Clinical Study Protocol

Drug Substance Esomeprazole

Study Code D961FC00003

A randomized, double-blind, parallel-group, multicentre, phase III study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA)

Sponsor:

AstraZeneca AB, 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

A randomized, double-blind, parallel-group, multicentre, phase III study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose ASA

International Principal Investigator

Study centre(s) and number of subjects planned

This is a multicentre study and the plan is to randomize around 2400 subjects in approximately 200 centers in about 20 countries.

Study period	**Phase of development**
Estimated date of first subject enrolled	III
Estimated date of last subject completed	

Objectives

Primary objective:

The primary objective of the study is to compare the effect of esomeprazole 20 and 40 mg once daily (od) versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose ASA.

Secondary objectives

The secondary objectives of the study are to:

1. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of gastric ulcers during 26 weeks in subjects on continuous low-dose ASA.

2. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of duodenal ulcers during 26 weeks in subjects on continuous low-dose ASA.

3. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported dyspeptic symptoms at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by Reflux Disease Questionnaire (RDQ) in subjects on continuous low-dose ASA.

4. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported gastroesophageal reflux disease (GERD) symptoms (heartburn and regurgitation) at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by RDQ in subjects on continuous low-dose ASA.

5. Study the number of gastric and/or duodenal erosions during 26 weeks in subjects on continuous low-dose ASA, by treatment.

6. Assess safety and tolerability of treatment with esomeprazole 20 and 40 mg od during 26 weeks in subjects on continuous low-dose ASA.

Study design

This is a 26-week, randomized, double-blind, parallel-group, placebo-controlled study to investigate the effect of esomeprazole 20 and 40 mg od on the occurrence of peptic ulcers, in subjects on continuous low-dose ASA (75-325 mg daily; daily is defined as $\geq$5 days/week) treatment during the course of the study.

Target subject population

Male and female subjects requiring low-dose ASA (75-325 mg daily) who are *Helicobacter pylori (H. pylori)* negative and who are at increased risk of developing peptic ulcers.

Investigational product, dosage and mode of administration

Esomeprazole (Nexium™), capsules 20 and 40 mg, oral administration.

Comparator, dosage and mode of administration

Placebo capsules indistinguishable in appearance from the esomeprazole capsules, oral administration.

Duration of treatment

The duration of treatment is 26 weeks.

Outcome variables

Efficacy

Primary outcome variable:

The primary variable is time to occurrence of peptic ulcer(s) see definition of ulcer in Section 4.6.1.1).

Secondary outcome variables:

1. Time to occurrence of gastric ulcer.

2. Time to occurrence of duodenal ulcer.

3. Dichotomized RDQ score (0 versus >0) for the dyspepsia dimension during the week prior to the 26-week visit or the week prior to the last visit, unless the last visit is the baseline visit, as reported by the subject.

4. Dichotomized RDQ score (0 versus >0) for the GERD dimension (heartburn and regurgitation) during the week prior to the 26-week visit or the week prior to the last visit, unless the last visit is the baseline visit, as reported by the subject.

5. Number of gastric and/or duodenal erosions.

6. Adverse events (AEs), clinical laboratory tests and vital signs.

Patient-reported outcomes (PROs)

RDQ, as a self-administered questionnaire, that includes 12 items answered using a modified 6-point Likert scale.

Health economics (Not applicable)

Pharmacokinetics (Not applicable)

Pharmacodynamics (Not applicable)

Safety

AE, clinical laboratory tests including hematology and clinical chemistry, physical examination, vital signs (blood pressure and pulse rate).

Genetics (Not applicable)

Statistical methods

The main approach in the analysis of primary and secondary efficacy variables will be the intention-to-treat (ITT) cohort. For the primary efficacy variable, the per-protocol (PP) population will also be evaluated.

The primary objective, efficacy for peptic ulcers, and the two secondary objectives concerning efficacy for gastric and duodenal ulcers will be tested in a hierarchical closed test procedure. The closed test procedure will be done in parallel for the two different doses of esomeprazole and in each step adjustment for multiplicity will be done according to the Hochberg procedure.

To assess differences between the esomeprazole groups and the placebo group the log rank test will be used. Low-dose ASA dose group (75-100 mg and 101-325 mg) will be included as strata in the log rank analysis.

Peptic ulcer occurrence rates at the different low-dose ASA ranges of 75-100 mg and 101-325 mg will be presented descriptively, by treatment. Absolute and relative risk reduction of peptic ulcers will be presented for each of the esomeprazole groups as compared to placebo. Corresponding descriptive statistics will also be presented for gastric and duodenal ulcers.

The Mantel-Haenszel chi-square test will be used for the proportion of patients without any dyspeptic symptoms at the 26-week visit or the last visit, unless the last visit is the baseline visit, defined as patients with RDQ score equal to 0 for the dyspepsia dimension. The test will be stratified for baseline severity. GERD symptoms will be analyzed accordingly.

The number of gastric and duodenal erosions will be presented by treatment group as descriptive statistics in terms of frequency tables.

Baseline and demographic data will be presented descriptively.

Investigator-reported symptoms will be presented by using descriptive statistics for the ITT cohort.

Upper gastrointestinal (GI) complications will be presented by using descriptive statistics for the ITT cohort.

AEs, clinical laboratory tests and vital signs will be presented using descriptive statistics for the safety population.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ACS	Acute coronary syndrome
AE	Adverse event (see definition in Section 4.7.1.1)
Assessment	An observation made on a variable involving a subjective judgment (assessment)
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine transaminase (serum glutamic pyruvic transaminase)
ASA	Acetylsalicylic acid
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomical Therapeutic Chemical system
CABG	Coronary artery bypass graft
COX-2	Cyclooxygenase-2
CHMP	Committee for Medicinal Products for Human use
CRF	Case report form
CV	Cardiovascular
EF	Ejection fraction
EGD	Esophagogastroduodenoscopy
Endpoint	A status of the subject that constitutes the ‘endpoint’ of a subject’s participation in a clinical study and that is used as the final outcome
Ethics Committee	Synonymous to Institutional Review (IRB) and Independent Ethics Committee (IEC)
GERD	Gastroesophageal reflux disease
H_2-receptor	Histamine-2 receptor
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Haemoglobin
H. pylori	*Helicobacter pylori*
IB	Investigator’s Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

Abbreviation or special term	Explanation
IRB	Institutional Review Board
International Coordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator coordinating the investigators and/or activities internationally
ITT	Intention-to-treat
LA classification	Los Angeles classification of esophagus
Measurement	An observation made on a variable using a measurement device
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
NYHA II-IV	New York Heart Association Functional Classification II–IV
OAE	Other significant adverse event (ie adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.7.1.1)
od	Once daily
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective
PCI	Percutaneous coronary intervention
Peptic ulcer	Gastric and/or duodenal ulcer
PP	Per protocol
PPI	Proton pump inhibitor
Principal investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator
PRO	Patient-reported outcomes
RDQ	Reflux Disease Questionnaire
SAE	Serious adverse event (see definition in Section 4.7.1.1)
SAP	Statistical Analysis Plan
SD	Standard deviation
SDV	Source data verification
S-Fe	Iron saturation
S-TIBC	Total iron-binding capacity saturation
UBT	Urea breath test
Variable	A characteristic or a property of a subject that may vary eg, from time to time or between subjects
WBC	White blood cell

Abbreviation or special term	Explanation
WBDC	Web-Based Data Capture

1. INTRODUCTION

1.1 Background

For at least 2 decades low-dose acetylsalicylic acid (ASA) has been used for the prevention of thromboembolic events both cardiovascular as well as cerebrovascular. The dose range of low-dose ASA is 75 to 325 mg daily. The exact dose for the indications varies between countries. The antithrombotic effect of low-dose ASA is similar within the whole dose range (Patrono C et al 2005).

Continuous low-dose ASA treatment is accompanied by a variety of undesirable AEs. These include upper gastrointestinal (GI) symptoms such as dyspeptic symptoms, abdominal pain and/or heartburn (Laheij RFJ et al 2003), peptic ulcers which might be followed by serious ulcer complications such as bleeding, gastric or duodenal perforation and obstruction (Lanas A et al 2005, Yeomans ND et al 2005, García Rodríguez LA and Hernández-Díaz S 2004, CAPRIE Steering Committee 1996, Weil J et al 1995). Even taking aspirin in doses as low as 75 mg daily doubles the risk of having upper GI bleeding compared with not taking aspirin (Weil J et al 1995, Kelly JP et al 1996).

Peptic ulcers account for approximately 50% of the events of acute hemorrhage in the upper GI tract (Laine L and Peterson WL 1994). In a large clinical trial in non-steroidal anti-inflammatory drug (NSAID)-treated patients, approximately 80% of the bleedings were associated with peptic ulcers (Bombardier C et al 2000). It is reasonable to believe that the presence of a peptic ulcer will increase the subsequent risk of clinically relevant upper GI bleeding events. By reducing the occurrence of peptic ulcers, the risk of such complications will be diminished (Chan FK 2005, Lai KC et al 2002).

Proton pump inhibitors (PPI) have been shown to reduce the risk of peptic ulcers in patients taking NSAIDs (Scheiman JM et al 2006, Ekström P et al 1996). Furthermore, data from a recently completed AstraZeneca-sponsored study (Yeomans ND et al 2006) comparing esomeprazole 20 mg once daily (od) with placebo for risk reduction of peptic ulcers in patients on low-dose ASA treatment demonstrated a statistically significant ($p=0.0007$) reduction in the occurrence of peptic ulcers in patients treated with esomeprazole. However, additional clinical trials are needed for further evaluation of the benefit of PPI therapy in patients on continuous low-dose ASA treatment (Vallurupalli NG and Goldhaber SZ 2006).

1.2 Rationale

A recently completed study (Lanas A et al 2005) compared esomeprazole 20 mg od with placebo for prevention of peptic ulcers in patients taking continuous low-dose ASA, and who were at increased risk for developing peptic ulcers (age $\geq$60 years). The study demonstrated a statistically significant lower occurrence of peptic ulcers in patients treated with esomeprazole. The observed ulcer occurrence rate was 5.4% in the placebo group, and 1.6% in the esomeprazole group, representing a 70% reduction in the rate of peptic ulcers.

The current study will further explore the efficacy of esomeprazole in preventing peptic ulcers in patients on continuous low dose aspirin treatment who are at increased risk for developing peptic ulcers.

In the Asterix study (Yeomans ND et al 2006) esomeprazole 20 mg od versus placebo was used. In the current study both marketed doses of esomeprazole, 20 and 40 mg od, will be investigated.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose ASA.

2.2 Secondary objectives

The secondary objectives of the study are to:

1. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of gastric ulcers during 26 weeks in subjects on continuous low-dose ASA.

2. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of duodenal ulcers during 26 weeks in subjects on continuous low-dose ASA.

3. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported dyspeptic symptoms at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by the Reflux Disease Questionnaire (RDQ) in subjects on continuous low-dose ASA.

4. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported gastroesophageal reflux disease (GERD) symptoms (heartburn and regurgitation) at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by RDQ in subjects on continuous low-dose ASA.

5. Study the number of gastric and/or duodenal erosions during 26 weeks in subjects on continuous low-dose ASA, by treatment.

6. Assess safety and tolerability of treatment with esomeprazole 20 and 40 mg od during 26 weeks in subjects on continuous low-dose ASA.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

The Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

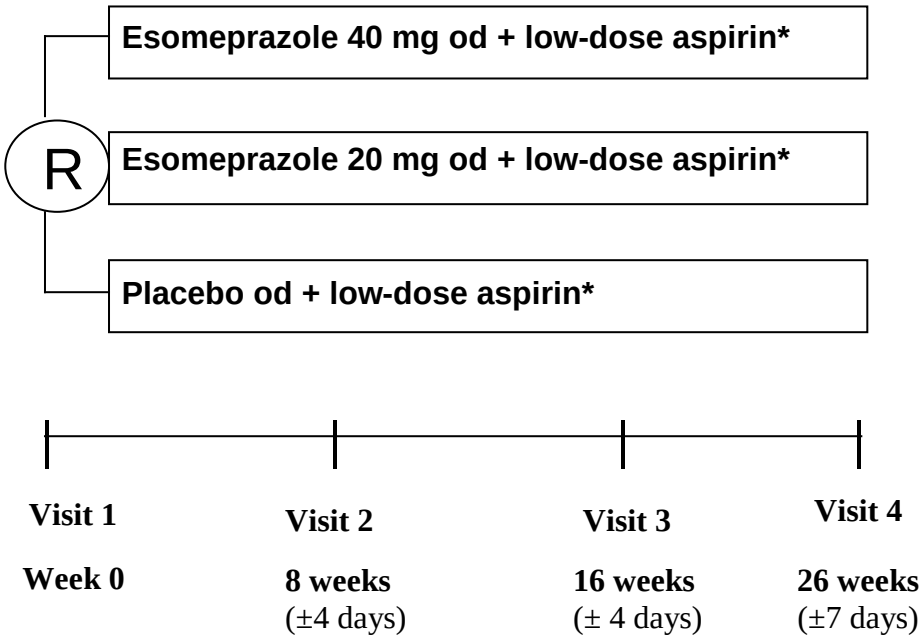
It is a 26-week, randomized, double-blind, parallel-group, placebo-controlled study to investigate the effect of esomeprazole 20 and 40 mg od on the occurrence of peptic ulcers.

All subjects randomized must have a daily intake of low-dose ASA (75-325 mg daily; daily is defined as at least ≥5 days/week) on thee basis of a physicians' prescription or recommendation. In addition, all subjects should be *H. pylori* negative and fulfill at least one of the subcriteria listed under the third inclusion criterion (see Section 3.3.2).

This is a multicentre study and the plan is to randomize around 2400 subjects in approximately 200 centres (10 to 15 patients per centre) in about 20 countries. Cardiologists, primary care physicians and gastroenterologists are the primary target investigators.

An esophagogastroduodenoscopy (EGD) will be performed at baseline, 8 and 26 weeks and also if the subject withdraws from the study or when clinically indicated. The endoscopic examination will be carried out using a fiber optic or digital flexible endoscope according to normal hospital routines. The presence of a peptic ulcer(s), (see definition, Section 4.6.1.1) is the primary study endpoint. Subjects will be asked about their medical/surgical history at the baseline visit. Subject-reported upper GI symptoms will be assessed by using the RDQ at each visit. Clinical laboratory evaluations will be completed at each visit, and AEs will be recorded at 8, 16 and 26 weeks. A pregnancy test will performed at the baseline visit (only for women of childbearing potential). A physical examination and vital signs will be performed at baseline and at the final visit. Antacids with an acid binding capacity of <16 mmol HCl will be used as rescue medication during the study in case of intolerable upper GI symptoms.

Figure 1 Study design



*** any aspirin dose from 75 to 325 mg od**
R = randomization

Table 1 Study plan

Assessment	Visit 1 Week 0	Visit 2 8 weeks (±4 days)	Visit 3 16 weeks (±4 days)	Visit 4 26 weeks (±7 days)	Unscheduled Visit[5]
Informed Consent	X[1]				
Eligibility check	X				
EGD	X[2,3]	X[2]		X[2]	X[2]
Pregnancy test	X[3,4]				
RDQ	X	X	X	X	X
Randomization	X				
History of low-dose aspirin	X				
Specific GI and CV history	X				
Nicotine use	X				
Demography	X				
Medical/surgical history	X				
Vital signs	X			X	X
Height and weight	X				
Check of low-dose ASA dose		X	X	X	X
GI complications		X	X	X	X
Laboratory samples	X[3]	X	X	X	X
Physical examination	X			X	X
Investigator assessed upper GI symptoms	X	X	X	X	X
Initial *H. pylori* test (local routines)	X[6]				
Confirmatory *H. pylori* test (UBT)	X[2]				

Assessment	Visit 1 Week 0	Visit 2 8 weeks (±4 days)	Visit 3 16 weeks (±4 days)	Visit 4 26 weeks (±7 days)	Unscheduled Visit[5]
Concomitant medication	X	X	X	X	X
Dispense of study drug	X	X	X		
Study drug accountability		X	X	X	X
AE recording	X[7]	X	X	X	X

[1]Signed informed consent must be obtained before any study-related assessments are performed
[2]Subjects need to be fasting at least 6 hours before this procedure or test
[3]This procedure or test can be done within 14 days prior to visit 1 if full informed consent is obtained
[4]Only for women of childbearing potential
[5]Depending on reason for visit, assessments might vary
[6]This procedure can be done within 14 days prior to visit 1. Signed screening consent is sufficient
[7]From obtained informed consent until first administration of study drug, only SAE will be collected

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

The randomized, double-blind, placebo-controlled parallel-group design has been chosen to limit bias.

No drugs are currently approved for the prevention of peptic ulcers associated with low-dose ASA use and placebo is therefore chosen as the comparator.

Subjects considered at increased risk of developing peptic ulcers and on continuous dose of low-dose ASA within the range 75 to 325 mg daily will be included in the study. Doses within this range are used as treatment for prevention of thromboembolic events as specified by the professional labeling for low-dose ASA, clinical guidelines and medical literature (DeBacker GD et al 2003, Harrington RA et al 2004, Patrono C et al 2005).

The choice of doses for esomeprazole, 20 mg and 40 mg od, and the study duration are based on the outcome of the ulcer prevention studies showing that esomeprazole 20 mg and 40 mg od over 6 months significantly reduced the cumulative occurrence of gastric and duodenal ulcers during continued non-aspirin NSAID use (Scheiman JM et al 2006).

3.2.2 Risk/benefit and ethical assessment

An overall risk benefit assessment of esomeprazole is presented in the Investigator's Brochure (IB) for Nexium for oral use (Edition No. 9, 2006).

The risk/benefit assessment is based on extensive pre-clinical and clinical experiences of esomeprazole gathered pre- and post launch. Esomeprazole was first approved March 10, 2000. Since then, post-marketing surveillance safety data and safety data from numerous clinical studies have been collected and evaluated. In total, more than 400 million treatments

courses have been delivered and more than 76.000 patients have been included in clinical trials.

The safety experience of esomeprazole treatment is mainly based on the approved doses 40 mg daily and 20 mg daily. The following common adverse events have been identified and included in the labeling: headache, diarrhea, constipation, abdominal pain, nausea/vomiting and flatulence.

In this study esomeprazole will be combined with low-dose ASA in doses 75 to 325 mg daily in subjects recommended to be treated with low-dose ASA for the prevention of cardiovascular/cerebrovascular diseases. A randomized placebo controlled study, using the same low-dose ASA dose range (75 to 325 mg) and esomeprazole 20 mg od with a similar primary objective has been completed. The study included 991 subjects and the study duration was 6 months. The evaluation of the safety parameters of this combination treatment, esomeprazole plus low-dose ASA, did not show any clinically relevant differences compared with the safety profile of esomeprazole single treatment (data on file).

Aspirin is one of the most widely used therapeutic agents, not only for its analgesic, antipyretic, and anti-inflammatory properties but also for its anti-thrombotic properties of value in states of platelet hyperaggregability. Aspirin is hydrolyzed to salicylic acid in the gut wall and liver. Side effects are mainly dyspeptic symptoms, gastrointestinal lesions and increased gastrointestinal and overall bleeding, which are mainly consequences of blockade of prostaglandin synthesis through inhibition of cyclooxygenases. Existing data for combination treatment of esomeprazole and low-dose ASA (Yeomans ND et al 2006) and literature reports of co-treatment with PPI and low-dose treatment have not revealed any increased safety concerns.

This study is designed to explore the occurrence of upper peptic ulcers, which have the potential to cause serious and potentially life-threatening GI complications (bleeding, perforation and obstruction).

The methods of evaluation that will be used in this study are all well-known and safe.

In summary, the benefit/risk assessment of this study is deemed favorable.

Based upon published clinical experience of increased risk of peptic ulcer bleeding, upper GI bleeding and uncomplicated peptic ulcer among subjects who take prophylactic low-dose ASA, there is a need to provide adjuvant treatment to reduce the risk of gastric and/or duodenal ulcer in this risk population.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of all consecutive subjects who were considered for enrolment but were never enrolled eg, subject screening log. This information is necessary to establish that the subject population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Provision of written informed consent.

2. Physician prescribed or recommended daily intake of low-dose ASA (75-325 mg daily) that is expected to continue for the duration of the study (daily intake is defined as at least ≥5 days per week).

3. The subject must fulfill at least one of the following (a-e):

    a) Aged ≥65 years.

    b) Aged ≥18 years and with a documented history of uncomplicated peptic ulcer(s).

    c) Aged ≥60 years and naïve to low-dose ASA (ie, treatment started within 1 month prior to randomization).

    d) Aged ≥60 years with stable coronary artery disease.

    e) Aged ≥60 years with complains of upper GI symptoms that, as judged by the investigator, requires an EGD and with the finding of ≥5 gastric and/or duodenal erosions at the baseline endoscopy.

4. *H. pylori* negative. (*H. pylori* test to be performed according to local routines. Eradication treatment completed at least 4 weeks prior to randomization is allowed.).

5. Able to read and write.

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Reflux esophagitis Los Angeles (LA) classification grade C or D at baseline EGD or within the last year as known by the investigator, or severe esophagitis within the last year as known by the subject (for definition, see Section 4.6.1.1).

2. Peptic ulcer(s) at baseline EGD.

3. History of peptic ulcer complications such as clinically significant bleeding and/or perforation.

4. Any previous surgery of the stomach and/or the duodenum (except for laparoscopic fundoplication).

5. Any of the following vascular diseases:
   - Unstable hypertension
   - History of Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Graft (CABG) within the last 3 months
   - Clinically relevant valvular disease
   - Serious cardiac failure: New York Heart Association Functional Classification II–IV (NYHA II-IV), Ejection Fraction (EF) <40 %
   - Cerebrovascular accident within the last 3 months.

6. Any current or historical evidence of the following diseases/conditions:
   - Malabsorption
   - Known esophageal stricture
   - Known Barrett's esophagus with documented dysplastic changes of any grade
   - Zollinger-Ellison syndrome
   - Signs and symptoms of gastric outlet obstruction (eg, abdominal distension or multiple episodes of vomiting)
   - Pancreatitis
   - Unstable diabetes mellitus (as judged by the investigator). Stable diabetes controlled by diet, oral agents or insulin is acceptable
   - Atrophic gastritis
   - Short bowel syndrome.

7. Evidence of any malignant disease within the last 5 years, except minor superficial skin disease.

8. Continuous treatment with a NSAID including a cyclooxygenase-2 (COX-2)-selective NSAID during the last 2 months prior to randomization. During this period occasional use up to 1 day/per week is allowed.

9. Ongoing anticoagulant therapy, such as warfarin or other vitamin K antagonists. Antiplatelets such as clopidogrel are allowed.

10. Need for concomitant therapy with medication that could interact with esomeprazole, ie, phenytoin, ketoconazole, itraconazole, voriconazole, cisapride, atanzanavir, ritonavir.

11. Known or suspected intolerance or hypersensitivity to esomeprazole or other PPIs or aspirin.

12. Any use of a PPI or prostaglandin analogue within 14 days prior to the baseline EGD and between baseline EGD and randomization, or daily use of a histamine H_2-receptor antagonist during the last 14 days prior to the baseline EGD (occasional use of H_2-receptor antagonist less than daily is permitted during this period).

13. Need for continuous concurrent therapy with:
    - Prostaglandin analogues
    - Sucralfate.

14. Any condition that, in the opinion of the investigator, may either put the subject at risk or influence the result of the study (eg, cardiogenic shock or severe haemodynamic instability, risk for non-compliance, risk for being lost to follow-up), as judged by the investigator.

15. Pregnancy, planned pregnancy or lactation. Women of childbearing potential must use reliable and medically accepted methods of birth control, as judged by the investigator.

16. Alcohol and/or drug abuse or any other condition associated with poor compliance, as judged by the investigator.

17. Use of any other investigational compound or participation in another clinical study within the last 30 days prior to randomization.

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

19. Previous enrolment or randomization in the present study.

3.3.4 Restrictions

Each EGD and UBT will be done on fasting subjects (subjects need to be fasting at least 6 hours before each EGD and before the UBT). Subjects cannot donate blood during their participation in this study.

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

1. Voluntary discontinuation by the subjects who are at any time free to discontinue their participation in the study, without prejudice to further treatment.

2. Safety reasons as judged by the investigator and/or AstraZeneca.

3. Severe non-compliance to the protocol as judged by the investigator and/or AstraZeneca.

4. Incorrect enrolment (ie, the subject does not meet the required inclusion/exclusion criteria for the study).

5. Lack of therapeutic response (development of a gastric and/or a duodenal ulcer and/or upper GI symptoms requiring active intervention, as judged by the investigator).

6. Other reason as specified by the investigator.

7. Lost to follow-up.

3.3.5.2 Study specific discontinuation criteria

Low-dose ASA treatment permanently stopped.

3.3.5.3 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any AEs. If possible, they should be seen and assessed by an investigator(s). AEs should be followed up; RDQ should be completed and investigational products should be returned by the subject.

When the discontinuation occurs between scheduled visits an unscheduled visit should be performed, if possible. The unscheduled visit includes the following procedures:

- EGD
- Physical examination
- AE assessment
- Concomitant medication review
- Laboratory tests
- Investigator assessed upper GI symptoms
- Vital signs
- RDQ
- Signs of GI complications
- Check of low-dose ASA
- Drug accountability

If a peptic ulcer is determined by EGD prior to visit 4, the subject is to be discontinued from blinded medication and discharged from the study. The reason for discontinuation should be entered in the case report form (CRF) as “lack of therapeutic response”. If this occurs between scheduled visits an unscheduled visit should be performed (see above).

Subjects may be withdrawn from study treatment and assessments at any time, at the discretion of the investigator.

Incorrectly randomized subjects and subjects for whom the treatment code has been prematurely broken will be withdrawn from further study treatment and assessments. A subject may, however, continue the study if, for example, continuation of study treatment or follow-up actions are necessary for the subject's safety and well-being, or if only a follow-up period remains, and the continuation of the study is not expected to be associated with any risk or discomfort for the subject as judged by the investigator.

3.4 Treatments

3.4.1 Identity of investigational product, comparators and additional drugs

Esomeprazole

Generic name:	Esomeprazole
Dosage form:	Capsules
Strength:	20 mg
Article number:	H 1189-04-01
Manufacturer:	AstraZeneca Tablets Production, Sweden

Generic name:	Esomeprazole
Dosage form:	Capsules
Strength:	40 mg
Article number:	H 1222-04-01
Manufacturer:	AstraZeneca Tablets Production, Sweden

Placebo

Generic name:	Placebo
Dosage form:	Capsules
Article number:	H 0459-06-03
Manufacturer	AstraZeneca Tablets Production, Sweden

Rescue medication (additional drug)

Generic name:	Antacids
Dosage form:	Tablets
Acid binding capacity:	<16 mmol HCl
Manufacturer:	Will be purchased locally in each participating country.

3.4.2 Doses and treatment regimens

Subjects will be randomized at visit 1. One bottle will be dispensed to each subject at each visit. A total of 3 bottles will be dispensed to each patient over the course of the study. (Therefore, one box containing 3 bottles will be assigned to a patient.)

Subjects will be instructed to take their investigational product daily, beginning in the morning after the first study visit and throughout the study. Investigational product should be taken before breakfast with a glass of water. Subjects should not chew, crush, cut or break the capsules. On visit days, when fasting is required, subjects should take the investigational product as instructed by the investigator.

Rescue medication, ie, antacids with an acid-binding capacity of <16 mmol HCl/tablet, will be provided together with the investigational drug throughout the study. The subject will be instructed to use the rescue medication only when needed. The maximum dose of rescue medication is 6 tablets per day. If dyspeptic and/or GERD symptoms are not relieved by adequate antacid use (up to 6 tablets per day), the subject should contact the investigator for further consultation. The number of tablets will be assessed at each study visit by counting returned antacid tablets.

Subjects will be instructed to return investigational product containers and rescue medication containers and all unused medication at each visit for reconciliation.

3.4.3 Labeling

The packaging and labeling of the investigational product will be done under the responsibility of Investigational Products, AstraZeneca R&D Mölndal, Sweden. A two-part tear-off label will be attached to each bottle. One part will be permanently fixed to the bottle, and the tear-off portion of the label should be inserted in the source data document.

The bottle labels will contain at least the following information:

Study code: D961FC00003
Randomization code
Number of capsules
Esomeprazole capsules 20/40 mg/placebo
For clinical trial use only
One capsule to be swallowed whole with water in the morning prior to breakfast
Dr……(to be filled in by hospital staff)*
Visit no…….(to be filled in by hospital staff)
Expires end: MM.YYYY*
Store at room temperature 15-25C°
Keep out of reach of children
Order No.:
"Name, address and telephone number of sponsor"

*)not required by US regulatory

The rescue medication label will contain at least the following information:

Study code: D961FC00003
Randomization code……. (to be filled in by hospital staff)
For clinical trial use only
For the treatment of upper GI symptoms
Dr……(to be filled in by hospital staff)
Visit no……(to be filled in by hospital staff)
Keep out of reach of children
"Name, address and telephone number of sponsor"

Maximum intake is six tablets per day
Label printing No.:

In some countries, the rescue medication will not be labeled according to a local drug law.

All labels will be translated into local language to meet local regulatory requirements.

3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product label and in the investigator brochure.

3.4.5 Accountability

No investigational drugs will be delivered to the investigational site before the required regulatory approvals have been obtained.

The amount of investigational drug that is dispensed and returned will be recorded in the subject specific CRF. The unused investigational drug will be returned and destroyed according to local routine procedures.

3.5 Method of assigning subjects to treatment groups

Subject eligibility will be established before treatment randomization. Subjects will be randomized strictly sequentially, as subjects are eligible for randomization. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

The esomeprazole and placebo capsules will be of identical appearance and packed in identical bottles.

The treatment codes, indicating the treatment allocation for all randomized subjects, will be kept by Investigational Products, AstraZeneca R&D Mölndal, Sweden.

3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the investigator(s) or pharmacists at the study centre.

The treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomization. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are

unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.7 Pre-study, concomitant and post-study treatment(s)

Medication, other than study medication, considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF. EGD-related medication administered according to normal routines should not be recorded in the CRF.

Concomitant use of the following medications during the course of the study is prohibited:

- H_2-receptor antagonists, occasional use is allowed. Occasional use is defined as a single dose not more than once a week.
- PPI (other than investigational product).
- Phenytoin, ketoconazole, itraconazole, voriconazole, cisapride, atazanavir, ritonavir.
- Anticoagulants such as warfarin or other vitamin K antagonists.
- Continuous treatment with a NSAID including a COX-2 selective NSAID. Occasional and/or intermittent use up to 1 day/per week is allowed.
- Prostaglandin analogues.
- Sucralfate.
- *H. pylori* eradication therapy if not completed at least 4 weeks prior to randomization.

3.8 Treatment compliance

Subjects will be instructed to return all unused investigational products at each visit. Returned capsules will be counted and documented.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary variable is time to occurrence of peptic ulcer(s) (see definition of ulcer in Section 4.6.1.1).

4.2 Screening and demographic measurements

At visit 1, demographic data, (ie, date of birth, sex, race, and nicotine use) will be recorded. The investigator will do an eligibility check to ensure that the subject has no medical conditions or abnormalities that might disqualify him/her from enrolment. Medical and surgical history as well as GI and cardiovascular history will be obtained and a physical examination will be performed. The physical examination will include: general appearance, cardiovascular, lungs and abdomen. Vital signs will also be recorded and include blood pressure and pulse. Body weight and height will be measured only at visit 1.

All data will be recorded in the CRF.

4.3 Patient-Reported Outcomes

The methods for collecting Patient-Reported Outcomes (PRO) data are presented below.

4.3.1 Reflux Disease Questionnaire

The RDQ is a brief, reliable and valid self-administered questionnaire designed for symptom evaluation (Shaw et al 2001). It was originally developed for English-speaking GERD patients in the USA.

The RDQ contains 12 items answered on a 6-point Likert scale. Six items concern the frequency of symptoms, anchored at ‘Did not have’ for the lowest frequency, and ‘Daily’ for the highest one (Did not have; 1 day a week, 2 days a week, 3-4 days a week, 5-6 days a week; Daily). The other six items rate the severity of those symptoms, from ‘Did not have’ to ‘Severe’ (did not have; very mild; mild; moderate; moderately severe; severe). The recall period is the past 7 days.

The RDQ items can be combined into 4 dimensions:

- Regurgitation
  - Acid taste in the mouth
  - Unpleasant movement of materials upward from the stomach

- Heartburn
  - Burning feeling behind the breastbone
  - Pain behind your breastbone

- Dyspepsia
  - Burning feeling in the centre of the upper stomach
  - Pain in the centre of the upper stomach

- GERD
  -Heartburn dimension
  -Regurgitation dimension

Dimension scores are obtained from the arithmetic mean of their items scores.

4.3.2 Administration of Patient Reported Outcome questionnaires

It is important to administer the questionnaires according to the guidelines for standardized administration and prior to other examinations. The subject should be informed about how important his/her participation is. The questions should be completed in a quiet place without influence from study personnel or accompanied family or friend. The staff at the clinic should never help the subject to choose an answer and must be neutral in their response to the subject's questions. The staff at the clinic is not allowed to interpret or rephrase the questions for the subject. After the subject has completed the questionnaire, the study personnel will review the questionnaire for completeness only.

4.4 Health Economic measurements and variables (Not applicable)

4.5 Pharmacokinetic measurements and variables (Not applicable)

4.6 Efficacy measurement and variables

Objective	Variable(s)
Primary	The primary variable is time to occurrence of peptic ulcer(s) (see definition, Section 4.6.1.1).
Secondary	Time to occurrence of gastric ulcer.
	Time to occurrence of duodenal ulcer.
	Dichotomized RDQ score (0 versus >0) for the dyspepsia dimension during the week prior to the 26-week visit or the week prior to the last visit, unless the last visit is the baseline visit, as reported by the subject.
	Dichotomized RDQ score (0 versus >0) for the GERD dimension (heartburn and regurgitation) during the week prior to the 26-week visit or the week prior to the last visit, unless the last visit is the baseline visit, as reported by the subject.
	Number of gastric and/or duodenal erosions.
	AEs, clinical laboratory tests and vital signs.

4.6.1 Esophagogastroduodenoscopy

An EGD examination will be done in fasting subjects (fasting for at least 6 hours) as part of the baseline, visit 2 and visit 4 or when a subject withdraws from the study prior to visit 4. Each EGD will include evaluation of the esophagus, stomach, and duodenum. Any abnormality in the esophagus, stomach or duodenum will be recorded in the CRF.

4.6.1.1 Methods of assessment

The EGD examination will be carried out and evaluated by an experienced endoscopist using a fiber optic or digital flexible endoscope according to normal endoscopist routines. In order to ensure that EGDs are evaluated in a consistent manner for this study, all endoscopists will be asked to review study materials regarding EGD procedures and evaluation and to certify their review of this material. The EGD findings will be recorded in the CRF.

Subjects participating in the study must not have an active peptic ulcer according to definition at the baseline EGD. The baseline EGD will be done on the same day as visit 1 or within 14 days prior to visit 1. The absence of peptic ulcers at a subsequent EGD indicates prevention of low-dose ASA-associated peptic ulcers for the purpose of this study.

An ulcer is defined as a mucosal break with the following features:

- ≥3 mm in largest diameter
- A base – a circular or elliptical white or grey-white punched-out defect in the mucosa that could be smooth and regular
- A margin – discrete, sharply demarcated, regular, smooth, and usually raised in relation to the ulcer base
- Lack of an associated mass lesion or other features suggesting malignancy

The size of ulcers will be measured using endoscopy forceps. This will allow tabulation of the size distribution of ulcers at the end of the study. If several ulcers are found, record the largest diameter of the largest ulcer.

If an ulcer is determined by EGD after the baseline EGD, the subject should immediately be discontinued from blinded medication, and be discharged from the study. The reason for discontinuation should be recorded in the CRF as “lack of therapeutic response”.

In addition to assessing peptic ulcers and their sizes, the number of gastric and duodenal erosions will be recorded separately.

A gastric or duodenal erosion is defined as a superficial break in the mucosa that does not penetrate the muscularis mucosae into the submucosae. The lesions are generally multiple with white bases and commonly encircled by a halo of erythema. If the erythema has recently bled, the bases may be black.

The presence or absence of esophageal lesions will also be recorded, using the LA classification (Lundell L et al 1999).

LA classification

Grade A	One (or more) mucosal break(s) no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break(s) more than 5 mm that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break(s) that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference
Grade D	One (or more) mucosal break(s) that involves at least 75% of the circumference

EGD should also be done in the study whenever judged clinically necessary by the investigator and must be recorded in the CRF.

4.6.2 Helicobacter pylori

To be able to include *H. pylori* negative subjects in the study, the absence of *H. pylori* will be assessed before visit 1 using *H. pylori* test according to local routines.

To be able to claim that the subjects were *H. pylori* negative before entering the study, a second test must be done to confirm the *H. pylori* negative status. For this purpose, a UBT test will be used. If a UBT sample is lost, destroyed or impossible to evaluate, the subject should be asked to do an extra test as soon as possible.

The UBT test will be provided and analyzed by the central laboratory.

Results of the UBT evaluation of each subject's *H. pylori* status will be used for reporting purposes as concerns the subject's *H. pylori* status, regardless of the result of the screening test.

The UBT samples will be sent to the same central laboratory as samples for hematology and clinical chemistry. Sample shipment will be described in a laboratory manual, which will be distributed by the central laboratory..

4.6.3 Upper Gastrointestinal Symptoms Assessment by Investigator

The investigator will assess the number and severity of upper GI symptoms during the last 7 days using a 4-graded Likert scale for each subject at every visit and record this in the CRF. The symptoms to be assessed are epigastric pain, epigastric burning, epigastric discomfort, heartburn, acid regurgitation, nausea, bloating, sleep disturbance and chest pain. Definitions are described in Section 4.6.3.1.

An unscheduled EGD should be considered in subjects reporting new or aggravated upper GI symptoms, as judged by the investigator.

4.6.3.1 Methods of assessment

The definitions for the symptoms being assessed are:

Epigastric pain: Pain centered in the central part of the upper abdomen

Epigastric burning: A burning feeling centered in the upper abdomen

Epigastric discomfort: An unpleasant or troublesome non-painful sensation centered in the upper abdomen

Heartburn: A burning feeling behind the breastbone

Acid Regurgitation: Flow of sour or bitter fluid into the mouth

Nausea: A sensation of needing to vomit

Bloating: Sensation of visceral distension located in the upper abdomen. It should be distinguished from visible abdominal distension

Sleep disturbance: Sleep disturbances includes but are not limited to:

- Trouble falling asleep due to GERD symptoms, or
- Unwanted awakenings by GERD symptoms or by coughing or choking because of fluid or an acid or bitter taste, or food in the throat, or
- Overall poor sleep quality caused by nocturnal heartburn, reflux, or any other GERD symptom

Chest pain: Pain behind the breastbone

The investigator will assess the intensity of these symptoms as follows:

None: No symptoms

Mild: Awareness of sign or symptom, but easily tolerated

Moderate: Discomfort sufficient to cause interference with normal activities

Severe: Incapacitating, with inability to perform normal activities

4.6.4 Signs of Gastrointestinal Complications

At visit 2, 3 and 4 the investigator will ask for occurrence of events/signs of GI complications since the previous visit. The options are haematemis, malaena, haematochezia, perforation, gastric outlet obstruction and other. If other GI complications have been found, this has to be specified.

4.7 Safety measurements and variables

The methods for collecting safety data are described below.

4.7.1 Adverse Events

4.7.1.1 Definitions

The definitions of AEs, SAEs and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse Event

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, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious Adverse Event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

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

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?”. For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as “yes”.

Other Significant Adverse Events

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as 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. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of adverse events

SAEs will be collected after signing of the informed consent and throughout the study. Non-serious AEs will be collected from the time of the first administration of investigational product until the end of study and will be recorded in the CRF at visits 2, 3 and 4 and at any unscheduled visit.

Any AEs that are unresolved at the last AE assessment are to be followed up and recorded in the CRF 2 weeks after completion/discontinuation, and thereafter followed by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary.

Spontaneously reported AEs, objective findings and observations, as well as AEs reported in response to the standardized question ”Have you had any health problems since the previous visit?” will be recorded in the CRF. Start and stop date (or marked as ongoing), action taken regarding study drug, outcome and seriousness will be recorded.

The causality of all AEs and SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must 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 drug?” A guide to the interpretation of the causality question can be found in Appendix B to the Clinical Study Protocol.

Deterioration in laboratory values and vital signs need not be reported as AEs. However abnormal laboratory tests and other objective measurements or findings that meet the criteria

for a SAE or result in discontinuation of investigational product should be recorded and reported as SAEs or AEs.

SYMPTOMS OR SIGNS OF THE DISEASE UNDER STUDY

Symptoms as defined in Section 4.6.3.1 (ie, epigastric pain, epigastric burning, epigastric discomfort, heartburn, acid regurgitation, nausea, bloating, sleep disturbance and chest pain) will be reported as AEs only if they are not in accordance with the subject's normal symptoms, as judged by the subject or the investigator. If any symptom fulfils any criteria of an SAE according to the definition (see Appendix B) or result in discontinuation of investigational product, it should be reported as an SAE or AE respectively.

Findings determined by endoscopic evaluation should not be reported as AEs unless they result in discontinuation of investigational product.

The occurrence of a peptic ulcer (either gastric or duodenal) is considered an efficacy endpoint of the disease under study and should not be recorded as an AE. For description of recording of ulcer, see Section 4.6.1.1. Complications associated with peptic ulcer should not be reported as AEs unless they result in discontinuation of investigational product.

If any finding meets the criteria of an SAE according to the definition (see Appendix B), it must be reported as a SAE.

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study 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.

SAE information will be entered and submitted into the Web-Based Data Capture (WBDC) system on the relevant CRF modules. An automated e-mail alert will be sent to the designated AstraZeneca representative who will work with the investigator to ensure that all the necessary information is available in the system within the required time frames, but taking advantage of the time allocated in those timelines. The AstraZeneca representative will notify the appropriate AstraZeneca Drug Safety department through the WBDC system via email

that a completed electronic SAE module and relevant information from other appropriate CRF modules is available in the WBDC system.

If the Investigator is not able to enter SAE information into the WBDC system, a SAE paper form will be available as back-up. The AstraZeneca representative should be contacted for guidance on whether to use this form or not. If the AstraZeneca representative cannot be contacted the SAE paper back-up form should always be used. As soon as the WBDC system is (again) available to the investigator, any SAE reported on the paper form must also be entered into the WBDC system.

The investigator is responsible for completing the CRF as soon as the system becomes available again.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If follow-up indicates a change in the SAE from serious to fatal or life-threatening, this information needs to be available in the WBDC system within 1 calendar day.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that becomes serious but which is not fatal or life-threatening a report should be received within 5 days.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the CRF. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca (see Section 8.1).

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Methods of assessment

A laboratory screening, which includes hematology and clinical chemistry, will be done at each visit. A laboratory screening will also be done in case of premature withdrawal from the study. The visit 1 laboratory screening must be done prior to the first dose of study medication and is regarded as baseline data. Samples for clinical laboratory tests will be obtained by standardized techniques and assessed by a central laboratory for serum chemistry and hematology.

Clinical laboratory tests will include:

- Serum Chemistry: Creatinine, total bilirubin, alkaline phosphatase, ASAT (SGOT), ALAT (SGPT), Iron saturation S-Fe, S-TIBC.

- Hematology: Hemoglobin, white blood cell count (WBC), and platelet count.

A central laboratory will analyse the hematology and clinical chemistry samples. Sample collection, labeling, storage and shipment will be described in a laboratory manual, which will be distributed by the central laboratory before the first subject is randomized. The samples may be taken in a subject regardless of whether he/she is fasting since the intra-individual changes are the ones studied. The procedures used for individual subjects should be kept constant. The central laboratory will provide the investigator and AstraZeneca with test results including units, relevant reference ranges and updates as necessary.

4.7.3 Vital signs and physical examination

Vital signs (blood pressure and pulse) will be measured after 5 minutes supine rest and physical examination will be done at baseline, last visit and in case of discontinuation. The following organ systems will be examined according to normal hospital routines (results expressed as normal/abnormal) and recorded in the CRF.

- General appearance
- Cardiovascular
- Lungs
- Abdomen

4.7.4 Other safety measurements and variables

Not applicable.

4.8 Volume of blood sampling and handling of biological samples

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

Table 2 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Pharmacodynamic		NA		
Pharmacokinetic		NA		
Safety	Clinical chemistry	10	4	40
	Hematology	5	4	20
Total				**60**

4.8.1 Analysis of biological samples

The analyte stability limits defined by the central laboratory will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory will not analyze samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central laboratory may be amended in accordance with its Standard Operating Procedures.

If the central laboratory chooses to sub-contract the analytical work to another laboratory, the central laboratory must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analyzed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first gives informed consent to take part in the study.

4.9 Genetic measurements and co-variables (Not applicable)

5. DATA MANAGEMENT

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the CRF Instructions. The CRF Instructions will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered reviewed, edited and Source Data Verification (SDV) performed the principal investigator will be notified to sign the CRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the CRF will be archived at the study site.

The investigator will also sign the causality for AEs.

It is the responsibility of the Investigator to complete SAE forms when applicable. It is the AstraZeneca monitor's responsibility to ensure that any SAE form is fully completed.

Adverse Events and Medical and Surgical history will be classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary, the Anatomical Therapeutic Chemical (ATC) system and the Committee for Medicinal Products for Human use (CHMP) route of administration dictionary. All coding will be done at AstraZeneca.

All data editing and data validation activities will be done by investigators, monitors and data management staff on blinded data. The randomization code will not be broken until all data editing and data validation procedures have been carried out and the AstraZeneca "clean file" procedure has been completed. Clean file is defined as a status where the data in the CRFs and the reference values are complete and logical according to the study protocol, general guidelines and data management plan. Prior to breaking of the treatment codes, all decisions on the evaluability of the data from each individual subject must have been made and documented.

The data management plan written by AstraZeneca will describe the methods used to collect, check, transfer and process clinical data in the study. It also clarifies the roles and responsibilities of the different functions and personnel involved in the data management process.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

This is a therapeutic confirmatory multicentre, randomized, double-blind, parallel-group, controlled trial of esomeprazole versus placebo in subjects on continuous low-dose ASA. The statistical considerations presented here will address issues related to efficacy. Complete documentation of all efficacy and safety analysis will be presented in a Statistical Analysis Plan (SAP) prior to unblinding the study.

6.2 Description of outcome variables in relation to objectives and hypotheses

The primary objective of the study is to compare the effect of esomeprazole 20 and 40 mg od versus placebo on the time to occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose ASA.

Furthermore, the following secondary outcome variables will be evaluated:

- Time to occurrence of gastric ulcer.
- Time to occurrence of duodenal ulcer.

- Dichotomized RDQ score (0 versus >0) for the dyspepsia dimension during the week prior to the 26-week visit or the week prior to the last visit, unless the last visit is the baseline visit, as reported by the subject.

- Dichotomized RDQ score (0 versus >0) for the GERD dimension (heartburn and regurgitation) during the week prior to the 26-week visit or the week prior to the last visit, unless the last visit is the baseline visit, as reported by the subject.

- Number of gastric and/or duodenal erosions.

- AEs, clinical laboratory tests and vital signs.

The secondary objectives are to:

- Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of gastric ulcers during 26 weeks in subjects on continuous low-dose ASA.

- Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of duodenal ulcers during 26 weeks in subjects on continuous low-dose ASA.

- Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported dyspeptic symptoms at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by RDQ in subjects on continuous low-dose ASA.

- Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported GERD symptoms (heartburn and regurgitation) at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by RDQ in subjects on continuous low-dose ASA.

- Study the number of gastric and/or duodenal erosions during 26 weeks in subjects on continuous low-dose ASA, by treatment.

- Assess safety and tolerability of treatment with esomeprazole 20 and 40 mg od during 26 weeks in subjects on continuous low-dose ASA.

6.3 Description of analysis sets

Populations to be identified prior to unblinding the study include the safety population, which consists of all subjects who were documented to have taken at least one dose of investigational product and for whom any post-dose data are available; the intention-to-treat (ITT) population, which consists of all randomized subjects without any peptic ulcer at baseline; and the per-protocol (PP) population, which consists of a subset of subjects who do not violate any major inclusion or exclusion criteria. These criteria will be specified in the SAP.

6.4 Method of statistical analysis

The main approach in the analysis of primary and secondary efficacy variables will be the ITT cohort. For the primary variable the PP population will also be evaluated.

The primary objective, efficacy for peptic ulcers, and the two secondary objectives concerning efficacy for gastric and duodenal ulcers will be tested in a hierarchical closed test procedure. If there is a significant difference for peptic ulcers, then efficacy for gastric ulcers will be tested in the next step, and finally if there is a significant difference for gastric ulcers, efficacy for duodenal ulcers will also be tested. Each step of the closed test procedure contains two tests, placebo versus esomeprazole 20 mg and placebo versus esomeprazole 40 mg. The closed test procedure will be done in parallel for the two different doses of esomeprazole and in each step the two resulting p-values will be adjusted according to the Hochberg procedure.

To assess differences between the esomeprazole groups and the placebo group the log rank test will be used. Low-dose ASA dose group (75-100 mg and 101-325 mg) will be included as strata in the log rank analysis. Homogeneity over the two dose ranges will also be tested. Kaplan-Meier life-table estimation will be used to graphically illustrate the primary variable, time to occurrence of peptic ulcer, for each treatment group.

Peptic ulcer occurrence rates at the different low-dose ASA dose ranges of 75-100 mg and 101-325 mg will be presented descriptively by treatment. Absolute and relative risk reduction of peptic ulcers will be presented for each of the esomeprazole groups as compared to placebo. Corresponding descriptive statistics will also be presented for gastric and duodenal ulcers.

The Mantel-Haenszel chi-square test will be used for the proportion of patients without any dyspeptic symptoms at the 26-week visit or the last visit, unless the last visit is the baseline visit, defined as patients with RDQ score equal to 0 for the dyspepsia dimension. The test will be stratified for baseline severity.

The statistical analysis of GERD symptoms will be done in the same way as for dyspeptic symptoms.

No adjustments for multiplicity will be done for any of the secondary variables concerning symptoms.

The number of gastric and duodenal erosions will be presented by treatment group as descriptive statistics in terms of frequency tables.

Baseline and demographic data will be presented descriptively.

Investigator-reported symptoms will be presented by treatment group as descriptive statistics in terms of frequency tables.

Upper GI complications will be presented by treatment group as descriptive statistics in terms of frequency tables.

Vital signs will be presented by treatment group as descriptive statistics in terms of median, mean and standard deviation (SD) at baseline, last visit and changes from baseline.

Clinical laboratory data will be presented by treatment group as descriptive statistics in terms of median, mean and SD at baseline, subsequent visits and changes from baseline. Furthermore, transitions from baseline to last visit will be presented in shift tables showing the distribution of patients with values below and above the reference range before and after treatment. In addition, scatter plots by treatment group using values at baseline and last visit will be presented.

Adverse events will be presented using descriptive statistics for the safety population.

6.5 Determination of sample size

The sample size is 2400 (800 subjects per treatment arm). Assumptions are primarily based on the results of a recently completed AstraZeneca-sponsored study (Yeomans ND et al 2006) the Asterix study.

The assumed event rate for peptic ulcer in the placebo arm is 8%. In the Asterix study, the observed event rate of peptic ulcers was 5.4%. The event rate 8% reflects an assumed increase due to a study population with a higher risk. The proportion of gastric ulcers is assumed to be 70%, corresponding to an event rate of 5.6%, as observed in the Asterix study.

The relative risk reduction for peptic ulcer is assumed to be 60%, which is a compromise between the assumed relative risk reduction for the Asterix study, 50%, and the observed, 70%. This implies an event rate for peptic ulcer of 3.2% in the esomeprazole groups. Further, the relative risk reduction is assumed to be the same for gastric and duodenal ulcers, as observed in the Asterix study. This implies an event rate for gastric ulcer of 2.24% in the esomeprazole groups.

The study is dimensioned to achieve at least 90% power for the primary variable, time to occurrence of peptic ulcer. With this number of patients, the power will be 80% to detect a difference in time to gastric ulcer using a log rank test at the significance level of 0.025 and a dropout rate of 15%.

6.6 Interim analyses (Not applicable)

6.7 Data monitoring board

There will be no data monitoring board in this study. The project has judged that there is no need for a data monitoring board as the continues surveillance during the study is extensive and sufficient to ensure safety for the individual patient. Data from the CRF, SAE and discontinuation due to AEs will be compiled and evaluated regularly by the special in-house cross-functional study team.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first subject enters into the study, a representative of AstraZeneca or delegate will visit the investigational study site to:

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

During the study, a monitor from AstraZeneca or company representing AstraZeneca 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 recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRF with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre need information and advice. More details about this will be documented in the Clinical Study Agreement between AstraZeneca and the investigator.

7.2 Audits and inspections

Authorized representatives of AstraZeneca or delegate, a regulatory authority, an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca 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, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca or delegate immediately if contacted by a regulatory agency about an inspection at his or her centre.

7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first subject is entered into the study, the investigational staff will be trained to use the WBDC system by AstraZeneca personnel or delegates.

7.4 Changes to the protocol

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

If it is necessary for the Clinical Study Protocol to be amended, the amendment and/or a new version of the Clinical Study Protocol (Amended Protocol) must be notified to or approved by each Ethics Committee, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

If a Clinical Study Protocol amendment requires a change to a particular center's Informed Consent Form, then AstraZeneca or delegate and the center's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca or delegate will distribute amendments and new versions of the Clinical Study Protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

7.6 Study timetable and end of study

Before a subject's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between AstraZeneca or delegate and the Principal Investigator/Study Site.

- Approval of the study by the Ethics Committee.
- Approval of the study, if applicable, by the regulatory authority.

The planned overall timetable for the study is as follows:

FSI

LSI

LSO

Database lock

End of study is defined as database lock, which is the time point after which no subjects will be exposed to study-related activities.

Enrolment will be stopped when about 2400 subjects have been randomized.

8. ETHICS

8.1 Ethics review

See Section 3.2.2 for risk/benefit and ethical assessment of this study.

AstraZeneca or delegate will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an Ethics Committee as appropriate. The investigator must submit written approval to AstraZeneca or delegate before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the Clinical Study Protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

The Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca or delegate will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

8.2 Ethical conduct of the study

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

8.3 Informed consent

The principal investigator(s) at each centre will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study, including the following:

- Withholding or discontinuing of any treatment
- Fasting prior to any study-related procedure or test
- EGD
- Collection of blood
- Pregnancy test
- RDQ assessment

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by subject number and study code.

The Master Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca or delegate, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

In this study, a Screening Consent can also be used to detect *H. pylori* positive subjects who are not allowed to be included in the study.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	**Name**	**Address & telephone number**
The local AstraZeneca representative could be found in the Supplement 2, Study Delivery Team Contacts in the Event of Emergency'		

9.2 Procedures in case of medical emergency

The principal investigator(s) 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 should be reported as such, see Section 4.7.1.1.**

9.3 Procedures in case of overdose

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

All intake of esomeprazole corresponding to 120 mg/day or more is considered as an overdose in this study. Should an overdose (accidental or deliberate) occur, it must be reported according to the following:

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRFs.
- An overdose with associated non-serious AEs should be recorded as the AE diagnose/symptoms on the relevant AE forms in the CRFs. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."
- An overdose without associated symptoms should not be recorded as an AE in the CRFs. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

9.4 Procedures in case of pregnancy

Pregnant women, as well as those who are planning pregnancy or are breast-feeding, are excluded from the study. In addition, fertile women not using acceptable contraceptive measures, as judged by the investigator, should not be included.

Clinical experience with esomeprazole in pregnant women is limited and subjects that become pregnant must be discontinued from the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

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Clinical Study Protocol: Appendix A

Drug Substance	Esomeprazole
Study Code	D961FC00003
Appendix Edition Number	1.0

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A randomized, double-blind, parallel-group, multicentre, phase III study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA)

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

I agree to the terms of this study protocol.

AstraZeneca Research and Development
site representative

ASTRAZENECA SIGNATURE(S)

A randomized, double-blind, parallel-group, multicentre, phase III study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA)

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

I agree to the terms of this study protocol.

AstraZeneca Research and Development
site representative

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A randomized, double-blind, parallel-group, multicentre, phase III study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA)

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.: *<<If the International Co-ordinating Investigator is not responsible for a specific centre please delete the Centre No.:. This may be hand-written onto the page at the time the signature is collected. It is not necessary for any one investigator to sign the protocol more than once ie, if the international co-ordinator is a principal investigator at a centre it is not necessary for them to sign the investigator signature page>>*

Signature:

Clinical Study Protocol: Appendix B

Drug Substance	Esomeprazole
Study Code	D961FC00003
Appendix Edition Number	1.0

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

<<*Examples of such events are:*

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Esomeprazole
Study Code	D961FC00003
Appendix Edition Number	1.0

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Appendix C
Reflux Disease Questionnaire

Reflux Disease Questionnaire (RDQ)

Please answer each question by ticking **one** box per row.

1. Thinking about your symptoms over the past 7 days, how often did you have the following?

		Did not have	1 day	2 days	3-4 days	5-6 days	Daily
a.	A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b.	Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c.	A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d.	A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e.	An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f.	Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐

2. Thinking about symptoms over the past 7 days, how would you rate the following?

		Did not have	Very mild	Mild	Moderate	Moderately severe	Severe
a.	A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b.	Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c.	A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d.	A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e.	An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f.	Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐