center, open-label, randomized, 2-way cross-over study designed to assess the pharmacodynamic and pharmacokinetic interaction between clopidogrel and esomeprazole 20 mg/acetylsalicylic acid 81 mg.

Target subject population

Healthy males, aged between 18 and 45 years inclusive, and females, aged between 18 and 55 years inclusive, with a body mass index between 19 and 30 kg/m^2 inclusive

Investigational product, dosage and mode of administration

Each healthy volunteer will receive oral administration of 2 treatments in randomized order:

- Treatment A: clopidogrel tablet 75 mg once daily for 9 days
- Treatment B: clopidogrel tablet 75 mg once daily for 4 days followed by esomeprazole 20 mg/acetylsalicylic acid 81 mg with clopidogrel tablet 75 mg once daily for 5 days

Comparator, dosage and mode of administration

None

Duration of treatment

The total study duration for each healthy volunteer is approximately 2.5 months. This includes a pre-entry visit within 28 days prior to randomization, 2 treatment periods of 9 days, washout periods of at least 14 days between the treatment periods (ie, between the last dose in period 1 and the first dose in period 2) and a follow-up visit 7 to 10 days after the last dose.

Outcome variable(s):

- Pharmacodynamics

  The primary variable is maximal inhibition of platelet aggregation which will be based on maximum platelet aggregation to 20 µmol/L adenosine diphosphate assessed at baseline (Day -1 for Period 1 and pre-dose on Day 1 in Period 2) and 24 h after dose on Day 9.

- Pharmacokinetics

  Area under the plasma concentration-time curve from time zero to infinity (AUC, primary variable), Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration ($AUC_{0\text{-last}}$, primary variable), maximum steady state concentration in plasma ($C_{ss,max}$, primary variable) and time to reach maximum concentration (t_{max}) of the active metabolite of clopidogrel after dose on Day 9

- Safety

  Adverse events, vital signs, clinical laboratory variables, electrocardiogram, physical examination

Statistical methods

The pharmacokinetic variables and maximal inhibition of platelet aggregation will be analyzed using linear mixed models (1 for each variable) with fixed effects for period and treatment and a random effect for subject within sequence. The mean differences between the treatments in the maximal inhibition of platelet aggregation model will be calculated with 95% confidence interval for the differences. The ratio ((esomeprazole 20 mg/acetylsalicylic acid 81 mg + clopidogrel)/clopidogrel) of AUC, $AUC_{0\text{-last}}$ and $C_{ss,max}$ with corresponding 90% CI for the ratios will be calculated.

Subpopulation analysis by genotype may be performed if found necessary and if data allows.

Safety data will be presented with 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 (CSP).

Abbreviation or special term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.3.1)
AMC	Active metabolite of clopidogrel
APTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AUC	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
B	Blood (eg, B-Hb)
BP	Blood pressure
CI	Confidence interval
CPA	Clinical Pharmacology Alliance
CRF	Case report form (electronic/paper (eCRF/pCRF))
CSA	Clinical Study Agreement
CSP	Clinical study protocol
CSR	Clinical study report
$C_{ss,max}$	Maximum steady state concentration in plasma
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram (paper (pECG))
F	Faeces (eg, F-Hb)
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
Hb	Haemoglobin
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonisation
IP	Investigational product
IPA	Inhibition of platelet aggregation
IUD	Intrauterine device
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mIPA	Maximal IPA
mPA	Maximal PA
MS	Mass spectrometry
NSAID	Non-steriodal anti-inflammatory drug
OAE	Other significant adverse event (see definition in Section 11.1.1)
od	Once daily
OTC	Over-the-counter
PA	Platelet aggregation
PD	Pharmacodynamic/pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic/pharmacokinetics
PPI	Proton pump inhibitor
PR (PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	The time between corresponding points on 2 consecutive R waves on ECG

Abbreviation or special term	Explanation
S	Serum (eg, S-Calcium)
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SOP	Standard Operating Procedure
t_{max}	Time to reach maximum concentration
U	Urine (eg, U-Hb)
WI	Work Instruction

1. INTRODUCTION

1.1 Background

The proposed therapeutic indication for combination product of the proton pump inhibitor (PPI) esomeprazole and acetylsalicylic acid (ASA) is prevention of cardio- and cerebrovascular events in patients at risk of developing gastric and/or duodenal ulcers associated with ASA.

Esomeprazole is the S-enantiomer of the PPI omeprazole, and acts through inhibition of the proton pumping enzyme H^+/K^+-ATP-ase located in the parietal cells of the gastric oxyntic mucosa, thus preventing hydrochloric acid secretion to the gastric lumen. Esomeprazole for oral use is currently approved for a variety of acid-related conditions, including the prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug (NSAID) therapy. Esomeprazole was first approved for marketing in Sweden in 2000, and is now approved in 125 countries.

The clinical development program includes 2 studies (D9617C00011 and D961FC00003) that contributed efficacy data showing that esomeprazole at doses of 20 mg and 40 mg once daily (od) prevents peptic (gastric and/or duodenal) ulcers in patients on continuous low-dose ASA treatment (for prevention of cardio- and cerebrovascular events) at risk of developing peptic ulcers. Both studies were randomized, double-blind, 26-week studies evaluating the efficacy and safety of esomeprazole 20 mg od (Study D9617C00011) or 20 mg and 40 mg od (Study D961FC00003) compared with placebo in patients on continuous low-dose ASA treatment.

1.2 Rationale for conducting this study

Clopidogrel has proven its efficacy in reducing atherothrombotic events after percutan coronar intervention, a considerable interindividual variability in response has been reported. Clopidogrel is administered as an inactive prodrug requiring metabolization by the hepatic cytochrome P450 system for its antiplatelet activity. The formed active thiol metabolite of clopidogrel (AMC) irreversibly inhibits adenosine diphosphate (ADP) mediated platelet activation and aggregation by antagonizing the P2Y12-receptor. In the formation of the AMC, different cytochrome P450 (CYPs) (CYP1A2, CYP2B6, CYP2C19, CYP2C9 and CYP3A4) have been shown in vitro to be involved in 2 different oxidative steps; some contribute more than others (Kazui et al), but based on several large studies assessing the role of genetic variation in clopidogrel responsiveness (Mega et al 2009, Shuldiner et al 2009) the role of CYP2C19 seems to be of major importance. In vitro studies suggest that both omeprazole and esomeprazole have a potential to inhibit CYP2C19 and thus to inhibit the metabolism of drugs metabolized by CYP2C19 (Li et al 2004). Previous interaction studies between clopidogrel and omeprazole or esomeprazole showed inconsistent results (Cuiseet et al 2009, Furuta et al 2010, Gilard et al 2008, Jermano et al 2009, Lapuerta et al 2008, Moceri et al 2009, Sibbing et al 2009, Siller-Matula et al 2009, Zuern et al 2009). In a recent study referenced in the US Plavix® Prescribing Information

using omeprazole 80 mg as a tool/probe to inhibit CYP2C19 in healthy subjects, the formation of AMC decreased by 46%, indicating an inhibition of CYP2C19 by this dose of omeprazole. Some of the previous PD studies indicated a dose response relationship with the presence or absence of interaction (Lapuerta et al 2008). As the combination product esomeprazole/ASA is given in order to prevent cardio– and cerebrovascular events in patients at risk, it is important to clarify if there is any drug-drug interaction between esomeprazole 20 mg/ASA 81 mg and clopidogrel as clopidogrel is commonly used for the same purpose together with ASA.

Light transmission aggregometry is regarded as the gold standard and has been chosen for measuring platelet aggregation (PA). The absolute change in platelet reactivity when measured with light transmittance aggregometry induced by 20 µmol/L ADP showed strong correlation with the C_{max} value of the AMC. In contrast, no significant association was observed between the C_{max} value of the AMC and inhibition of PA (IPA) using a lower concentration of 5 µmol/L ADP, hence only the higher dose of ADP will be used (Bouman et al 2009).

The aim of this study is to assess whether there is a pharmacological interaction between esomeprazole 20 mg/ASA 81 mg and clopidogrel.

1.3 Benefit/risk and ethical assessment

Acetylsalicylic acid, esomeprazole and clopidogrel have been available for marketed use for several years. The safety profiles are well described in the package inserts for esomeprazole and clopidogrel, respectively, at the following links:
http://www1.astrazeneca-us.com/pi/Nexium.pdf (esomeprazole)
http://products.sanofi-aventis.us/PLAVIX/PLAVIX.html (clopidogrel)

This is a standard drug-drug interaction study. There will be no direct medical benefits to the healthy volunteers who participate.

Healthy volunteers will be administered clopidogrel, a platelet inhibitor that may increase the risk of bleeding. Healthy volunteers will be observed at the study unit during the treatment period when clopidogrel is administered with esomeprazole 20 mg/ASA 81 mg and safety will be monitored. Any minor or major bleeding events will be required to be reported by the healthy volunteers to the study personnel.

2. STUDY OBJECTIVES

2.1 Primary objective

To assess the effect of esomeprazole 20 mg/ASA 81 mg on the pharmacodynamics (PD) of clopidogrel by assessing maximal IPA (mIPA) after 9 days of clopidogrel treatment relative to baseline

2.2 Secondary objectives

- To assess the effect of esomeprazole 20 mg/ASA 81 mg on the pharmacokinetics (PK) of AMC by assessing AUC, $AUC_{0\text{-last}}$ and $C_{ss,max}$ of AMC on Day 9

- To assess the safety and tolerability of clopidogrel given alone and concomitantly with esomeprazole 20 mg/ASA 81 mg by assessing adverse events (AEs), vital signs, laboratory variables, electrocardiogram (ECG) and physical examination

2.3 Exploratory objective

To summarize the PD and PK variables in relation to CYP2C19 genotype

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca standard procedures.

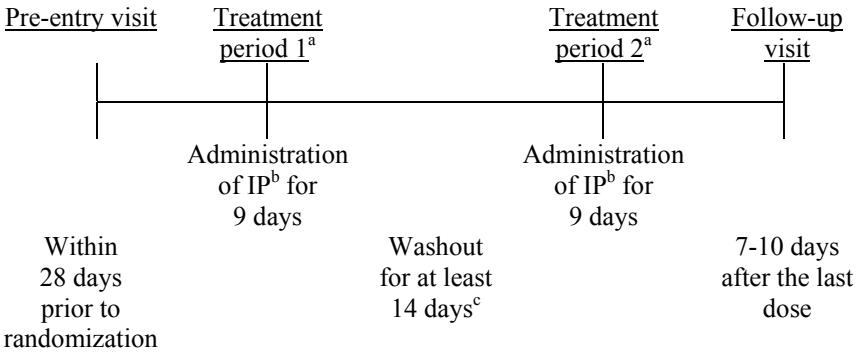
3.1 Overall study design and flow chart

The study will be performed at Quintiles AB, Uppsala, Sweden. This is an open-label, randomized, 2-way cross-over study designed to assess the PD and PK interaction between clopidogrel and esomeprazole 20 mg/ASA 81 mg. Fifty-nine (59) healthy male and female volunteers will be enrolled and randomized to treatment.

The total study duration for each healthy volunteer is approximately 2.5 months. This includes a pre-entry visit within 28 days prior to randomization, 2 treatment periods of 9 days, washout periods of at least 14 days between the treatment periods (ie, between the last dose in period 1 and the first dose in period 2) and a follow-up visit 7 to 10 days after the last dose. See Figure 1.

In each treatment period, the healthy volunteers will arrive at the study unit on Day -1 and start treatment on Day 1. For treatment A, the healthy volunteers will take the subsequent doses on Days 2 to 8 at home and receive the dose on Day 9 at the study unit (they will return to the study unit in the evening of Day 8). For treatment B, the healthy volunteers will take the subsequent doses on Days 2 to 4 at home and they will return to the study unit to receive the doses on Days 5 to 9.

Figure 1 Study flow chart



a Healthy volunteers will be administered the following treatments in randomized order (see Section 5.5.2) in Period 1and 2:
Treatment A: clopidogrel 75 mg once daily for 9 days
Treatment B: clopidogrel 75 mg once daily for 4 days followed by esomeprazole 20 mg/ASA 81 mg with clopidogrel 75 mg once daily for 5 days
b Investigational product (IP, esomeprazole 20 mg/ASA 81 mg and clopidogrel)
c The washout period will be at least 14 days between the last dose in period 1 and the first dose in period 2.

Healthy volunteers will be administered IP for 9 days. Blood sampling for PD assessment will be drawn on Day -1 (Period 1)/pre-dose on Day 1 (Period 2) as baseline and 24 h after dose on Day 9. Blood samples for determination of AMC will be drawn pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after the last dose on Day 9. Safety monitoring will be performed during the treatment periods. Standardized food will be served during the residential periods. The study plan and study time schedule are found in Table 1 and Table 2, respectively.

A genetic sample will be taken to assess CYP2C19 status on Day -1 in Period 1, once the informed consent has been signed.

Table 1 Study plan

Event	Pre-entry	Period 1		Period 2		Follow-up
Study Day	**within 28 days prior to randomization**	**Day -1 (admission)**	**Day 1 to 10[a]**	**Day -1 (admission)**	**Day 1 to 10[a]**	**7-10 days after the last dose**
Informed consent[b]	X					
Inclusion/exclusion criteria	X	X	X[c]			
Randomization			X[d]			
Demographics	X					
Body weight and height	X					
Nicotine, alcohol and caffeine use	X					
Medical and surgical history	X					
Physical examination	X					X
Laboratory screening[e]	X	X	X[f]	X	X[f]	X
Alcohol and drug screen	X	X		X		
CYP2C19 blood sample		X				
Paper ECG (pECG)	X	X		X		X
Vital signs (BP/pulse)	X	X	X[g]	X	X[g]	X
Administration of IP			X[h]		X[h]	
PK blood sampling			X[i]		X[i]	
PD blood sampling		X	X[j]		X[k]	
Standardized food[l]		X	X	X	X	
Concomitant medication	X	X	X	X	X	X
AE/serious adverse event (SAE) recording[m]	X	X	X	X	X	X

a For treatment A, the subjects will leave the study unit after dosing on Day 1 and return in the evening on Day 8. For treatment B, the subjects will leave the study unit after dosing on Day 1 and return prior to dose on Day 5. For both treatment periods, they will be discharged from the study unit after the assessments 24 h post dose on Day 9 (ie, on Day 10).

b If an extra pre-entry visit is needed prior to randomization, the healthy volunteers will only need to sign the informed consent once.

c Only AEs and concomitant medication will be checked before randomization on Day 1.

d Randomization will be done on Day 1.

e See Section 6.3.5 for assessments. At the pre-entry visit, also including human immunodeficiency virus (HIV), hepatitis B and C.

f On Day 9 (see Table 2)

g Pre-dose on Days 1 and 9 (see Table 2)

h For treatment A, administration will take place at study unit on Day 1, at home on Days 2 to 8 and at the study unit on Day 9. For treatment B, administration will take place at study unit on Day 1, at home on Days 2 to 4 and at the study unit on Days 5 to 9.

i Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after the last dose on Day 9 (see Table 2)

j 24 h post dose on Day 9 (see Table 2). The baseline sample will be obtained on Day -1.

k Pre-dose on Day 1 (as baseline) and at 24 h post dose on Day 9 (see Table 2)

l Standardized food will be served during the residential periods.

m Serious adverse events will be collected from the time when informed consent is obtained until the follow up visit. Adverse events will be collected from the first administration of IP until the follow up visit.

Table 2 Study time schedule, Days 9 and 10

Protocol time (hhmm)	Study day	Administration of IP	PK blood sampling	PD blood sampling	Laboratory safety	Vital signs	Other
Pre-dose	9		X		X	X	
0000		X					
0015			X				
0030			X				
0100			X				Breakfast
0130			X				
0200			X				
0300			X				
0400			X				Lunch
0600			X				
0700							Snacks
0800			X				
1000			X				Dinner
1200			X				Snacks
2400	10			X[a]			Breakfast after PD sampling

a The baseline sample will be taken on Day -1 for Period 1 and pre-dose on Day 1 for Period 2.

3.2 Rationale for study design, doses and control groups

This single-center, open-label, randomized, 2-way cross-over study is designed to assess the PD and PK interaction between clopidogrel and esomeprazole 20 mg/ASA 81 mg. The crossover design improves reliability with each healthy volunteer being his/her own control by eliminating the impact of between-subject variability in the clopidogrel response.

The study will be conducted in healthy male and female volunteers to avoid interference from disease processes or other drugs. The selection criteria are defined such that subjects selected for participation in the study are known to be free from any significant illness.

Pharmacokinetic and PD sampling in each treatment period is judged to be sufficient to fulfil the objectives of the study.

The combination product esomeprazole/ASA will be developed using 2 strengths of esomeprazole (20 mg and 40 mg) and the lower strength will be used in this study. Two strengths of ASA (81 mg and 325 mg) will also be developed. For safety reasons, only the lower strength of ASA, 81 mg, will be used in this study. The recommended maintenance dose of clopidogrel, 75 mg, will be administered.

Clopidogrel will be administered for 9 days in order to reach steady-state conditions (steady state is reached between Day 3 and Day 7 (Plavix® Prescribing Information). A 5 day co-administration of esomeprazole 20 mg/ASA 81 mg is chosen to ensure steady-state of esomeprazole and to ensure full potential inhibition.

Due to irreversible binding with AMC, platelets are affected for the remainder of their lifespan (approximately 7 to 10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. The washout period of 14 days will ensure complete platelet turnover between treatment periods.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the subject screening log, of healthy volunteers who entered pre-study screening.

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

4.1 Inclusion criteria

For inclusion in the study, healthy volunteers should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures (including pharmacogenetic sampling for CYP2C19 genotyping)

2. Male (aged between 18 and 45 years inclusive) or female (aged between 18 and 55 years inclusive) healthy volunteers with suitable veins for cannulation or repeated vein puncture. Female healthy volunteers must be of non-childbearing potential (post-menopausal, have had a hysterectomy and/or bilateral oophorectomy) or be of childbearing potential, be non-lactating and have a negative serum human chorionic gonadotropin (S-hCG) pregnancy test during the pre-entry visit and be using 1 clinically accepted method of contraception. Clinically accepted methods of contraception that may be used by the subject and/or partner include: diaphragm with spermicide, intrauterine device (IUD, except for Mirena®) or condom with vaginal spermicide. Females will be defined as postmenopausal if last menstruation period was >1 year ago and serum follicle stimulating hormone (FSH) is within the postmenopausal range, or if age >50 years and with last menstruation period >2 years ago.

3. Have a body mass index between 19 and 30 kg/m^2 inclusive

4. No clinically significant abnormal findings at the physical examination at the pre-entry visit, as judged by the investigator

4.2 Exclusion criteria

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

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

2. Previous randomization in the present study

3. Participation in another clinical study with an IP during the last 3 months. The period of exclusion begins at the time of the last dose in the prior study. Note: healthy volunteers consented and screened but not dosed in this study or a previous phase I study, will not be excluded.

4. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the healthy volunteer at risk because of participation in the study, or influence the results or the healthy volunteer's ability to participate in the study, eg, history of any bleeding disorder or ongoing or history of liver disease

5. History or presence of gastrointestinal (GI) (eg, GI ulcer), hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs

6. Any clinically significant illness within 4 weeks of the first administration of IP. Any medical/surgical procedure or trauma within 3 months of the treatment period; scheduled surgery, including dental surgery, within 2 weeks of the scheduled completion of the study.

7. Any clinically significant abnormalities in clinical chemistry, haematology (eg, history or presence of thrombocytopenia, abnormal activated partial thromboplastin time (APTT) and prothrombin complex) or urinalysis (>+1 urine-haemoglobin (U-Hb) at the pre-entry visit) or positive feaces-haemoglobin (F-Hb) results, as judged by the investigator

8. Healthy volunteers who will need to drastically change their lifestyle activities in order to comply with restrictions during the study considering their exercise volume or their diet

9. Suspicion of or known Gilbert's disease

10. Any positive result on screening for hepatitis B surface antigen, hepatitis C antibody and HIV

11. After 10 min supine rest abnormal vital signs (diastolic blood pressure (BP), systolic BP, pulse rate) as judged by the investigator

12. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG. This includes healthy volunteers with any of the following:

    - Clinically significant PR (PQ) interval prolongation
    - Intermittent second or third degree AV block
    - Incomplete, full or intermittent bundle branch block (QRS <110 ms with normal QRS and T wave morphology is acceptable if there is no evidence of left ventricular hypertrophy)
    - Abnormal T wave morphology, particularly in the protocol defined primary lead

13. Prolonged QTcF >450 ms or shortened QTcF <350 ms or family history of long QT syndrome

14. Known or suspected history of drug abuse as judged by the investigator

15. Smoking or other sort of nicotine use within the previous 30 days prior to the first administration of IP

16. History of alcohol abuse or excessive intake of alcohol as judged by the investigator

17. Positive screen for drugs of abuse or alcohol at the pre-entry visit or on admission to the study unit

18. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to IPs

19. 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)

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

21. Use of any prescribed or non-prescribed (over-the-counter (OTC)) medication including aspirin, NSAIDs such as ibuprofen, or any other drug known to increase the propensity for bleeding or need for antacids, or analgesics (other than paracetamol/acetaminophen), nasal anticongestants, herbal remedies, vitamins and minerals during the 2 weeks prior to the first administration of the IP or longer if the medication has a long half-life. Occasional use of paracetamol/acetaminophen is allowed for minor pains and headache.

22. Any intake of grapefruit, grapefruit juice, cranberry juice, Seville oranges, Seville orange marmalade or other products containing grapefruit, cranberry or Seville oranges within 14 days before the first administration of IP

23. Plasma donation within 1 month of the pre-entry visit or any blood donation/blood loss >500 mL during the 3 months prior to the pre-entry visit

24. Judgement by the investigator that the healthy volunteer should not participate in the study if they are considered unlikely to comply with study procedures, restrictions and requirements

25. Platelet count <150 x 10^9/L on Day -1 or any other conditions that would increase the risk of bleeding

26. Previous bone marrow transplant (applies to the requirement for CYP2C19 genotyping)

27. Whole blood transfusion within 120 days of the date of genetic sample collection (applies to the requirement for CYP2C19 genotyping)

Procedures for withdrawal of incorrectly enrolled healthy volunteers see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Volunteers will be required to:

1. Fast from at least 10 h before dose on Day 9 (water is allowed up to 1 h prior to dose). Food and water is allowed 1 h after dose on Day 9.

2. Abstain from consuming any of the following:

   - Alcohol from 72 h before admission, during the treatment periods and for 72 h before the follow-up visit

   - Energy drinks containing taurine or glucuronolactone, eg, Red Bull, from 72 h before admission, during the treatment periods and for 72 h 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 (more than 5 cups of coffee or equivalent per day) should be avoided during the periods when IP are administered at home, the washout period and between discharge from the unit and the follow-up visit.

   - Poppy seeds found in speciality bread from time of consent until after the final medical examination at the follow-up visit

- Grapefruit, grapefruit juice, cranberry juice, Seville oranges, Seville orange marmalade or other products containing grapefruit, cranberry or Seville oranges from 14 days before the first administration of IP and St John's Wort from 3 weeks before the first administration of IP, until after final medical examination at the follow-up visit

3. Abstain from nicotine use, smoking and drugs of abuse from time of consent until after the final medical examination at the follow-up visit

4. Healthy volunteers should refrain from strenuous physical activity, which is not within the healthy volunteer's normal daily routine, and any activities that have a risk of trauma from 7 days prior to admission to the study unit until after the final medical examination at the follow-up visit

5. Abstain from blood and plasma donation during the study and until 3 months after the final medical examination at the follow-up visit

6. Female volunteers of childbearing potential should use one clinically accepted method of contraception. Clinically accepted methods of contraception that may be used by the subject and/or partner include: diaphragm with spermicide, IUD (except for Mirena®) or condom with vaginal spermicide.

7. Not participate in any other clinical study

5.2 Subject enrolment and randomization

The Principal Investigator (PI) will:

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

2. Assign potential healthy volunteer a unique enrolment number, beginning with 'E0001001'

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

4. Assign eligible healthy volunteer unique randomization code (subject number), beginning with '1001'

If a healthy volunteer withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

If a patient has withdrawn from participation in the study, then he/she cannot re-enter into the study.

5.2.1 Procedures for randomization

A randomization scheme will be generated by Quintiles using the validated global randomization system (GRand). The randomization will be done for 60 subjects in blocks. The healthy volunteers will be randomized to 1 of 2 treatment sequences (A-B and B-A):

- Treatment A: clopidogrel 75 mg once daily for 9 days
- Treatment B: clopidogrel 75 mg for 4 days followed by esomeprazole 20 mg/ASA 81 mg with clopidogrel 75 mg once daily for 5 days

Randomization codes will be assigned strictly sequentially as healthy volunteers become eligible for randomization. With 59 subjects included, this implies the last randomized block not being completely filled (one of the 2 possible permutations will not be used), ie, the last treatment sequence in the randomization list will not be allocated to any subject.

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

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

Where healthy volunteers that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where healthy volunteers subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Physician and the Investigator regarding whether to continue or discontinue the healthy volunteer from treatment.

The AstraZeneca Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the healthy 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
Esomeprazole/ASA	Oral capsule, 20 mg/81 mg (esomeprazole 20 mg/ASA 81 mg)	AstraZeneca
Clopidogrel	Oral tablet, 75 mg	Bristol-Myers Squibb/Sanofi-Aventis

Esomeprazole 20 mg/ASA 81 mg will be for clinical trials appropriately labelled by AstraZeneca in bulk packaging and delivered to Quintiles.

Clopidogrel (commercial available clopidogrel) will be purchased through pharmacy by Quintiles. Quintiles will repack clopidogrel into subject specific containers. The packaging will be performed in compliance with Good Manufacturing Practice (GMP). Labels for the subject specific containers will be provided by AstraZeneca R&D, Sweden.

The IPs will be individually packed by treatment period according to the randomization scheme by Quintiles. Individual containers, including labels, and packaging instructions will be supplied by AstraZeneca.

5.5.2 Doses and treatment regimens

This study has 2 treatment arms and 2 treatment periods separated by a washout period of at least 14 days. All study medications will be administered via the oral route. Each volunteer will receive 2 treatments in randomized order (see Section 5.2.1):

- Treatment A: clopidogrel 75 mg once daily for 9 days
- Treatment B: clopidogrel 75 mg for 4 days followed by esomeprazole 20 mg/ASA 81 mg with clopidogrel 75 mg once daily for 5 days

For treatment A, the healthy volunteers will receive the first dose of clopidogrel at the study unit on Day 1, take the subsequent doses on Days 2 to 8 at home and at the study unit on Day 9. For treatment B, the healthy volunteers will receive the first dose of clopidogrel at the study unit on Day 1, take the subsequent doses on Days 2 to 4 at home and at the study unit on Days 5 to 9.

At the study unit, IPs will be administered with approximately 240 mL of water. The capsules/tablets must not be chewed, crushed or divided, but should be swallowed whole. The healthy volunteers will be instructed to have the same dosing procedures (including at approximately the same time) at home.

On Day 9, IP will be administered following a fast of at least 10 h (moderate amounts of water will be allowed until 1 h before dosing) and volunteers will continue to fast for 1 h after dosing. Healthy volunteers will be in an upright position (upper part of the body erect at least 45 degrees from horizontal) at the time of IP administration and will be asked to remain in an upright position for at least 1 h following IP administration.

Healthy volunteers will be instructed to record the date and time of each dose taken at home of IP in a medication log and instructed to return the medication log at the next visit to the study unit. The healthy volunteers will be instructed to, if they forgets to take a dose of IP, take the missed dose as soon as possible if it is less than or equal to 12 h since the dose was missed or to skip that dose and wait to take the next scheduled dose if it has been longer than 12 h since the dose was missed.

5.5.3 Labelling

Labels will be prepared by AstraZeneca in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

5.5.4 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The IP labels specify the appropriate storage.

5.6 Concomitant and post-study treatment(s)

The use of potent CYP inhibitors, eg, ketoconazole, gemfibrozil and macrolide antibiotics or potent CYP inducers, eg, rifampicin, will not be allowed from 30 days before the first administration of IP until the follow up visit.

The volunteers are not allowed to use any prescribed or non-prescribed OTC medication including aspirin, NSAIDs, such as ibuprofen, or any other drug known to increase the propensity for bleeding, antacids, or analgesics (other than paracetamol/acetaminophen), nasal anticongestants, herbal remedies, vitamins and minerals from 2 weeks prior to the first administration of IP or longer if the medication has a long half-life until the follow-up visit. Occasional use of paracetamol/acetaminophen is allowed for minor pains and headache.

Other medication, which is considered necessary for the healthy volunteer's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the case report form (CRF).

5.7 Treatment compliance

The administration of all medication (including IPs) should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by supervised administration of IP by the Investigator or representative during the study. The dose, date and time of administration of the IP will be recorded.

5.7.1 Accountability

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

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

Study site pharmacist 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. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

5.8 Withdrawal from study

Healthy volunteers may be discontinued from study treatment and assessments in the following situations:

- Healthy volunteer decision. The healthy volunteer is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event
- Severe non-compliance to study protocol as judged by the investigator and/or AstraZeneca
- Eligibility criteria not fulfilled
- Volunteer lost to follow-up
- Any clinically relevant bleeding or repeated minor bleeding according to the judgement of investigator
- Any trauma or accident with the consequences of surgery even during the washout period
- Any need for medication that could influence the outcome of the study

5.8.1 Procedures for discontinuation of a subject from the study

Healthy volunteers are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such healthy volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.3.3 and 6.3.4); study drug (including medication log) should be returned by the subject.

Withdrawn healthy volunteers will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The investigator will ensure that data are recorded on paper CRFs (pCRFs) or electronic CRFs (eCRFs) as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, legibility (applicable for pCRFs) 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 pCRFs/eCRFs. A copy of the completed pCRF/eCRF will be archived at the study site.

For occasions when more than one assessment is required at a particular time point, PK samples should be prioritized.

Pre-dose vital signs assessments may be performed within 60 min prior to dosing and pre-dose PK blood samples should be taken within 5 min prior to dosing. The allowed time deviation for post-dose PD and PK samples is ±5% from planned time, or ±15 min whichever is the shortest.

See also Section 10.

6.2 Data collection and enrolment

Each healthy volunteer will undergo an enrolment medical examination within 28 days before first dose of IP, see also Table 1. This will consist of:

- Demographic data: date of birth, sex and race
- Weight (measured in kg), height (measured in cm, without shoes) and habits of nicotine, alcohol and caffeine consumption
- Significant medical and surgical history
- A physical examination including general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen and a neurological examination (only reflexes)
- Resting pulse and BP measurement
- Blood sample for clinical chemistry, haematology and coagulation (including S-hCG for females), a mid-stream urine sample for urinalysis and drugs of abuse test, a faeces sample for F-Hb and an alcohol breath test
- A blood sample to test for hepatitis B surface antigen and antibodies to hepatitis C virus and HIV, for the safety of the site personnel
- pECG
- Check of concomitant medications and SAEs

6.2.1 Follow-up procedures

A follow-up visit will be scheduled 7 to 10 days after the last dose. This visit will include a physical examination, collection of safety blood and urine samples, assessments of BP and pulse, a pECG and a check of concomitant medications and AEs.

6.3 Safety

The PI 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 pre-existing 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, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, 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 non-serious AEs.

6.3.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 healthy volunteer or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a 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 the first administration of IP 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 healthy volunteer's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any healthy volunteer with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be recorded for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity on a scale of 1 to 3:
    1. mild (awareness of sign or symptom, but easily tolerated)
    2. moderate (discomfort sufficient to cause interference with normal activities)
    3. severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused healthy volunteer's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE 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)
- Causality assessment in relation to other medication
- 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 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 other medication and 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 healthy 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 CRF. 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 protocol mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfil 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, anaemia versus low haemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated 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 CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one 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 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.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics for clopidogrel.

6.3.5 Laboratory safety assessment

Blood, urine and faeces samples for determination of clinical chemistry, haematology, coagulation, urinalysis and F-Hb will be taken at the times indicated in the study plan (see Table 1).

The following laboratory variables will be measured:

Table 3 Laboratory variables

Clinical chemistry	**Haematology**
S-Alanine Aminotransferase	B-Hb
S-Aspartate Aminotransferase	B-Leukocyte count
S-Alkaline Phosphatase	B-Platelet count
S-Bilirubin, total	
S-Calcium, total	**Coagulation**
S-Creatinine	P-Prothrombin complex (International normalized ratio)[a]
S-C-reactive protein (high sensitive)	P-APTT[a]
S-Potassium	
S-Sodium	**Urinalysis**
S-hCG (females)[a, b]	U-Hb (dipstick)
S-FSH[c]	U-Protein (dipstick)
	U-Glucose (dipstick)
Faeces	
F-Hb[a]	

a Only at the pre-entry visit
b Females only
c Only at the pre-entry visit and only for all postmenopausal women, except for women >50 years old who had their last menstruation >2 years ago.

At the pre-entry visit all healthy volunteers will be tested for HIV, hepatitis B surface antigen and antibodies to hepatitis C. Alcohol breath test will be performed and urine will be tested for drugs of abuse (amphetamines, opiates, benzodiazepine, cannabinoid, cocaine) at the pre-entry visit and on Day -1 in all treatment periods.

The safety laboratory samples will be analyzed by Quintiles AB, Safety Laboratory, Uppsala, Sweden using standard methods.

Laboratory values outside the reference limits suspected to be of any clinical significance will be retaken. Healthy volunteers in whom the suspected clinical significance is confirmed on repeated sampling will either not be included or, if already included, will be followed until normalization or for as long as medically indicated.

For reporting of AEs based on examinations and tests, see Section 6.3.3. For blood volume, see Section 7.1.

6.3.6 Physical examination

A physical examination including general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen and a neurological examination (only reflexes) will be performed at the pre-entry visit and at the follow-up visit.

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

6.3.7 ECG

12-lead pECGs will be obtained after the healthy volunteers have been lying down for 10 min in each case. For timing of individual measurements, see the study plan (Table 1). Date, time, and "normal" or "abnormal" will be recorded. In case of abnormalities, the reason will be recorded. All pECGs will be evaluated by the Investigator or a qualified cardiologist. He/she will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. Heart rate, PR, RR, QRS, QT, and QTcF intervals will be recorded from standard lead (lead II) of the 12-lead pECG.

If indicated, additional ECG assessments can be made 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

Supine BP (in mmHg) and pulse rate (in bpm) will be measured using standard equipment with an appropriate cuff size after 10 min rest. For timing of individual measurements, refer to the study plan (Table 1). For reporting of AEs based on examinations and tests, see Section 6.3.3.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (4 mL) for determination of AMC concentrations in plasma will be taken at the times presented in the study plan (Table 1).

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

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for the determination of drug concentration in plasma will be analyzed by Advion BioServices, Ithaca, USA, on behalf of AstraZeneca Clinical Pharmacology & DMPK, by

derivatisation and using HPLC-MS/MS after solid phase extraction. The lower limit of quantification (LLOQ) of AMC derivate will be 0.071 ng/mL.

6.5 Pharmacodynamics

6.5.1 Collection of samples

Blood samples (3 tubes á 6 mL) for platelet aggregometry will be taken at the times presented in the study plan (Table 1) to determine maximal PA (mPA) induced by 20 µmol/L ADP.

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

For blood volume see Section 7.1.

6.5.2 Determination of platelet aggregometry

Light transmission aggregometry will be used for measuring PA. Samples will be analysed by Quintiles AB, Safety Laboratory, Uppsala, Sweden on behalf of AstraZeneca.

6.6 CYP2C19 Genotyping

6.6.1 Collection of samples

A mandatory blood sample for CYP2C19 genotyping will be obtained on Day -1 in Period 1. No other research will be performed on the samples. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

Genotyping will be performed by a contract research organisation on behalf of AstraZeneca.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 4 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3.5	6	21
	Haematology	3	6	18
	Coagulation	2.7	1	2.7
	Serology	3.5	1	3.5
PK		4	24	96
PD		18	4	72
Genotyping		2	1	2
Total				**215.2**

The number of samples taken, as well as the volume required for each analysis, may be changed during the study. 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.

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 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of after the CSR has been finalized.

7.2.2 CYP2C19 genotyping samples

The processes adopted for the coding and storage of samples for CYP2C19 genetic analysis are important to maintain subject confidentiality. For all samples irrespective of the type of coding used the deoxyribonucleic acid (DNA) will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the

individual will be available to any person (AstraZeneca employee or contract laboratory staff) working with the DNA.

The samples and data for CYP2C19 genetic analysis in this study will be single coded. The link between the subject enrolment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of CYP2C19 genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. Samples for CYP2C19 genotyping will be destroyed by AstraZeneca genetics laboratories, or at the designated contract laboratory after finalization of the CSR.

7.3 Labelling and shipment of biohazard samples

The PI ensures that samples are labelled 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 healthy volunteer unless agreed with AstraZeneca and appropriate labelling, 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 lifecycle.

The PI keeps full traceability of collected biological samples from the healthy 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 healthy 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 subject is withdrawn from further study participation.

The PI:

- Ensures healthy volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that healthy 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 healthy 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 Harmonisation/Good Clinical Practice (ICH/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.

AstraZeneca will not provide individual genotype results to healthy volunteers, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the healthy volunteer. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a healthy volunteer. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a healthy volunteer's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the healthy volunteer's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the healthy volunteers. The investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any healthy volunteer into the study.

The EC should approve all advertising used to recruit healthy 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 protocol should be re-approved by the EC annually.

Before enrolment of any healthy volunteer into the study, the final study protocol, 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, ECs and PIs with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The PI(s) at the center will:

- Ensure each healthy volunteer is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each healthy volunteer is notified that they are free to discontinue from the study at any time
- Ensure that each healthy volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each healthy 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(s) is/are given to the healthy volunteer

- Ensure that any incentives for healthy volunteers who participate in the study as well as any provisions for healthy volunteers harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

8.5 Changes to the protocol and informed consent form

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

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

The amendment should be approved by each EC and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a center's Informed Consent Form, AstraZeneca and the center's EC should 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 EC.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC 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 protocol, 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

9.1 Training of study site personnel

Before the first healthy volunteer is entered into the study, the PI(s) 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 by Quintiles 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 protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that IP accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the healthy volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating healthy volunteers. This will require direct access to all original records for each healthy volunteer (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the healthy 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 healthy volunteer.

The monitor will be available between visits if the investigator(s) or other staff at the investigational site(s) needs information and advice about the study conduct. Monitoring will be conducted in agreement with the Quintiles Phase I Global CPA clinical monitoring plan.

9.2.1 Source data

Refer to the "Source data identification and location"-document for location of source data (CRF or other source documents).

9.3 Study agreements

Quintiles 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 CSP shall prevail with respect to the conduct of the study and the treatment of healthy volunteers and in all other respects, the terms of the CSA shall prevail.

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

The PI should comply with all the terms, conditions and obligations of this CSP.

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 subject undergoing the study'.

The study is expected to start in Q1 2011 and end during Q3 2011.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with the combination product esomeprazole/ASA.

10. DATA MANAGEMENT

Data management will be performed by Quintiles AB, Uppsala, Sweden.

The study data management plan will describe the methods used to collect, check and process clinical data in detail.

Paper CRFs or eCRFs will be used to record all data except from bioanalysis concentration data and safety laboratory data or any other data that will be transferred electronically from an external source. For pCRFs data should be recorded legibly onto the pCRFs in blue or black ballpoint pen. Correction fluid or covering labels must not be used.

Paper CRF and eCRF operations are following Quintiles Standard Operating Procedures (SOPs) and data is processed in validated CFR 21 Part 11 compliant systems.

Screening failures (subjects who signed consent to take part in the study but were not allocated a screening 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 of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the latest AstraZeneca Drug Dictionary.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate. Genotype data will be transferred to the clinical

database, and merged with the clinical data from the main study, prior to the statistical analysis and reporting of the study.

11. EVALUATION AND CALCULATION OF VARIABLES

In all analyses, change from baseline will be calculated as the post-baseline value minus the baseline value, where baseline is defined as the last non-missing value before first administration of IP in each treatment period.

11.1 Calculation or derivation of safety variable(s)

11.1.1 Other significant adverse events (OAE)

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 DAEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (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 haematological and other laboratory abnormalities, and 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 patient reported outcome variables (Not applicable)

11.3 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at Quintiles AB, Global Phase I Services, Uppsala, Sweden. Quintiles' SOPs and Work Instructions (WIs) will be used as the default methodology if not otherwise specified.

Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2, or higher, (Pharsight Corp., Mountain View, California). All PK computations will be performed using WinNonlin Professional 5.2, or higher or SAS® Version 9.1, or higher (SAS Institute, Inc., Cary, North Carolina). Graphics may be prepared with SAS Version 9.1, or higher; or WinNonlin Professional 5.2, or higher.

Healthy volunteers who withdraw from the study following dosing, but prior to study completion, will be included in the PK analysis provided they have evaluable concentrations over the planned collection period. Healthy volunteers with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

If data permits, the following PK parameters will be determined for AMC for Day 9:

AUC	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
$C_{ss,max}$	Maximum steady state concentration in plasma
t_{max}	Time to reach maximum concentration

Additional PK parameters may be determined if deemed appropriate.

11.4 Calculation or derivation of pharmacodynamic variable(s)

Analysis of the PD of clopidogrel will be the responsibility of the study biostatistician at Quintiles, Global Phase I Services, Uppsala, Sweden. Quintiles SOPs and WIs will be used as the default methodology if not otherwise specified.

The primary PD variable is mIPA which will be based on mPA to 20 μmol/L ADP assessed at baseline (Day -1 for Period 1 and pre-dose on Day 1 for Period 2) and 24 h after dose on Day 9. If data permits, mIPA will be calculated as:

mIPA [1 − (postdose mPA) on Day 9)/(mPA at baseline)] × 100

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 General principles

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety PD, PK, respectively. The as-treated principle will be applied to all evaluations; ie, healthy volunteers who receive another treatment than the one assigned in the randomization list will be analyzed as belonging to the actual treatment group and not that assigned by randomization.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all healthy volunteers who received at least 1 dose of IP (esomeprazole 20 mg/ASA 81 mg, clopidogrel) and have at least 1 measured AMC plasma concentration at a scheduled PK time point post dose with no important protocol deviations or violations thought to significantly affect the PK of the drug. A strategy for dealing with data affected by such protocol violations and deviations will be agreed by at least the study pharmacokineticist and study statistician, prior to clean file.

12.1.3 Pharmacodynamic analysis set

The PD analysis set will include all healthy volunteers who received at least 1 dose of IP (esomeprazole 20 mg/ASA 81 mg, clopidogrel) and have at least 1 post dose PD assessment appropriate for the evaluation of interest with no important protocol deviations or violations thought to significantly affect the PD of the drug. A strategy for dealing with data affected by such protocol violations and deviations will be agreed by at least the study pharmacokineticist and study statistician, prior to clean file.

12.1.4 Safety analysis set

All healthy volunteers who received at least 1 dose of randomized IP (esomeprazole 20 mg/ASA 81 mg, clopidogrel) and for whom any post dose data are available will be included in the safety population.

12.2 Methods of statistical analyses

The PK analysis of the AMC will be the responsibility of the study pharmacokineticist at Quintiles AB, Global Phase I Services, Uppsala, Sweden. The PD, PK and safety summaries, selected figures and data listings as well as the statistical analysis of the PD and PK variables will be the responsibility of the study biostatistician at Quintiles AB, Global Phase I Services, Uppsala, Sweden (using SAS® version 9.2 or higher and, where appropriate, additional validated software).

Quantitative continuous variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, minimum (min) and maximum (max) values. Additionally, for PK parameters, (except for t_{max}), geometric means and geometric coefficient of variation (CV%) will be reported. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The geometric CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the standard deviation of the data on a log scale. Mean, SD, geometric mean and geometric CV% will not be calculated for t_{max}. In general, descriptive statistics will follow the rounding convention as in Quintiles SOPs and WIs.

Categorical variables will be summarized in frequency tables.

12.2.1 Baseline characteristics

Baseline characteristics will be presented with descriptive statistics.

12.2.2 Pharmacokinetics and pharmacodynamics

Listings of PD and PK blood sample collection times as well as derived sampling time deviations and in addition listings of PD (observed and change from baseline) and PK variables will be provided. Plasma concentrations and PD and PK variables will be summarized using descriptive statistics.

Plasma AMC concentrations below LLOQ will be handled as follows for descriptive statistics:

- At a time point where at least 1 value is above LLOQ but less than or equal to 50% of the values are below LLOQ, all values below LLOQ are set to LLOQ and mean (arithmetic and geometric), median, SD and CV% are calculated.

- At a time point where more than 50% of the observations are below LLOQ only individual values are reported; mean, SD, geometric mean and CV% will be set to NQ (not quantifiable). The min value and the median are set to <LLOQ.

- If all values are below LLOQ at any time point no descriptive statistics are calculated for that time point. Write NA (not applicable) in the field for SD and CV% and write <LLOQ in fields for mean, geometric mean, min, median and max in the table.

- The number of observations greater than LLOQ (n>LLOQ) will be reported in the table.

Geometric mean concentration-time profiles will be presented for both treatments on both linear and log-linear scale. Individual concentration-time data will be graphically presented on linear scale only. Linear plots ("spaghetti") of PK variables vs treatment will be displayed. The PK variables will be on the y-axis and include (if applicable): AUC, $AUC_{0\text{-last}}$, C_{max}, and t_{max} for AMC. The x-axis will include "clopidogrel" and "clopidogrel + esomeprazole 20 mg/ASA 81 mg". Each subject will be presented by 1 line within the graph.

Data from healthy volunteers excluded from an analysis population will be included in the data listings, but not in the summaries.

The PK variables and mIPA will be analyzed using linear mixed models (1 for each variable) with fixed effects for period and treatment and a random effect for subject within sequence. Kenward-Rogers approximation for degrees of freedom will be used. Model diagnostics such as residual plots, normality tests and Q-Q plots will be checked for all models. The results of these checks might result in different model definitions than the above or different statistical methods employed.

The mean differences between the treatments in the mIPA model will be calculated with 95% confidence interval (CI) for the differences. If deemed necessary judging by the PD variables' distribution, the PD data will analysed on log-scale and the corresponding estimates and CIs back-transformed to the original space giving true estimates of the ratios between treatments.

The ratio ((esomeprazole 20 mg/ASA 81 mg + clopidogrel)/clopidogrel) of AUC, $AUC_{0\text{-last}}$ and $C_{ss,max}$ with corresponding 90% CI for the ratios will be calculated.

12.2.3 Pharmacogenetics

Listings of CYP2C19 alleles and metabolic status will be provided. Subpopulation analysis of selected PD and/or PK variables by CYP2C19 genotype may be performed if found necessary and if data allows.

12.2.4 Safety

Continuous variables will be summarized using descriptive statistics by treatment. Categorical variables will be summarized in frequency tables (frequency and percentage) by treatment.

For qualitative variables, the sample size (N), the number of available data (n) and the percentage (of available data) for each class of the variable will be presented.

Adverse events will be summarized by treatment by preferred term and system organ class using MedDRA vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of volunteers who had any AEs, SAEs, AEs that led to withdrawal and AEs with severe intensity will be summarized.

In tables (and figures if any), AEs will be summarized by treatment and washout periods. The washout periods will be defined as "Washout Clopidogrel" and "Washout Esomeprazole 20 mg/ASA 81 mg " on an individual level depending on the preceding treatment. The washout periods ends at the first drug administration in the following treatment period or, in case of the washout after the last treatment period, at the end of study for the subject (follow-up). The washout periods are considered to start 24 h after the dose on Day 9 (ie, on Day 10) in the treatment periods.

Tabulations and listings of data for vital signs, clinical laboratory tests and physical examination findings parameters will be presented. A listing of screening pECG data will be presented. Where applicable, data will be summarized for the absolute value at each scheduled assessment, together with the corresponding changes from the baseline. For clinical laboratory tests, listings of values for each volunteer will be presented with abnormal or out-of-range values flagged.

For the purpose of tabulations and graphical presentations of safety laboratory data, if several measurements have been taken for the same subject, protocol time point and laboratory variable, the last non-missing value will used if taken before first administration of IP. Otherwise, the first non-missing value will be used.

12.3 Determination of sample size

The study is sized to estimate the absolute mean difference in IPA with and without the PPI with a specified precision. With 54 healthy volunteers, a 95% CI with length of at most 9 percentage units is achieved with at least 96% probability. With a projected dropout rate of 10%, a total of 59 healthy volunteers will be randomized.

The calculation assumes a SD of paired difference of 14% units, derived from the root mean square error of the analysis of internal data on ADP-induced maximum extent IPA for $\%IPA_{max}$ (20 µmol/L).

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The PI 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 Clinical Pharmacology Alliance (CPA) Study Physician. If the CPA Study Physician is not available, contact the CPA Program Director.

Name	Role in the study	Address & telephone number

13.2 Overdose

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized. Refer to the "Overdose" section of the official prescribing information at: http://www1.astrazeneca-us.com/pi/Nexium.pdf

Symptoms associated with ASA overdose include: vertigo, tinnitus, auditory impairment, hyperactivity, irritation, hallucinosis, tremor, asterixis, hyperventilation, thirst, erythema of the skin, hyperhidrosis, nausea, vomiting, and abdominal pain. Symptoms of severe intoxication with ASA include: unconsciousness, convulsions, and hyperthermia. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

Clopidogrel- refer to the "Overdose" section of the official prescribing information at: http://products.sanofi-aventis.us/PLAVIX/PLAVIX.html

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel 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 SAE, 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.

Females of childbearing potential must adhere to the birth control methods outlined in Section 4.1. If the Investigator receives information that a pregnancy has occurred during the study despite these restrictions, the designated Quintiles representative should be informed.

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Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An Open-label, Randomized, Single-center, 2-way Cross-over Interaction Study, Evaluating the Effect of Esomeprazole 20 mg/Acetylsalicylic acid 81 mg on the Pharmacodynamics and the Pharmacokinetics of Clopidogrel on Days 1 and 9 in Healthy Volunteers

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

ASTRAZENECA SIGNATURE(S)

An Open-label, Randomized, Single-center, 2-way Cross-over Interaction Study, Evaluating the Effect of Esomeprazole 20 mg/Acetylsalicylic acid 81 mg on the Pharmacodynamics and the Pharmacokinetics of Clopidogrel on Days 1 and 9 in Healthy Volunteers

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

SIGNATURE OF PRINCIPAL INVESTIGATOR

An Open-label, Randomized, Single-center, 2-way Cross-over Interaction Study, Evaluating the Effect of Esomeprazole 20 mg/Acetylsalicylic acid 81 mg on the Pharmacodynamics and the Pharmacokinetics of Clopidogrel on Days 1 and 9 in Healthy Volunteers

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

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.

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.