Clinical Study Protocol

Drug Substance	Omeprazole/Esomeprazole
Study Code	D9612C00034
Edition Number	1
Date	

An open-label, randomized, 4-treatment, 3-period, crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel 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

PROTOCOL SYNOPSIS

An open-label, randomized, 4-treatment, 3-period, crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy volunteers

Coordinating Principal Investigator

Study center(s) and number of volunteers planned

This protocol will be conducted utilizing from 1 to 3 study centers. Approximately 101 volunteers will be randomized in order to have 81 evaluable volunteers.

Study period		Phase of development
Estimated date of first volunteer enrolled	June 2010	Phase I
Estimated date of last volunteer completed	December 2010	

Objectives:

Primary objective

To assess the effect of esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg on the pharmacodynamic (PD) profile of clopidogrel by assessing maximum inhibition of platelet aggregation (mIPA) at Days 2, 6, 15 and 30 relative to baseline.

Secondary objectives

- To assess the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacokinetic (PK) profile of clopidogrel active metabolite by assessing the AUC, AUC_{0-t} and C_{max} after the loading dose of clopidogrel (Day 1) and $AUC_{0-t,ss}$ and $C_{ss,max}$ at Days 5, 14, and 29.

- To evaluate safety and tolerability of clopidogrel given concomitantly with esomeprazole, omeprazole, or lansoprazole.

Exploratory objectives

- To assess the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the PD profile of clopidogrel by assessing change in platelet reactivity index (ΔPRI), derived from flowcytometric assay (VASP) results, at Days 2, 6, 15, and 30 relative to baseline.

- To assess the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamic (PD) profile of clopidogrel excluding low responders (mIPA of 25% or less at Day 2 when receiving clopidogrel alone) by assessing maximum inhibition of platelet aggregation (mIPA) at Days 2, 6, 15 and 30 relative to baseline.

Study design

This is an open-label, randomized, 4-treatment, 3-period cross-over study designed to assess the PD and PK interaction between clopidogrel and esomeprazole, omeprazole or lansoprazole. Each volunteer will be randomized to receive a sequence of clopidogrel alone and two of the PPIs plus clopidogrel.

The reference treatment arm will consist of a clopidogrel loading dose of 300 mg administered on Day 1 and then clopidogrel 75 mg administered once daily for 28 days. The 3 test treatment arms will have the same clopidogrel dosing used in the reference treatment arm co-administered with either esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg once daily for 29 days. The route of administration is oral. The treatment periods will be separated by washout periods of at least 14 days. The randomization will be performed as a partially balanced design with 18 sequences, including clopidogrel alone in all treatment sequences.

Volunteers will be seen in the clinic for Screening (pre-entry) and Day -1 for clinic admission. Volunteers will be randomized on Day 1 (Treatment period 1 only) and visits for PD measurements will occur predose (baseline) and predose on Days 2, 6, and 15 as well as on Day 30 (24 hour after the Day 29 dose). Blood samples for quantitation of the active metabolite of clopidogrel will be taken prior to and 0.25, 0.5, 1, 1.5, 2, 4, and 6 hours after the first dose of clopidogrel on Day 1 and prior to and 0.25, 0.5, 1, 1.5, 2, and 4 hours after the clopidogrel doses on Days 5, 14 and 29. Volunteers will be admitted to the clinic on Days -1, 4, 13, and 28 and released on Days 2, 6, 15 and 30 after the scheduled PK and PD assessments are obtained. The total study duration is approximately 146 days which includes a 21 day pre-entry screening and a 7 day follow up visit.

Target volunteer population

The target population is healthy males within age of 18-45 years and females within age of 18-55 years and Body Mass Index (BMI = weight/height^2) greater than or equal to 19 kg/m^2 and less than or equal to 30 kg/m^2.

Outcome variable(s):

- Pharmacodynamic:
  The primary endpoint of this study is maximum inhibition of platelet aggregation (mIPA) based on maximum platelet aggregation (mPA) to 20 μM ADP assessed at baseline and on Days 2, 6, 15, and 30. In addition, VASP (flowcytometric VASP-assay) parameters of platelet reactivity index (PRI) and change in platelet reactivity index (ΔPRI), exploratory PD endpoints, will be assessed at these same time points.

- Pharmacokinetics:
  AUC, AUC_{0-t}, and C_{max} will be calculated after the loading dose of clopidogrel on Day 1 and $AUC_{0-t,ss}$ and $C_{ss,max}$ on Days 5, 14, and 29 for clopidogrel active metabolite.

- Safety:
  Adverse events, vital signs, and safety laboratory variables will be assessed throughout the study.

Statistical methods

Plasma concentrations of clopidogrel active metabolite and the derived PK parameters will be summarized by treatment using descriptive statistics.

Both PD and PK variables will be analyzed using a linear mixed effect analysis of variance (ANOVA) model with fixed effect for period, sequence, site, and treatment and a random effect for volunteer within sequence. The clopidogrel alone treatment will be the reference for the 3 test interaction treatment arms.

Safety data will be presented with descriptive statistics. Adverse events will be summarized by incidence within treatment. Laboratory safety tests and vital signs will be summarized by treatment group and time points within treatment groups.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event
ALT	Alanine aminotransferase
AMC	active thiol metabolite of clopidogrel
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve from time zero to infinity
AUC_{0-t}	Area under the curve from time zero to last quantifiable concentration
AV	Atrioventricular block
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum observed concentration
CPA	Clinical Pharmacology Alliance
CK	Creatine kinase
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
CYP2C19	Cytochrome P450 2C19
DAE	Discontinuation of Investigational Product due to Adverse Event
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EDC	Electronic data capture
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
h	Hours
Hb	Hemoglobin

Abbreviation or special term	Explanation
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine device
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
max	Maximum
NC	Not calculable
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
min	Minimum
mIPA	Maximum inhibition of platelet aggregation
mPA	Maximum platelet aggregation
NSAID	Nonsteroidal anti-inflammatory drug
OAE	Other Significant Adverse Event
OTC	Over-the-counter
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex.
PICTS	Phase I clinical trial system (brand name for Quintiles, Inc EDC)
pECG	Paper ECG
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PRI	Platelet Reactivity Index
ΔPRI	Change from baseline in PRI
QRS	ECG interval measured from the onset of the QRS complex to the J point.

Abbreviation or special term	Explanation
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	The time between corresponding points on 2 consecutive R waves on ECG
Rsq	Regression coefficient
SAE	Serious adverse event
SD	Standard deviation
SDV	Study data verification
SI	Système International
SOC	System organ class
SOP	Standard Operating Procedure
SS	Steady state
ST	ST interval of ECG
STEMI	ST segment elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$, Interval	Time interval of the log-linear regression to determine $t_{1/2}$
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
ULN	Upper limit of normal
VASP	Vasodilator-stimulated phosphoprotein

1. INTRODUCTION

1.1 Background

Clopidogrel is a platelet aggregation inhibitor approved for use in patients with a history of recent myocardial infarction (MI), recent stroke or established peripheral arterial disease, in patients with acute coronary syndrome, and in patients with ST-segment elevation myocardial infarction (STEMI). Its use is also recognized in US and European guidelines as the standard of care for patients with coronary stent placement. The widespread clinical usage of clopidogrel is based on studies that showed an important reduction in cardiovascular mortality and morbidity with clopidogrel (Smith et al 2006, Silber et al 2005). Most of these trials involved concomitant use of clopidogrel and aspirin (Yusuf et al 2001, Sabatine et al 2005, Steinhubl et al 2002, Chen et al 2005). Concomitant use of clopidogrel and aspirin has been associated with a significantly increased risk of bleeding. The bleeding has been generally accepted, since the benefits of concomitant therapy are substantial in terms of cardiovascular risk reduction. In recent years, the concomitant use of clopidogrel and aspirin has been strongly recommended in cardiology guidelines around the world, so bleeding has become a more common event.

Due to the common occurrence of acid related diseases patients with cardiovascular diseases commonly receive proton pump inhibitors (PPIs). In addition, in an effort to ameliorate the gastrointestinal side effects associated with clopidogrel, PPIs have in the past been routinely co administered with clopidogrel. Clopidogrel is administered as an inactive prodrug requiring metabolism by cytochrome P450 isozymes for its antiplatelet activity. A commonly prescribed PPI, omeprazole (when administered as a once daily 80 mg dose) has been shown to inhibit the conversion of clopidogrel to the active metabolite. Current prescribing information for clopidogrel includes a warning about its use with omeprazole.

The aim of this study is to determine if there is a pharmacological interaction between clopidogrel and different types of PPIs, and if the extent of this possible interaction would change over time.

1.2 Research hypothesis

The effect of PPI co-administration on the pharmacodynamics (PD) and pharmacokinetics (PK) of clopidogrel is not similar across this class of compounds but will differ based on the physical and chemical characteristics of each unique PPI.

1.3 Rationale for conducting this study

Clopidogrel has proven its efficacy in reducing atherothrombotic events after percutaneous coronary intervention (PCI), although considerable interindividual variability in response has been reported. Clopidogrel is administered as an inactive prodrug requiring metabolism 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 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 (Karzui et al 2010), 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 very important. 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 PD interaction studies between clopidogrel and omeprazole or esomeprazole showed inconsistent results (Jermano et al 2009, Lapuerta et al 2008, Gilard et al 2008, Sibbing et al 2009, Zuern et al 2009, Cuisset et al 2009, Siller-Matula et al 2009, Moceri et al 2009, Furuta et al 2010).

In a recent study referenced in the Plavix® Prescribing Information and using omeprazole 80 mg as a tool/probe to inhibit *CYP2C19* in healthy volunteers, the formation of clopidogrel active metabolite decreased by 46%, indicating a substantial 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). In this study, clopidogrel will be given without PPIs as the reference treatment and omeprazole 80 mg daily will be administered concurrently and serve as a positive control. Esomeprazole 40 mg daily has been chosen for this study to be administered concurrently with clopidogrel as it is the approved dose healing of reflux esophagitis. A previous interaction study showed a small but significant interaction between lansoprazole 30 mg and clopidogrel 75 mg (Small et al 2008). In an approach similar to the approach taken in a study performed by Sanofi-Aventis which utilized the 80 mg dose of omeprazole as a probe, lansoprazole 60 mg daily will be administered concurrently with clopidogrel to serve as a probe to examine this potential drug-drug interaction.

There is also a possibility that the extent of the PD interaction may change over time. Due to irreversible binding, platelets are affected for the remaining of their lifespan (approximately 7 to 10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Hence an increase in the PD effect of clopidogrel over time is expected with repeated doses of 75 mg clopidogrel that reaches steady state between Day 3 and Day 7 (Plavix® Prescribing Information). A study has shown that the platelet response to clopidogrel improved up to thirty days in patients exhibiting clopidogrel resistance at baseline (Kalantzi et al 2009). In one study, it was shown that to obtain a PD effect of clopidogrel (percent PRI) on Day 29 similar to that on Day 1, only 25% of the AUC of day 1 was needed on Day 29 (Wallentin et al 2008). Another study showed a negative effect of PPIs on the PD effect of clopidogrel in the initial phase of clopidogrel administration (loading dose group) but not during maintenance therapy (DeBoer et al 2009).

Two different methods for measuring the PD effect of clopidogrel are utilized, the newer Flowcytometric Vasodilator-Stimulated Phosphoprotein (VASP)-analysis and Light Transmission Aggregometry, the later has been chosen for measuring the primary variable as it is regarded as the gold standard. The absolute change in platelet reactivity when measured with Light Transmittance Aggregometry induced by 20 µM ADP showed strong correlation

with the C_{max} value of the Active Metabolite of Clopidogrel (AMC). In contrast, no significant association was observed between the C_{max} value of the AMC and inhibition of platelet aggregation using a lower concentration of 5µM ADP, hence only the higher dose of ADP will be used (Bouman et al 2009).

The aim of this study is to determine if there is a pharmacodynamic and/or pharmacokinetic interaction between clopidogrel with different types of PPIs, and if the extent of this possible interaction would change over time.

1.4 Benefit/risk and ethical assessment

Clopidogrel, esomeprazole, omeprazole or lansoprazole have been available for marketed use for several years. The safety profiles are well described in the respective package inserts for these products. The following are links to the official prescribing information for each study medication:

clopidogrel- http://products.sanofi-aventis.us/PLAVIX/PLAVIX.html

esomeprazole- http://www1.astrazeneca-us.com/pi/Nexium.pdf

omeprazole- http://www1.astrazeneca-us.com/pi/Prilosec.pdf

lansoprazole- http://www.tpna.com/products/default.aspx

This is a standard drug interaction study. Safety will be monitored during the study. There are no direct benefits for the volunteers participating in this study. They will be compensated for their time and inconvenience. All payments will be approved by an Ethics Committee.

2. STUDY OBJECTIVES

2.1 Primary objective

To assess the effect of esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg on the pharmacodynamic (PD) profile of clopidogrel by assessing maximum inhibition of platelet aggregation (mIPA) at Days 2, 6, 15 and 30 relative to baseline.

2.2 Secondary objectives

- To assess the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacokinetic (PK) profile of clopidogrel active metabolite by assessing the AUC, AUC_{0-t} and C_{max} after the loading dose of clopidogrel (Day 1) and $AUC_{0-t,ss}$ and $C_{ss,max}$ at Days 5, 14, and 29.

- To evaluate safety and tolerability of clopidogrel given concomitantly with esomeprazole, omeprazole or lansoprazole.

2.3 Exploratory objectives

- To assess the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the PD profile of clopidogrel by assessing change in platelet reactivity index (ΔPRI), derived from flowcytometric assay (VASP) results, at Days 2, 6, 15, and 30 relative to baseline.

- To assess the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamic (PD) profile of clopidogrel excluding low responders (mIPA of 25% or less at Day 2 when receiving clopidogrel alone) by assessing maximum inhibition of platelet aggregation (mIPA) at Days 2, 6, 15, and 30 relative to baseline.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is an open-label, randomized, 4-treatment, 3-period crossover multicenter study designed to assess the PD and PK interaction between clopidogrel and esomeprazole, omeprazole or lansoprazole. This protocol will be conducted utilizing from 1 to 3 study centers. Approximately 101 volunteers will be randomized in order to have 81 evaluable volunteers. Each volunteer will be randomized to receive a sequence of clopidogrel alone and two of the PPIs plus clopidogrel.

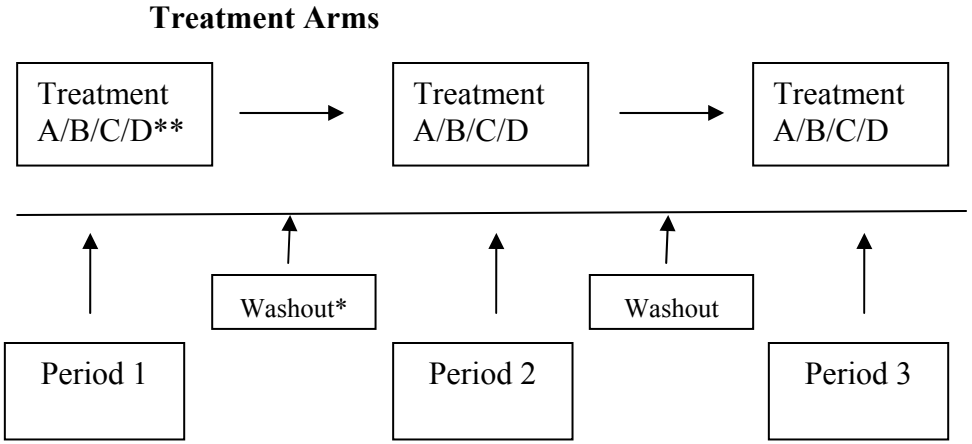
The reference treatment arm will consist of a clopidogrel loading dose of 300 mg administered on Day 1 and then clopidogrel 75 mg administered once daily for 28 days. The 3 test treatment arms will have the same clopidogrel dosing used in the reference treatment arm co-administered with either esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg once daily for 29 days. The route of administration is oral. The treatment periods will be separated by washout periods of at least 14 days. The randomization will be performed as a partially balanced design with 18 sequences, including clopidogrel alone in all treatment sequences.

Volunteers will be in the clinic for screening (pre-entry) and Day -1 for clinic admission. Volunteers will be randomized on Day 1 (Treatment period 1 only) and visits for PD measurements will occur predose (baseline) and predose on Days 2, 6, and 15 as well as on Day 30 (24 hour after the Day 29 dose). Blood samples for quantitation of the active metabolite of clopidogrel will be taken prior to and 0.25, 0.5, 1, 1.5, 2, 4, and 6 hours after the first dose of clopidogrel on Day 1 and prior to and 0.25, 0.5, 1, 1.5, 2, and 4 hours after the clopidogrel doses on Days 5, 14, and 29. Volunteers will be admitted to the clinic on Days -1, 4, 13, and 28 and released on Days 2, 6, 15, and 30 after the scheduled PK and PD assessments are obtained.

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

For a summary of study design, see Figure 1. For an overview of study procedures see Table 1.

Figure 1 Study design



A – lansoprazole 60 mg + clopidogrel 300 mg /75mg
B – omeprazole 80 mg + clopidogrel 300/75 mg
C – esomeprazole 40 mg + clopidogrel 300/75 mg
D – clopidogrel 300/75 mg alone (all volunteers will receive this treatment)
* 14 *day washout periods*
** *30 day treatment periods with a total treatment duration based on treatment periods and wash out periods =118 days*

Table 1 Study plan

Event	Screening [a]		All Treatments											Washout[b]	Follow up [c]
Study Day	**Day -21 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3 & 4 [d]**	**Day 5**	**Day 6**	**Day 7 to 13 [d]**	**Day 14**	**Day 15**	**Day 16 to 28 [d]**	**Day 29**	**Day 30**		
Informed consent	X														
Review of inclusion/exclusion criteria	X	X													
Demography	X														
Randomization			X [a]												
Medical and surgical history	X														
Viral serology	X														
Physical examination	X	X								X			X		X
Laboratory safety tests (clinical chemistry, hematology, urinalysis)	X	X								X			X		X
aPTT, PT, and Fecal Hb –test [e]		X													
hCG (females only)		X								X			X		X
Body weight and height	X [f]									X			X		X
pECG [g]	X	X								X			X		X
Blood pressure and pulse [g]	X	X	X	X		X			X	X		X	X		X
Alcohol and drugs of abuse screen	X	X													
CYP2C19 blood sample (1st period only)		X													
Admission to clinic		X			X [h]			X [h]			X [h]				
Clopidogrel administration [i]			X	X	X	X	X	X	X	X	X	X			
PPI administration [j]			X	X	X	X	X	X	X	X	X	X			
Clopidogrel active metabolite PK blood sampling [k]			X			X			X			X			
PD assessments (platelet aggregometry and VASP) [l]		X [m]	X [n]	X			X			X			X		
Standardized food [o]			X	X	X	X		X	X	X	X	X	X		
Concomitant medication review	Assessed throughout the study														
Adverse event (AE)/SAE collection [p]			Assessed throughout the study after the first dose of study medication												
Discharge from clinic [q]				X			X			X			X		

a Only completed prior to Period 1.

b Only completed following Periods 1 and 2.
c. Only completed at least 7 days after the last dose of Period 3.
d. Conducted as outpatient visits.
e. Three stool occult blood cards (or jars) with instructions will be given to each volunteer at screening and volunteers will be instructed to return the cards at the Day -1 visit.
f. Height is to be measured at screening only.
g. pECGs and vital signs will be taken after volunteer has been supine for 10 minutes and predose where applicable.
h. Admission to clinic on Days 4, 13 and 28.
i. Clopidogrel loading dose (300 mg) on Day 1 followed by clopidogrel 75 mg once daily for 28 days.
j. Once daily dosing of esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg based on randomization schedule for 29 days.
k. Day 1 samples will be obtained predose and 0.25, 0.5, 1, 1.5, 2, 4, and 6 hours postdose . Days 5, 14 and 29 samples will be obtained predose and 0.25, 0.5, 1, 1.5, 2, and 4 hours postdose
l. PD measurements (platelet aggregometry using 20 μM ADP and VASP) will be done prior to dosing to obtain measurements at baseline (Day -1 for Period 1 and Day1 for Periods 2 and 3) and then predose on Days 2, 6, and 15 as well as Day 30 (24 hours after the Day 29 dose).
m. Baseline PD samples obtained on Day -1 for Period 1 only
n. Baseline samples obtained on Day 1 for Periods 2 and 3, no Day -1 sample is collected for Periods 2 and 3.
o. Standardized meals will be consumed on in-patient study days.
p. All AEs will be collected from the time of the first administration of IP until the end of the study (including the follow-up visit). Before the first administration of IP, only SAEs will be collected.
q. Volunteers will be discharged after all PK and PD assessments have been obtained

3.2 Rationale for study design, doses and control groups

In an effort to ameliorate the upper gastrointestinal side effects associated with clopidogrel, proton pump inhibitors (PPIs) have in the past been routinely co administered with clopidogrel. Clopidogrel is administered as an inactive prodrug requiring metabolism by cytochrome P450 isozymes for its antiplatelet activity. A commonly prescribed PPI, omeprazole (when administered as a once daily 80 mg dose) has been shown to inhibit the conversion of clopidogrel to the active metabolite. Current prescribing information for clopidogrel includes a warning about its use with omeprazole.

Some previous studies indicated a dose response relationship with the presence or absence of interaction (Lapuerta et al 2008). In this study, clopidogrel will be given without PPIs as the reference treatment and omeprazole 80 mg daily will be administered concurrently and serve as a positive control. Esomeprazole 40 mg daily has been chosen for this study to be administered concurrently with clopidogrel as it is the approved dose healing of reflux esophagitis. A previous interaction study showed a small but significant interaction between lansoprazole 30 mg and clopidogrel 75 mg. In an approach similar to the approach taken in a study performed by Sanofi-Aventis which utilized the 80 mg dose of omeprazole as a probe, lansoprazole 60 mg daily will be administered concurrently with clopidogrel to serve as a probe to examine this potential drug-drug interaction.

Due to irreversible binding with clopidogrel active metabolite, 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 30 day treatment duration in this study will increase the probability that maximum platelet inhibition has occurred and that the PPIs have reached steady-state conditions. In addition, the 14 day washout duration will ensure complete platelet turnover between treatment periods.

4. VOLUNTEER SELECTION CRITERIA

The Investigator should keep a record, the screening log, of volunteers who entered pre-study screening.

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

4.1 Inclusion criteria

For inclusion in the study volunteers must fulfilll the following criteria:

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

2. Healthy males within age of 18-45 years and females within age of 18-55 years with suitable veins for cannulation or repeated vein puncture. Females volunteers must

be of nonchildbearing potential (post-menopausal, had a hysterectomy and/or bilateral oophorectomy) or be of childbearing potential and have a negative serum hCG pregnancy test on Day -1. Female subjects of childbearing potential must consent to using 1 clinically accepted method of contraception for 10 days before receiving the first dose of study medication, throughout the entire study including each washout, and for 1 month after completion of the study. Clinically accepted methods of contraception that may be used by the subject and/or partner include: diaphragm with spermicide, IUD (except for Mirena®), condom with spermicidal foam, or condom with vaginal spermicide.

3. Weight of 50-95 kg, inclusive, and a BMI between 19-30 kg/m^2, inclusive.

4. No clinically significant abnormal findings as judged by the Investigator on enrollment physical exam.

4.2 Exclusion criteria

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

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

2. History or presence of gastrointestinal e.g. GI ulcer, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs.

3. Any clinically significant illness within 4 weeks of the first administration of investigational product. 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.

4. Any clinically significant abnormalities in clinical chemistry, hematology (e.g. history or presence of thrombocytopenia, abnormal activated partial thromboplastin time and prothrombin time) or urinalysis (> +1 U-Erythrocytes at the preentry visit) or positive feces-hemoglobin (F-Hb) results as judged by the Investigator.

5. 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.

6. Suspicion of or known Gilbert's disease.

7. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV)

8. Any clinically significant abnormal vital signs (diastolic blood pressure, systolic blood pressure, heart rate after 10 minutes rest in the supine position) as judged by the investigator.

9. Any clinically important abnormalities in rhythm, conduction or morphology of resting pECG. This includes 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 less than 110ms 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

10. Prolonged QTcF greater than 450 msec or shortened QTcF less than 350 msec or family history of long QT syndrome.

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

12. Smoking or other sort of nicotine use.

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

14. Positive screen for drugs of abuse at screening or on admission to the unit or positive screen for alcohol on admission to the unit prior to the first administration of investigational product.

15. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to investigational products.

16. Excessive use currently of caffeine containing drinks e.g., coffee, tea, caffeine containing energy drinks and cola (more than 5 cups of coffee or equivalent per day).

17. Use of drugs with enzyme inducing properties such as rifampicin or St John's Wort an inhibitors such as ketoconazole, gemfibrozil or macrolide antibiotics within 30 days prior to the first administration of investigational product.

18. Use of any prescribed or over-the counter (OTC) medication including use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or any other drug known to increase the propensity for bleeding within 2 weeks of the treatment period or need for antacids, or use of analgesics other than

paracetamol/acetaminophen, nasal anticongestants, herbal remedies, vitamins and minerals during the two weeks prior to the first administration of the investigational product or longer if the medication has a long half-life. Occasional use of paracetamol/acetaminophen is allowed for minor pains and headache.

19. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges within 14 days before the first administration of the investigational product.

20. Plasma donation within one month of screening or any blood donation/blood loss greater than 500mL during the three months prior to screening.

21. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within a minimum of 6 weeks prior to the first administration of investigational product in this study. The period of exclusion begins at the time of the last dose in the prior study. Note: volunteers consented and screened but not dosed in this study or a previous phase I study, are not excluded.

22. Previous randomization of treatment in the present study.

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

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

25. Platelet count less than 150,000 or any other conditions that would increase the risk of bleeding.

The following exclusion criteria apply to the requirement for CYP2C19 genotyping:

26. Previous allogeneic bone marrow transplant.

27. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5. STUDY CONDUCT

5.1 Restrictions during the study

Volunteers will have to comply with the following restrictions:

1. Fast (except for water) for at least 10 hours prior to dosing during inpatient visits. Patients will be allowed to drink a moderate amount (less than 500 mL) of water from midnight until 1 hour prior to dosing. No food consumption will be allowed for at least 1 hour postdose.

2. Abstain from consuming any of the following:
   - Alcohol from 72 hours before admission, during the residential period and for 72 hours before the study follow-up visit
   - Energy drinks containing taurine or glucuronolactone e.g. Red Bull from 72 hours before admission, during the residential period and for 72 hours before the study follow-up visit
   - Caffeine-containing drinks during the residential period. Excessive intake of caffeine (greater than 5 cups of coffee or equivalent) should be avoided between discharge from the unit and the study follow-up visit
   - Poppy seeds found in speciality bread from time of consent until after the final medical examination at the study follow-up
   - Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges and liquorice from 14 days before admission and St John's wort from 30 days before admission, until after final medical examination at the study follow-up

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

4. Abstain from taking any medication (prescribed or over the counter products), including use of aspirin, non-steriodal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or any other drug known to increase the propensity for bleeding, analgesics other than occasional paracetamol/acetaminophen and nasal ancicongestants, from two weeks prior to the first administration of investigational product until after the final medical examination at the study follow-up. However, this should not obviate necessary medical treatment. If any medication is necessary during the residential period, it should be prescribed by the investigator and the AstraZeneca Study Team Physician should be informed.

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

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

7. Female volunteers of childbearing potential must consent to using 1 clinically accepted method of contraception for 10 days before receiving the first dose of study medicaiton, throughout the entire study including each washout, and for 1 month after completion of the study. Clinically accepted methods of contraception that may be used by the subject and/or partner include: diaphragm with spermicide, IUD (except for Mirena®), condom with spermicidal foam, or condom with vaginal spermicide.

8. Not participate in any other clinical study.

9. Volunteers will be served standardized meals during the inpatient visits. Excessive intake of caffeine (greater than 5 cups of coffee or equivalent) should be avoided during the washout periods and prior to final follow-up.

10. Male volunteers and their partners should use appropriate contraception (double barrier method or vasectomy) throughout the entire study starting from the 1st dose of study medication including each washout and refrain from sperm donation until at least 3 months after the last dose of study medication, since no data on male reproduction is available.

5.2 Volunteer enrollment and randomization, and initiation of investigational product

The Investigator will ensure:

1. Signed informed consent is obtained from each potential volunteer before any study specific procedures are performed.

2. The PICTS Bedside Data Capture and Study Management system utilized by Quintiles has 3 different numbers assigned to identify volunteers throughout various stages of a study.

- Enrollment Number: Each screened volunteer will be identifiable by a unique enrollment number or Ecode beginning with the letter E, followed by the site number, and a unique 3 digit code for the screening order. For example, E0001022, where 0001 is the site number and 022 is the sequential number given to the volunteer based on the screening order for that study. The number will be used for the 'Screening' period and will not be re-used for any other volunteers in the study.

- Volunteer Number: Volunteers who meet all eligibility criteria will be assigned a unique number based on the randomization of the study. The unique number will be used for the remainder of the study and it will not be re-used for any other volunteers in the study. Each eligible volunteer is assigned a unique randomization code (volunteer number), beginning with "101".

3. The eligibility of each volunteer is determined, see Sections 4.1 and 4.2. Randomization will be performed on the morning of dosing for each group. Randomization codes will be assigned strictly sequentially as volunteers become eligible for randomization.

Volunteers who withdraw from the study may be replaced at the discretion of the sponsor and/or Investigator. All replacements must be approved by AstraZeneca. If a volunteer withdraws his/her participation in the study, then his/her enrollment/randomization code cannot be reused. In the event that a volunteer is replaced, an unblinded pharmacy delegate at the site will determine the appropriate randomization code (volunteer number) for the replacement volunteer so that each replacement volunteer will be assigned to the appropriate treatment and will receive the same study drug or placebo as the volunteer being replaced. Randomization codes (volunteer numbers) for replacement volunteers will be assigned as follows: the original volunteer's number plus 1000 (eg, if the original volunteer being replaced had a volunteer number of 104, the replacement volunteer's number will be 1104).

5.2.1 Procedures for randomization

A randomization scheme will be produced by using the AstraZeneca global randomization system (GRand). Approximately 101 will be randomized to have 81 evaluable volunteers complete the study. The randomization will be performed as a partially balanced design with 18 sequences, including clopidogrel alone in all treatment sequences. The 18 treatment sequences are shown in Figure 2.

Figure 2 Treatment sequences

C	C+O80	C+E40
C	C+O80	C+L60
C	C+E40	C+L60
C	C+E40	C+O80
C	C+L60	C+O80
C	C+L60	C+E40
C+O80	C	C+E40
C+O80	C	C+L60
C+E40	C	C+L60
C+E40	C	C+O80

C+L60	C	C+O80
C+L60	C	C+E40
C+O80	C+E40	C
C+O80	C+L60	C
C+E40	C+L60	C
C+E40	C+O80	C
C+L60	C+O80	C
C+L60	C+E40	C

C=clopidogrel
E=esomeprazole
O=omeprazole
L=lansoprazole

Randomization codes will be assigned strictly sequentially as volunteers become eligible for randomization.

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

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

Where volunteers that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where 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 volunteer from treatment.

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

5.4 Blinding and procedures for unblinding the study

Not applicable.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
lansoprazole	Oral capsule, 30 mg	Takeda Pharmaceuticals
clopidogrel	Oral tablet, 75 mg	Bristol-Myers Squibb/Sanofi-Aventis
esomeprazole	Oral capsule, 40 mg	AstraZeneca
omeprazole	Oral capsule, 40 mg	AstraZeneca

All study medications will be purchased by AstraZeneca in commercially available packaging. The responsible study staff will dispense the investigational product to the volunteers, according to the randomization scheme.

5.5.2 Doses and treatment regimens

This study has 4 treatment arms with 3 treatment periods separated by a 14 day washout period. Volunteers will receive 3 of the 4 following treatments. Treatment D, clopidogrel alone, will be administered to each volunteer. All study medications will be administered via the oral route.

Treatment A – Lansoprazole 60 mg (2x30-mg capsule) once daily coadministered with clopidogrel (see treatment D below) for 29 days.

Treatment B – Omeprazole 80 mg (2x40-mg capsule) once daily coadministered with clopidogrel (see treatment D below) for 29 days.

Treatment C – Esomeprazole 40 mg (1x40-mg capsule) once daily coadministered with clopidogrel (see treatment D below) for 29 days.

Treatment D – Clopidogrel 300 mg loading dose on Day 1 and then 75 mg daily for 28 days.

During the inpatient portions of the study, volunteers will be in an upright position (upper part of the body erect at least 45 degrees from horizontal) at the time of study drug administration and will be asked to remain in an upright position for at least 1 hour following study drug administration. During the inpatient portions of the study, all study medications will be administered following at least a 10 hour fast and volunteers will continue to fast for 1 hour after dosing.

During the outpatient portions of the study, volunteers will be instructed to take study medications at approximately the same time of day that dosing occurred in the clinic. Volunteers will be instructed to record the date and time of each dose of study medication in a medication log and instructed to return the medication log at each clinic visit. If a volunteer forgets to take a dose of study medication, they should be instructed to take the missed dose as

soon as possible if it is less than or equal to 12 hours since the dose was missed. If it has been longer than 12 hours since the dose was missed, the volunteer should be instructed to skip that dose and wait to take the next scheduled dose.

The tablets and capsules must not be chewed, crushed or divided, but should be swallowed whole with approximately 240 mL water.

An overview of the study procedures is given in Table 1.

5.5.3 Labelling

All supplies of commercially available product will be labelled in accordance with local law and trial requirements prior to dispensing.

5.5.4 Storage

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

5.6 Concomitant and post-study treatment(s)

Use of drugs with enzyme inducing properties such as rifampicin or St John's Wort and inhibitors such as ketoconazole, gemfibrozil or macrolide antibiotics are prohibited within 30 days prior to the first administration of investigational product.

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

If medications are necessary, these should be documented in the appropriate sections of the EDC system and the Investigator must decide if the volunteer should remain in the study or be withdrawn from the study.

5.7 Treatment compliance

Investigational product administration will be supervised by staff during the inpatient portions of the study. During the outpatient portions of the study, volunteers will record the date and time of each clopidogrel and PPI dose in a medication log. These log entries will be reviewed by clinic staff when the volunteer is admitted to the clinic for inpatient visits and the data will entered into the EDC system.

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 volunteer.

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

5.8 Discontinuation of investigational product and withdrawal from study

A volunteer who decides to discontinue investigational product 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(s). Adverse events will be followed up (See Sections 6.3.3 and Section 6.3.4).

Volunteers may be discontinued from investigational product or study treatment and assessments in the following situations:

- The volunteer is at any time free to discontinue treatment, without prejudice to further treatment.
- Any clinically relevant bleeding or repeated minor bleeding according to the judgment of investigator.
- Any trauma, accident, or medical condition with the consequences of surgery even during the washout period.
- Any need for medication that could influence the outcome of the study.
- Severe non-compliance to study protocol as judged by the Investigator and/or AstraZeneca.
- Risk to volunteer as judged by the Investigator and/or AstraZeneca.

Volunteers who discontinue prematurely from the study should complete the assessments listed for the follow up visit in Table 1 if possible.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

For this study, volunteer data will be collected by EDC. Where electronic data capture is not possible, the source data will be captured on paper.

The Investigator will ensure that data are recorded on the EDC as specified below. He/She ensures the accuracy, completeness, and timeliness of the data recorded for data queries and all required reports according to any instructions provided.

6.1.1 Electronic data capture at AstraZeneca clinical pharmacology units

Data are collected electronically for each study volunteer by an EDC data management and workflow system. Data are directly captured at the bedside where the data are collected electronically from instrumentation, or data are entered through touch-pad entry screens by the site personnel at the bedside. Investigators and study personnel will be responsible for the data capture and will respond to queries within the EDC data management system. For volunteers who discontinue or terminate from the study, the site personnel will complete a termination screen that clearly documents the reason for termination on the end-of-study screens.

The EDC collected data is real-time data collection and reflects the latest observations on the volunteers participating in the study. Correction of any data errors and other such changes are made by changing or updating the data in the system which also requires the entry of the user's name and a password for each change to be captured in the electronic audit trail.

Clinical data (including AEs and concomitant medications) will be entered into a 21 Code of Federal Regulations Part 11-compliant data management system provided by Quintiles, Inc. The data system includes password protection and internal quality checks, such as automatic verification range checks, to identify data that appear to be out of the specified ranges. Programmed edit specifications identify discrepancies in the data which may be addressed by the site.

When data have been entered, reviewed, edited, and source data verification performed by the AstraZeneca representative, the data will be frozen to prevent further editing.

6.2 Data collection and enrollment

Each volunteer will undergo an enrollment medical examination within 21 days prior to randomization (see Table 1). This will consist of:

- Demographic data: date of birth, sex and race.
- Weight, height, habits of nicotine and alcohol 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 (reflexes only).
- Resting pulse and blood pressure measurement.
- Blood sample for standard clinical chemistry, hematology, and a mid-stream urine sample for urinalysis and drugs of abuse test.
- hCG (females only).

6.2.1 Follow up procedures

A follow up visit will be scheduled at least 7 days after the last dose of study drug. This visit will include a check for concomitant medications and AEs, collection of blood and urine samples for clinical chemistry, (hCG- females only), hematology and urinalysis, assessment of vital signs, weight, pECG, and a physical examination.

6.3 Safety

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

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a 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, pECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or wash-out 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 fulfills 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 volunteer or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to the Clinical Study Protocol (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 study medication throughout all the treatment periods and washouts up to and including the follow-up visit.

Serious adverse events will be recorded from the time of informed consent up to and including the follow-up visit.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the 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 EDC system. AstraZeneca retains the right to request additional information for any volunteer with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be 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 Investigational Product (IP) (yes or no)
- Action taken with regard to IP
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- 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 and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

Adverse events based on signs and symptoms

All AEs spontaneously reported by the volunteer or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the EDC system. 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 CSR. Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

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

6.3.4 Reporting of serious adverse events

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

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 one calendar day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

The site will complete the AstraZeneca “Serious Adverse Event Report – Clinical Study” and forward to the following secure AstraZeneca SAE email address within 1 calendar day (AEMailboxClinicalTrialTCS@astrazeneca.com). If needed, the site may also fax the SAE Report to the following fax line: (302-886-4114).

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the study plan and time schedule (Table 1). The laboratory variables to be measured are summarized in Table 2.

Table 2 Laboratory variables

Clinical chemistry	**Hematology**
Serum (S)-Albumin	Blood (B)-Hemoglobin
S-ALT	B-Platelet count
S-AST	B-Red Blood Cell Count
S-Alkaline phosphatase	B-Hematocrit
S-Bilirubin, total	B-White Blood Cell Count with differential
S-Calcium, total	B-Reticulocyte Count
S-Creatinine	B-Mean Corpuscular Volume
S-glucose	B-Mean Corpuscular Hemoglobin Concentration
S-Potassium	B-Mean Corpuscular Hemoglobin
S-Sodium	B-Red Blood Cell Distribution Width
S-Blood Urea Nitrogen	**Urinalysis**
S-Calcium	Urine (U)-Glucose
S-Chloride	U-Red Blood Cells
S-Carbon dioxide	U-Protein
S-Creatine Phosphokinase	U-Occult Blood
S-Direct Bilirubin	U-Leukocyte esterase
S-Lipid Panel	U-Bilirubin
S-hCG (females only)	U-Ketones
Other tests[a]	U-Specific Gravity
Activated partial thromboplastin time (aPTT)	U-pH
Prothrombin time (PT)	U-Color
Fecal Hb –test	U-Appearance
Serology[b]	U-Urobilinogen
Hepatitis B surface antigen	U-Nitrites
Hepatitis C (antibodies)	
HIV (antibodies)	

[a] Only at Day -1
[b] Only at Screening

At screening, all volunteers will be tested for HIV, hepatitis B surface antigen, and antibodies to hepatitis C. Serum will be tested for alcohol and urine will be tested for drugs of abuse at the times specified in Table 1. Drugs of abuse to be tested for will include the following:

cocaine, cannabinoids, phencyclidine, amphetamines, benzodiazepines, barbiturates, opiates, propoxyphene, methaqualone, and methadone. Serum pregnancy tests will be performed in women of childbearing potential at the times specified in Table 1. If a volunteer tests positive on any of these tests he/she will be excluded or withdrawn from the study

Laboratory values outside the reference limits suspected to be of any clinical significance will be retaken. 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.

Samples for all laboratory tests listed in Table 2 will be analyzed for each center by local laboratory facilities (unless specified otherwise). For reporting of AEs based on examinations and tests see Section 6.3.3. For blood volume see Section 7.1.

Samples for all laboratory tests at Center #1 will be analyzed using routine methods at Physician's Reference Laboratory, Overland Park, Kansas, USA.

6.3.6 Physical examination

A complete physical examination will be performed at the times detailed in the Study plan (Table 1). A physical examination will include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen and a neurological examination (only reflexes).

Height will be measured in meters and weight in kilograms. Measurements should be taken without shoes and the same scale used for all measurements. BMI will be calculated from the height and weight.

6.3.7 ECG

Standard resting (at least 10-minutes supine) 12-lead pECGs will be obtained on the days detailed in the Study plan (Table 1). All pECGs will be documented in the EDC system by recording date, time of collection, heart rate, PR, RR, QRS, QT, and QTcF intervals from the 12-lead pECG. Investigator evaluation (normal or abnormal; if abnormal, clinically significant or not clinically significant) will be recorded and abnormalities will be described.

6.3.8 Vital signs

For timing of individual measurements, refer to the study plan and time schedules (Table 1). Pulse rate (in bpm) and BP (in mmHg) will be measured using standard equipment with an appropriate cuff size after 10 minutes rest in the supine position.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (3 mL) for determination of clopidogrel active metabolite 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 EDC system. The samples will be analysed 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 analysed by a laboratory to be decided on behalf of AstraZeneca Clinical Pharmacology & DMPK, by derivatisation and using HPLC-MS/MS after solid phase extraction. The lower limit of quantification of clopidogrel active metabolite derivate will be 0.1 ng/mL.

6.5 Pharmacodynamics

6.5.1 Collection of samples

Blood samples (6 mL) for platelet aggregometry will be used to determine maximum platelet aggregation induced by 20 µM ADP (mPA). Blood samples (5 mL) for VASP will be used to determine platelet reactivity index (PRI). Refer to Table 1 for sample collection schedule for pharmacodynamic variables.

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 EDC system. The samples will be analysed 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.

6.6 CYP2C19 Genotyping

6.6.1 Collection of pharmacogenetic samples

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

For blood volume see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each volunteer over approximately a 4.5 month period of time in this study is as follows:

Table 3 Volume of blood to be drawn from each volunteer

Assessment		**Sample volume[a] (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	8	11	88
	Alcohol screen	5	3	15
	PT/aPTT	3	3	9
	Hematology	4	11	44
	Viral serology	8	1	8
	S-hCG (females only)[b]	-	-	-
Pharmacodynamic	Platelet aggregometry	6	15	90
	VASP	5	15	75
Pharmacokinetic	Clopidogrel active metabolite	3	87	261
Genotyping	*CYP2C19*	2	1	2
Total Volume				592

a If a cannula is used, 1 mL of blood will be taken to flush the cannula.
b. hCG for females will be measured using the sample obtained for clinical chemistry.

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

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 clinical study report has been finalized, unless retained for future analyses.

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

If a volunteer withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, 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 Principal Investigator:

- Ensures volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that volunteer, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the volunteer and AstraZeneca are informed about the sample disposal.

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Volunteer data protection

The Informed Consent Form (ICF) 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 subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee 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 volunteers. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing.

The Investigator should submit the written approval to AstraZeneca before enrollment of any volunteer into the study. The Ethics Committee should approve all advertising used to recruit volunteers for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrollment of any volunteer into the study, the final study protocol, including the final version of the ICF, 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, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The Principal Investigator(s) will:

- Ensure each volunteer is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each volunteer is notified that they are free to discontinue from the study at any time

- Ensure that each volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each volunteer provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the volunteer
- Ensure that any incentives for volunteers who participate in the study as well as any provisions for volunteers harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

The Principal Investigator is responsible for ensuring that consent is given freely and that the volunteer understands that they may freely discontinue from the study at any time.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator 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 Clinical Study Protocol).

The amendment should be approved by each Ethics Committee 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 Principal Investigator. For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's Ethics Committee should approve the revised ICF before the revised form is used.

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

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee 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 Pre-study activities

Before the first volunteer is entered into the study, it is necessary for a representative of Quintiles to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate volunteers for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of Quintiles or its representatives. This will be documented in a Clinical Study Agreement between Quintiles and the investigator.

9.2 Training of study site personnel

Before the first volunteer is entered into the study, a Quintiles representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca/Quintiles representative will have 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 EDC system, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the EDC systems with the volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating volunteers. This will require direct access to all original records for each volunteer (eg, clinic charts)

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

The AstraZeneca/Quintiles representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Source Document Identification document for location of source data.

9.4 Study agreements

The Principal Investigator should comply with all the terms, conditions and obligations of the Clinical Study Protocol.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in local operating procedures.

9.5 Study timetable and end of study

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

The study is expected to start in 2nd Quarter 2010 and to end by 4th Quarter 2010.

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

10. DATA MANAGEMENT

Data management will be performed by Quintiles, Inc Data Management.

The Phase I Clinical Trial System, the EDC system used by Quintiles, Inc, will be used for EDC, in accordance with AstraZeneca case report form (CRF) standard operating procedures and any existing project CRF standards. Electronic Data Capture instructions are provided to sites for recording data. The data are verified and cleaned, and data sets are prepared according to AstraZeneca and study-specific procedures. The data management staff is responsible for conducting and/or overseeing the following information.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping 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.

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

Data Management will determine and coordinate the flow of data from external vendors. Also, Data Management will determine the format of the data from these external sources and ensure that reconciliation of the data occurs with the clinical database.

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

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

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

Data storage will be done in accordance with AstraZeneca/GCP guidelines. The Study Data Management Plan will describe the methods used to collect, check, and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Furthermore, the Study Data Management Plan will describe the data flow and timelines within the study.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

Change-from-baseline variables will be calculated for the safety variables listed below, as the posttreatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests: Day -1 value
- Vital signs (blood pressure and pulse): Day 1 predose value

- pECG: Day -1 values for heart rate, RR, PR, QRS, QT, and QTcF.

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 AEs that led to discontinuation of IP (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 Clinical Study Report. A similar review of laboratory, vital signs and pECG data will be performed for identification of OAEs.

Examples of these are marked hematological 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 pharmacokinetic variables

Analysis of the PK of clopidogrel active metabolite will be the responsibility of the clinical pharmacokineticist at Quintiles, Phase I Services, Overland Park, USA. Quintiles SOPs and Work Instructions will be used as the default methodology if not otherwise specified.

The actual sampling times will be used in the PK parameter calculations. 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; SigmaPlot® 9.0, or higher (Systat Software, Inc., San Jose, California) or WinNonlin Professional 5.2, or higher.

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. 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 single-dose PK parameters will be determined for clopidogrel active metabolite after the loading dose of clopidogrel on Day 1:

AUC	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable analyte concentration
C_{max}	Observed maximum plasma concentration
t_{max}	Time to maximum concentration

If data permits, the following steady-state PK parameters will be determined for clopidogrel active metabolite on Days 5, 14, and 29:

$AUC_{0\text{-}t,ss}$ Area under the plasma concentration-time curve from time zero to the time of the last quantifiable analyte concentration at steady state.

$C_{max,ss}$ Observed maximum plasma concentration at steady state.

$t_{max,ss}$ Time to maximum concentration at steady state.

Additional PK parameters may be calculated if deemed appropriate.

The following single-dose PK diagnostic parameters will be calculated for clopidogrel active metabolite as appropriate and will be listed but not summarized:

- The time interval (h) of the log-linear regression to determine t1/2, z (t1/2, interval)
- Number of data points (t1/2, N) included in the log-linear regression analysis
- Regression coefficient (Rsq), a goodness-of-fit statistic for calculation of λ_z. If Rsq is less than 0.80, then λ_z and related parameters will not be reported.
- Percentage of AUC obtained by extrapolation ($\%AUC_{ex}$). If the extrapolated area is greater than 20% of AUC, then AUC will not be reported.

11.3 Calculation or derivation of pharmacodynamic variable(s)

Analysis of the PD of clopidogrel will be the responsibility of the study biostatistician at Quintiles, Phase I services, Overland Park, USA. Quintiles SOPs and Work Instructions will be used as the default methodology if not otherwise specified.

If data permits, the following PD variables will be calculated:

mIPA Maximum inhibition of platelet aggregation calculated as
[1 – (postdose mPA) on Days 2/6/15/30)/(mPA at baseline)] × 100

ΔPRI Change in PRI calculated as
[PRI (on Days 2/6/15/30) – PRI (at baseline) / PRI (on Day 1, predose)] × 100.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Safety analysis set

All volunteers who received at least 1 dose of randomized IP and for whom any postdose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated volunteers will be accounted for in the actual treatment group.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all volunteers who receive clopidogel and have at least 1 quantifiable clopidogrel active metabolite concentration at a scheduled PK time point after start of dosing (with no important protocol violations thought to significantly affect the PK of the drug).

12.1.3 Pharmacodynamic analysis set

The PD population will consist of all volunteers who receive clopidogrel and have at least 1 platelet aggregation assessment at a scheduled PD time point after start of dosing (with no important protocol violations thought to significantly affect the PD of the drug).

12.2 Methods of statistical analyses

12.2.1 General Principles

The statistical analysis of the PK and PD variables, the individual PK figures and data listings will be the responsibility of the study biostatistician at Quintiles Overland Park, Kansas, USA (using SAS® version 9.1 or higher and, where appropriate, additional validated software). Quintiles SOPs and Work Instructions will be used as the default methodology if not otherwise specified.

Quantitative continuous variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum 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 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 CV% will not be calculated for t_{max}.

Data will be presented by treatment for the purposes of summarizing the study results. Missing data will result in a reduced sample size for that parameter. Since the statistical analyses will be predominantly presentations in tables and individual data listings, no action will be taken to handle missing data.

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

12.2.2 Volunteer characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, SD, min, median, max) by treatment group. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment group.

12.2.3 Safety and tolerability

Continuous variables will be summarized using descriptive statistics (n, mean, SD, min, median, max) by treatment group. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment group.

All AEs will be collected for each volunteer from the time of admission until the follow up visit. Adverse events that occur before dosing will be reported separately.

Adverse events will be summarized by PT (Preferred term) and SOC (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.

Tabulations and listings of data for vital signs (blood pressure and pulse), clinical laboratory tests, pECG assessments and interval data, and physical examination findings parameters 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. Clinical laboratory data will be reported in Système International (SI) units in the Clinical Study Report. Any additional conversion factors, if needed, will be applied on a case-by-case basis (Iverson et al 1998).

The pECG parameters will be summarized for the absolute value at each scheduled assessment, together with the corresponding changes from the predose value. The QT correction factor will be based on the Fridericia's formula. Further categorical summaries of absolute QT and QTcF values (greater than 450 ms, greater than 480 ms, greater than 500 ms) and change from predose values in QT and QTcF values (greater than 30 ms, greater than 60 ms) may also be presented.

12.2.4 Pharmacokinetics

Pharmacokinetic concentrations for clopidogrel active metabolite will be listed and summarized using descriptive statistics. For descriptive statistics, concentrations below lower limit of quantification (LLOQ) values will be handled as follows:

- 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 a mean (arithmetic and geometric) value and SD and CV are calculated.

- At a time point where more than half of the observations are below LLOQ only individual values are reported; mean, SD, geometric mean and CV% will be set to NQ. The minimum (min) value and the median are set to less than 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 standard deviation and less than LLOQ in fields for mean, min, median and maximum (max) in the table.

- The number of observations greater than LLOQ [number of observations above LLOQ (N>LLOQ)] will be reported in the table.

Mean and individual concentration profiles and PK parameters will also be illustrated graphically. Graphical presentations of PK data may be added at the discretion of the PK scientist.

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

Pharmacokinetic comparison of test treatments (esomeprazole + clopidogrel, omeprazole + clopidogrel, or lansoprazole + clopidogrel) to the reference treatment (clopidogrel alone) will be assessed using the standard two one-sided t-tests approach. The PK parameters AUC, AUC_{0-t} and C_{max} for the clopidogrel active metabolite for each of the test treatments will be compared with the PK parameters for the reference treatment. Comparisons between the test and reference treatments will be made for each assessment day by using a mixed effects analysis of variance (ANOVA) model for each PK parameter (AUC, AUC_{0-t} and C_{max}). PK parameters will be analyzed on the natural log scale with fixed-effects for treatment, period, site, and sequence. Volunteers within sequence will be included as a random effect in the model. The linear contrasts subtracting the least-squares means for the reference treatment from the least-squares means for the test treatment will be estimated and exponentiated to obtain least square estimates of the ratios of geometric means and the corresponding 90% CI.

12.2.5 Pharmacodynamics

Descriptive statistics will be used to summarize mPA, and mIPA, in volunteers by treatment and by day. In addition, VASP data (PRI and ΔPRI) will be summarized using descriptive statistics by treatment and by day. All PD variables will be presented in listings.

Pharmacodynamic comparison of test treatments (esomeprazole + clopidogrel, omeprazole + clopidogrel, or lansoprazole + clopidogrel) to the reference treatment (clopidogrel alone) will be assessed for each of the PD endpoints – mIPA and ΔPRI. These PD endpoints for each of the test treatments will be compared with the corresponding PD endpoints for the reference

treatment. Comparisons between the test and reference treatments will be made by using a mixed effects analysis of variance (ANOVA) model with fixed-effects for treatment, period, site, and sequence. Volunteers within sequence will be included as a random effect in the model. Log-transformations may be used to meet model assumptions. The linear contrasts subtracting the least-squares means for the reference treatment from the least-squares means for the test treatment will be estimated to obtain least square estimates of the difference in least square means and the corresponding 90% CI. P-values will also be presented.

The above analysis will be repeated on mIPA excluding volunteers defined as clopidogrel low responders (mIPA response of 25% or less at Day 2) when receiving clopidogrel alone.

12.3 Determination of sample size

The study is sized to estimate the absolute mean difference in mIPA with and without the PPI with a specified precision. With 54 volunteers, a 95% CI with length of at most 9 percentage units is achieved with at least 96% probability. As each of the 3 PPIs is included in two-thirds of the planned treatment sequences, a total of 81 volunteers are required. Assuming a 20% dropout rate for this study, 101 volunteers will be enrolled to ensure 81 volunteers complete the study.

The calculation assumes an SD of paired difference of 14% units, derived from the root MSE of the analysis of internal data on ADP-induced maximum extent IPA for %mIPA (20 μM ADP).

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency, the Investigator may contact the 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

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

Esomeprazole-refer to the "Overdose" section of the official prescribing information at http://www1.astrazeneca-us.com/pi/Nexium.pdf

Omeprazole- refer to the "Overdose" section of the official prescribing information at http://www1.astrazeneca-us.com/pi/Prilosec.pdf

Lansoprazole- refer to the "Overdose" section of the official prescribing information for PREVACID® at http://www.tpna.com/products/default.aspx

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 . Male volunteers must refrain from fathering a child, including sperm donation, during the study and 3 months following the last dose. If the investigator receives information that a pregnancy has occurred during the study (including pregnancy in the partner of a male volunteer) despite these restrictions, the designated Quintiles representative should be informed.

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Appendix A
Signatures

ASTRAZENECA SIGNATURE

An open-label, randomized, 4-treatment, 3-period crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy subjects

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)

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SIGNATURE OF COORDINATING PRINCIPAL INVESTIGATOR

An open-label, randomized, 4-treatment, 3-period crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy subjects

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 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.

Center No.: 1

Signature:

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).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). 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, hospitalization, 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 hospitalization
- 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 etiology 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 recognized 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.

AstraZeneca

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Omeprazole/Esomeprazole
Study Code	D9612C00034
Date	
Protocol Dated	

An open-label, randomized, 4-treatment, 3-period, crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy volunteers

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

Centers affected by the Amendment:

All centers

The protocol for the study is to be amended as follows:

Revisions and additions are underlined.

Section of protocol affected:

6.4 Pharmacokinetics

6.4.1 Collection of samples [Page 38, 1st paragraph]

Previous text:

Blood samples (3 mL) for determination of clopidogrel active metabolite in plasma will be taken at the times presented in the study plan (Table 1).

Revised text:

Blood samples (<u>4 mL</u>) for determination of clopidogrel active metabolite in plasma will be taken at the times presented in the study plan (Table 1).

6.5 Pharmacodynamics

6.5.1 Collection of samples [Page 38, 1st paragraph]

Previous text:

Blood samples (6 mL) for platelet aggregometry will be used to determine maximum platelet aggregation induced by 20 µM ADP (mPA). Blood samples (5 mL) for VASP will be used to determine platelet reactivity index (PRI). Refer to Table 1 for sample collection schedule for pharmacodynamic variables.

Revised text:

Blood samples (7 mL) for platelet aggregometry will be used to determine maximum platelet aggregation induced by 20 µM ADP (mPA). Blood samples (2.7 mL) for VASP will be used to determine platelet reactivity index (PRI). Refer to Table 1 for sample collection schedule for pharmacodynamic variables.

7.1 Volume of blood [page 39]

Previous text:

Table 3 Volume of blood to be drawn from each volunteer

Assessment		**Sample volume[a] (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	8	11	88
	Alcohol screen	5	3	15
	PT/aPTT	3	3	9
	Hematology	4	11	44
	Viral serology	8	1	8
	S-hCG (females only)[b]	-	-	-
Pharmacodynamic	Platelet aggregometry	6	15	90
	VASP	5	15	75
Pharmacokinetic	Clopidogrel active metabolite	3	87	261
Genotyping	*CYP2C19*	2	1	2
Total Volume				592

a. If a cannula is used, 1 mL of blood will be taken to flush the cannula.
b. hCG for females will be measured using the sample obtained for clinical chemistry.

Revised text:

Table 3 Volume of blood to be drawn from each volunteer				
Assessment		**Sample volume[a] (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	8	11	88
	Alcohol screen	5	3	15
	PT/aPTT	3	3	9
	Hematology	4	11	44
	Viral serology	8	1	8
	S-hCG (females only)[b]	-	-	-
Pharmacodynamic	Platelet aggregometry	7	15	105
	VASP	2.7	15	40.5
Pharmacokinetic	Clopidogrel active metabolite	4	87	348
Genotyping	*CYP2C19*	2	1	2
Total Volume				659.5

a. If a cannula is used, 1 mL of blood will be taken to flush the cannula.
b. hCG for females will be measured using the sample obtained for clinical chemistry.

3.1 Overall study design and flow chart

Table 1 Study plan [footnote (e), page 19]

Previous text:

e. Three stool occult blood cards (or jars) with instructions will be given to each volunteer at screening and volunteers will be instructed to return the cards at the Day -1 visit.

Revised text:

e. Three stool occult blood cards (or jars) with instructions will be given to each volunteer at screening and volunteers will be instructed to return the cards at the Day -1 visit for Period 1 only.

6.3.5 Laboratory safety assessment

Table 2 Laboratory variables [footnote (a), page 36]

Previous text:

a Only at Day -1

Revised text:

a aPTT and PT at Day -1 of each period and Fecal Hb-test at Day -1 of Period 1 only

4.2 Exclusion criteria, Item 9, bullet 4 (page 22)

Previous text:

- Abnormal T wave morphology, particularly in the protocol defined primary lead

Revised text:

- Abnormal T wave morphology, particularly in the protocol defined primary lead (Lead II)

Reason for Amendment:

The volume of the pharmacokinetic sample was increased 1 mL to allow for the preparation of a primary and backup sample. The volume for the platelet aggregometry sample was increased 1 mL to ensure an adequate volume for the test. The volume for the VASP sample was decreased from 5 mL to 2.7 mL based on input from the laboratory which will be performing this assay. To clarify that aPTT and PT will be assessed prior to each study period but the test for fecal occult blood will only be performed on Day -1 of Period 1. The primary lead for assessment of abnormal T wave morphology was not defined in the protocol.

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	Omeprazole/Esomeprazole
Study Code	D9612C00034
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An open-label, randomized, 4-treatment, 3-period crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy subjects

---

This Clinical Study Protocol and Amendment to the CSP have been subjected to an internal AstraZeneca peer review.

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

Signed on behalf of Medical Science Director

ASTRAZENECA SIGNATURE(S)

An open-label, randomized, 4-treatment, 3-period crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy subjects

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

SIGNATURE OF PRINCIPAL INVESTIGATOR

An open-label, randomized, 4-treatment, 3-period crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy subjects

This Clinical Study Protocol and Amendment to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this Protocol/amendment. 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 Investigator.

Centre No.:

Signature:

Clinical Study Protocol Amendment

Amendment Number	2
Drug Substance	Omeprazole/Esomeprazole
Study Code	D9612C00034
Date	
Protocol Dated	

An open-label, randomized, 4-treatment, 3-period, crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy volunteers

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

Centers affected by the Amendment:

All centers

The following sections of the study protocol are to be amended as follows:

4. VOLUNTEER SELECTION CRITERIA

4.1 Inclusion criteria

Criteria 3, page 21

Previous text:

Weight of 50-95 kg, inclusive, and a BMI between 19-30 kg/m^2, inclusive.

Revised text:

Weight of 50 kg or above and a BMI between 18 and 32 kg/m^2, inclusive.

Reason for Amendment:

The average BMI of the potential volunteers being screened for this study is slightly higher than expected. Expanding the BMI range will not adversely affect the objectives of the study as volunteers act as their own control.

4.2 Exclusion criteria

Criteria 3, page 21

Previous text:

Any clinically significant illness within 4 weeks of the first administration of investigational product. 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.

Revised text (revised text in bold):

Any clinically significant illness within 4 weeks of the first administration of investigational product. **In the opinion of the Investigator,** any **significant** 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.

Reason for Amendment:

This will allow subjects who have had minor procedures under local anaesthetic or a short duration of general anesthesia (eg, excision of an ingrown toenail, incision and drainage of a skin abscess, minor surgical skin incisions for lacerations, etc) to participate in the study.

Criteria 4, page 21

Previous text:

Any clinically significant abnormalities in clinical chemistry, hematology (e.g. history or presence of thrombocytopenia, abnormal activated partial thromboplastin time and prothrombin time) or urinalysis (> +1 U-Erythrocytes at the preentry visit) or positive feces-hemoglobin (F-Hb) results as judged by the Investigator..

Revised text:

Any clinically significant abnormalities in clinical chemistry, hematology or urinalysis or positive feces-hemoglobin (F-Hb) results as judged by the Investigator.

Reason for Amendment:

This will avoid excluding excluding volunteers with 1) minor and clinically insignificant abnormalities in APTT/PT who have otherwise normal LFTs and no history of a clotting/bleeding disorder or 2) a false positive urinalysis from menstruating females.

Criteria 6, page 21

Previous text:

Suspicion of or known Gilbert's disease.

Revised text:

This criteria is deleted.

Reason for Amendment:

It is estimated that from 5 to 10% of the volunteers screened for this study might have Gilbert's disease. This change will allow volunteers with Gilbert's disease to be enrolled if all other measure of liver function are within normal limits.

Criteria 9, page 22

Previous text:

Any clinically important abnormalities in rhythm, conduction or morphology of resting pECG. This includes 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 less than 110ms 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.

Revised text:

Clinically important ECG abnormalities as judged by the Investigator or a family history of long QT syndrome.

Reason for Amendment:

This wording is typical for for first in man or thorough QT studies where there is intensive ECG monitoring to look for possible QT effects. Clopidogrel and the 3 proton pump inhibitors being investigated have been used safely and extensively in patients who have a cardiovascular pathology. Young, fit volunteers can have PR prolongation due to high vagal tone and intermittent RBBB in an otherwise healthy volunteer can be a normal physiological variant. In addition, older women also often have a slightly longer QT. The proposed wording will ensure the exclusion of volunteers with any important ECG finding (including abnormal T wave morphology) that can affect either the safety of the subjects or the objectives of the study.

Criteria 10, page 22

Previous text:

Prolonged QTcF greater than 450 msec or shortened QTcF less than 350 msec or family history of long QT syndrome.

Revised text:

This criteria is deleted.

Reason for Amendment:

All clinically important ECG abnormalities, including a significant prolongation of the QTc interval, are now addressed in the revised text for exclusion criteria 9.

Clinical Study Protocol Amendment No 2
Appendix A

Drug Substance	Omeprazole/Esomeprazole
Study Code	D9612C00034
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An open-label, randomized, 4-treatment, 3-period, crossover interaction study, evaluating the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacodynamics and the pharmacokinetics of clopidogrel in healthy volunteers

---

This Clinical Study Protocol and Amendment to the CSP have been subjected to an internal AstraZeneca peer review.

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

Signed on behalf of Medical Science Director

AstraZeneca Research and Developme
site representative

ASTRAZENECA SIGNATURE(S)

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

AstraZeneca Research and Development site represent

SIGNATURE OF PRINCIPAL INVESTIGATOR

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Center No.:

Signature: