AstraZeneca

Amended Clinical Study Protocol

Drug Substance	esomeprazole
Study Code	D9612C00003
Edition Number	1
Date	

An open, randomized, multicenter, phase IIIB study during 10 years to assess long-term efficacy and tolerability of esomeprazole compared to laparoscopic anti-reflux surgery in adult subjects with chronic gastro-esophageal reflux disease - LOTUS.

AstraZeneca Research and Development site representative

Date

The following Amendment(s) and Administrative Changes are included in this amended protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			
2			
3			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			
2			

PROTOCOL SYNOPSIS

An open, randomized, multicenter, phase IIIB study during 10 years to assess long-term efficacy and tolerability of esomeprazole compared to laparoscopic anti-reflux surgery in adult subjects with chronic gastro-esophageal reflux disease - LOTUS.

Investigator

International principal investigator

International principal co-investigator

Study centre(s) and number of subjects planned

The number of planned subjects is 550 in 11 countries (Austria, Belgium, Denmark, France, Germany, Iceland, Italy, The Netherlands, Norway, Sweden and UK). 57-60 centres are planned with a minimum of 6 subjects per centre. All patients who enter the 5-year visit (visit 16) will be asked to participate in the prolongation of the study.

Study period	Phase of development
Estimated date of first subject enrolled	IIIB
Estimate date of first subject enrolled in the prolongation	
Estimated date of last subject completed	

Objectives

The primary objective of the study is:

To investigate the efficacy of long-term treatment of esomeprazole compared to anti-reflux surgery in the control of gastroesophageal reflux disease (GERD) by the assessment of time to treatment failure. (See Section 4.3 Table 3)

Other objectives are:

- Histopathological changes in the squamous epithelium of the distal esophagus, the mucosa of the z-line and of the gastric mucosa.
- Point/periodic prevalence of endoscopic and symptomatic recurrences during 0.5 to 10 years` treatment.
- Assessment of gastrointestinal (GI) symptoms associated with GERD over time.
- In cases with Barrett´s esophagus, the extent of columnar lined esophagus.
- Per-operative events.
- Post-operative symptoms.
- Post-fundoplication complaints.
- Assessment of 24 hour pH metry, manometry and Symptom Association Probability (SAP).
- Changes in the laboratory screen variables.
- All serious adverse events and those adverse events causing premature discontinuation of study drug and/or study.
- Patient reported outcomes (PRO) assessed by QOLRAD and GSRS.

Study design

This study is designed as a 5-year, randomized, open, parallel-group multicentre trial with a 5-year prolongation. The objectives are to estimate the efficacy and tolerability of esomeprazole compared with laparoscopic anti-reflux surgery, in a long-term treatment of adult subjects with chronic gastroesophageal reflux disease (objectively documented by endoscopy and/or abnormal 24 hour pH metry (see Section 4.3.8.)). The study will begin with a 12-week run-in period allowing recording of baseline values and responses to medical treatment with esomeprazole. This period will end with a randomization between the two therapeutic strategies.

Target subject population

The target population is adult subjects with confirmed gastroesophageal reflux disease requiring long-term medical treatment. All subjects should be eligible for anti-reflux surgery. Subjects should not have more than grade B esophagitis (LA classificiation) or more than mild symptoms of GERD at the time of randomization into the long-term treatment phase.

Investigational product, dosage and mode of administration

Esomeprazole, oral dose 20 or 40 mg daily. The healing dose is 40 mg o.d. and the maintenance dose is 20 mg o.d. Dose adjustments can be made according to subjects individual needs.

Comparator

Laparoscopic anti-reflux surgery

Duration of treatment

12 weeks run-in followed by a ten-year follow-up period.

Endpoints

-Efficacy (see Section 4.3 and Table 3)

- Time to treatment failure where **treatment failure** is defined as;

a/ in the medical arm:

Need for treatment other than esomeprazole for control of symptoms of reflux disease:

In order to allow for a stringent assessment of treatment failure ask the following question:

"Do you have sufficient control of your heartburn and acid regurgitation?"

If the answer is **No,** continue with:

"Do you need other regular drug treatment to control your symptoms?"

If the answer to this question is **Yes** and the dose of esomeprazole is 20 mg once daily, then the dose is to be increased to 40 mg once daily. The subject will be treated with the increased dosage for 8 weeks before a second dose adjustment can be made.

If the answer to this question is **Yes** and the dose is esomeprazole 40 mg once daily, then the dose is to be changed to 20 mg twice daily. The subject will be treated with the changed dosage for 8 weeks before being classified as a treatment failure if sufficient symptom control has not been achieved.

If the answer to this question is **Yes** and the dose is 20 mg twice daily, then the subject is a **treatment failure and will be withdrawn.**

b/ In the surgical arm**:**

Need for medical treatment for control of symptoms from reflux disease:

In order to allow for a stringent assessment of treatment failure ask the following question:

"Do you have sufficient control of your heartburn and acid regurgitation?"

If the answer is **No,** continue with:

"Do you need other regular drug treatment to control your symptoms?"

If the answer to this question is **Yes** the subject has to be classified as a **treatment failure and will be withdrawn.**

Furthermore, the subject will also be regarded as a **treatment failure** if the following occurs;

- Post-operative - post-fundoplication complaints requiring further medical actions to control symptom burden.
- Per-operative death
- Post-operative death within 30 days after surgery
- Dysphagia requiring further treatment. In case of esophageal stenosis, one dilatation is allowed.

Other efficacy endpoints

- Histopathological variables
- Scores of symptom variables.
- Endoscopic assessments.
- Assessment of 24 hr pH metry and SAP.

Safety (see Section 4.4 Table 4)

- Laboratory variables.
- All serious adverse events and those adverse events causing premature discontinuation of study drug and/or study.

Quality of Life (see Section 4.5 Table 5)

- Patient-reported outcomes assessed by GSRS and QOLRAD

Statistical methods

The treatment arms will be compared regarding time to evidence of treatment failure by a logrank test. The comparison will be made for an ITT population.

Other endpoints will be analysed descriptively.

Genetic

A blood sample for deoxyribonucleic acid (DNA) preparation and further genetic analysis will be taken. Patients who do not wish to participate in the genetic research are still eligible to participate in the Clinical Study.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

APPENDICES

Appendix I	SH-NEG-0003 LOTUS GSRS questionnaire
Appendix J	SH-NEG-0003 LOTUS QOLRAD questionnaire
Appendix K	Laboratory measurements and logistics
Appendix L	Outline Study plans
Appendix M	Subject Information and Consent Form for medical arm - 5 year prolongation
Appendix M	Subject Information and Consent Form for surgical arm - 5 year prolongation
Appendix N	Genetic Research Addendum to Informed Consent Form for use Globally (except in the US)
Appendix O	Genetic Research Component of the LOTUS Clinical Study
Appendix P	5 and 10 years follow-up questions for premature discontinued subjects

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or specialist term	Explanation
AE	Adverse event (see definition in Section 4.4.2.1)
ALAT	Alanine aminotransferase
ASA	Acetylsalicylic acid
ASAT	Aspartate aminotransferase
b.i.d.	Twice daily
CLE	Columnar lined esophagus
CRF	Case Report Form
CRO	Contract Research Organisation
ECL-cells	Enterochromaffin-like cells
FSI	First Subject In
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GI	Gastro-intestinal
GSRS	Gastro-intestinal Symptoms Rating Scale
H.p.	Helicobacter pylori
H_2RA	H_2 receptor antagonist
hr	hour
HRQL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
International principal investigator	The investigator who leads the whole study.
IRB	Institutional Review Board
ITT	Intention To Treat
LSI	Last Subject In
LSO	Last Subject Out
MedRA	Medical Dictionary for Regulatory Activities
mg	milligram
NB	nota bene
NSAID	Non-steroid anti-inflammatory drugs

OAE	Other significant adverse event (i.e., an adverse event of special interest in this clinical development; see definition in Section 4.4.2.1). The classification of OAEs will be made by AstraZeneca drug safety physicians when the study has been completed.
o.d.	once daily
OTC	Over-the-counter
PP	Per protocol
PPI	Proton pump inhibitor
Principal investigator	The investigator who leads the study conduct at an individual study centre. Every study centre has a principal investigator.
p.r.n.	pro re nata
PRO	Patient-Reported Outcomes
QOLRAD	Quality Of Life in Reflux And Dyspepsia
RBC	Red blood cell count
RE	Reflux esophagitis
SAE	Serious adverse event (see definition in Section 4.4.2.1).
SAP	Symptom Association Probability
WBC	White Blood Cells
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

Gastroesophageal reflux disease (GERD) is a common health problem causing a variety of symptoms, the most predominant being heartburn. Studies suggest that 20-40% of the adult population at some time experience heartburn, and approximately 7% of these subjects have this symptom every day (Spechler SJ 1992). In most subjects GERD symptoms are caused by acidic gastric juice refluxing into the esophagus. The severity of heartburn is determined by a number of factors of which the amount of acid reflux is one (Lind T et al 1997).

In about half of the subjects suffering from symptoms of GERD, endoscopy will demonstrate signs of esophageal lesions of at least grade A (Los Angeles classification). Despite symptoms of similar severity and intensity the remainder of GERD subjects have normal endoscopic findings, i.e. non-erosive disease (Spechler SJ 1992, Jones RH et al 1995, Heading RC 1989, Johnson F et al 1987). Of functional importance is, however that GERD symptoms have significant negative impact on health-related quality of life (Carlsson R et al 1998), irrespective of whether erosive esophagitis is present or not.

GERD is a chronic relapsing disease. The two main long-term treatment alternatives in use are medication and surgery.

Medical treatment today is based on proton pump inhibitors (PPIs) administration, e g omeprazole (Dent J et al 1999) to reduce gastric acid secretion and normalise acid reflux into the esophagus, thereby healing erosive esophagitis and relieving symptoms.

A recent long-term study comparing omeprazole maintenance treatment with the conventional open fundoplication operation has shown both strategies to be effective (Lundell L et al 2000).

Esomeprazole is a further development of the original omeprazole (PPI) concept. Esomeprazole offers a more profound and longer lasting inhibition of gastric acid secretion during a 24-hour period than omeprazole and the interindividual variation in intragastric acidity is reduced. Clinical studies have shown esomeprazole, given in the doses recommended, to be more effective than omeprazole, both in terms of healing esophagitis and in relieving reflux symptoms.

Anti-reflux surgery has undergone technical changes during the last decade. The most commonly favoured operation today is a laparoscopic approach. The laparoscopic operation seems to offer a less troublesome and a shorter post-operative convalescent period compared to the traditional open technique (Lundell L 2000).

1.2 Rational for this study

This study will compare the two main long-term therapeutic options in GERD, an up-to-date surgical therapy with modern medical treatment, over a ten year period. Valuable information

will be gained for the long-term efficacy and safety of esomeprazole maintenance treatment in GERD.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to investigate the efficacy of long-term treatment of esomeprazole compared to laparoscopic anti-reflux surgery in the control of gastroesophageal reflux disease by the assessment of time to treatment failure (see Section 4.3 and Table 3).

2.2 Other objectives

Other objectives of the study are to assess;

Efficacy measurements (see Section 4.3 and Table 3)

- Histopathological changes in the squamous epithelium of the distal esophagus, the mucosa of the z-line and in the gastric mucosa.
- Point/periodic prevalence of endoscopic and symptomatic recurrences during 0.5 to 10 years` treatment.
- GI symptoms associated with GERD.
- In cases of Barrett´s esophagus, the extent of columnar lined esophagus
- Per-operative events
- Post-operative symptoms and post-fundoplication complaints
- Assessment of 24hr pH metry, manometry and SAP (Symptom Association Probability)

Safety measurements (see Section 4.4 Table 4)

- Changes in the laboratory screen variables.
- All serious adverse events and those adverse events causing premature discontinuation of study drug and/or study.

Quality of Life

- Patient-reported outcomes assessed by GSRS and QOLRAD (see Section 4.5.Table 5)

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This study is designed as a 5-year, randomized, open, parallel-group multicentre trial with a 5-year prolongation with the objectives to estimate the efficacy and tolerability of esomeprazole compared with anti-reflux surgery, in a long-term treatment of adult subjects with confirmed, symptomatic gastroesophageal reflux disease with or without esophagitis (objectively documented by endoscopy and abnormal 24 hour pH metry). All subjects should be eligible for surgery.

The study will begin with a 12-week run-in period enabling the recording of baseline values and responses to medical treatment with esomeprazole 40 mg o.d. This period will end with a randomization into the 10-year study period. All subjects should have the need for continuous treatment to control reflux and be eligible for anti-reflux surgery. Subjects should not have more than LA grade B endoscopic-visualized mucosal breaks or more than mild symptoms of GERD prior randomization and should have responded to esomeprazole treatment in the 12-week run-in period.

The 10-year study period consists of 2 treatment arms, medical treatment (esomeprazole, start dose is 20 mg o.d.) and anti-reflux surgery (laparoscopic fundoplication). Subjects willing to accept randomization to either surgery or long-term medical treatment will receive treatment according to a randomization list.

Helicobacter pylori (*Hp*) status will be assessed based on biopsy material.
In case of confirmed peptic ulcer disease and positive *Hp* testing eradication therapy should be given prior to enrolment. Subject should not be enrolled within 3 months after therapy.

In case of a first episode of peptic ulcer disease during the 10-year study period and confirmed positive *Hp* testing eradication therapy is allowed.

In all other cases of *Hp* infection not associated with peptic ulcer disease eradication therapy is not allowed.

The planned number of subjects is 550 randomized in 11 countries, with at least 6 subjects per centre.

Visits 1, 2, 3, 4, 5, 6, 7, 8, 12,16, 31, 33, 35, 37 and 39 will be regular visits with the investigator and visits 9, 10, 11, 13, 14 and 15 may be done by the study nurse.

During the 5-year prolongation, all subjects will visit the hospital after 6, 7, 8, 9 and 10 years for assessments. At 5.5, 6.5, 7.5, 8.5 and 9.5 the subjects will have a telephone visit (hospital visit optional). The hospital visit should be done by the investigator and the telephone should preferable be done the investigator.

Randomized subjects who have discontinued but not withdrawn their informed consent will be followed-up by a phone call from the investigators at 5 and 10 years after randomization. This will also be applicable for subjects who discontinue during the prolonged period. The follow-up phone call consists of questions about the subject's surgery related to GERD, present medical treatment of GERD and present symptom load. For more information see Appendix P to the amendment

Run-in period

The study will start with a 12-week run-in period. Subjects will have either been treated or untreated with a PPI prior to entering this phase of the study. The subjects will receive both oral and written subject information and sign a consent form. At visit 1 all subjects will undergo a physical examination, including vital signs and demographics. Medical and surgical history, especially for GERD will be recorded.

All subjects will attend an "Investigational week". This "week" will allow the collection of baseline data, such as endoscopy with biopsy sampling, 24-hour pH metry, manometry, SAP and laboratory measurements. A 24-hour pH metry performed within 12 months prior to enrolment could be accepted, if made according to the method stated i.e. no antisecretory medication 7 days prior to investigation. Manometry will only be performed at the first occasion of pH metry in all subjects.

The "investigational week" can take place either immediately or 6 weeks after treatment with esomeprazole 40 mg o.d. depending on:

- Whether the subject was treated or untreated with PPI prior to enrolment
- Whether the clinic can offer 24 hr pH metry and SAP within 2 weeks from visit 1 for the untreated subjects.

Esomeprazole must be withheld at least 7 days (visit 2) prior to the "Investigational week".

Dose adjustments are not allowed during the run-in period.

Subjects <u>treated</u> with PPI prior to study start will be treated in one of two ways depending on:

(i) if the subject is known (endoscopically) to the investigator prior to entry into the study. These subjects need not undergo an endoscopy at visit 1, but will receive esomeprazole 40 mg o.d. and continue with visit 2 and 3 as scheduled.

(ii) if the subject is referred to endoscopy, the subject will undergo endoscopy at visit 1 and receive esomeprazole 40 mg o.d. and continue with visit 2 and 3 as scheduled.

The "Investigational week" will take place during visit 3. In case of mucosal breaks classified as LA grade C or D at visit 3 a new endoscopy must be done at visit 4 prior to randomization to exclude the presence of LA C or D at randomization.

Subjects <u>untreated</u> with PPI prior to study start will (if possible):

(i) start the run-in period with the "investigational week" at visit 1. In such cases an endoscopy with biopsy sampling will be made at visit 1. If insufficient biopsies have been taken at visit 1 then another endoscopy with biopsy sampling will be done at visit 3. In cases of mucosal breaks classified as LA grade C or D at visit 1 or 3 a new endoscopy must be performed at visit 4 prior to randomization. Furthermore, laboratory measurements, 24 hr pH metry, manometry and SAP will be made. If these assessments can be made within 2 weeks from visit 1 then visit 2 and 3 can be left out. The study drug (esomeprazole 40 mg o.d.) will then be dispensed and the subject will continue the run-in period. If the time between first endoscopy (visit 1) and the 24 hour pH metry is more than 2 weeks, the study drug must be dispensed at visit 1 and the subject will follow the same routine as the **<u>treated</u> subject (i).**

<u>10-year study period</u>

If reflux esophagitis LA grade C or D is found at visit 3, a new endoscopy must be done at visit 4 prior to randomization.

- Subjects will be randomized to either medical treatment or surgery at visit 4. Medical treatment is 20 mg o.d. (start dose) and can be adjusted, but is not to exceed 40 mg daily. Surgery must be performed within 3 months after randomization. The subject is allowed to be treated with esomeprazole 20 mg o.d. and can be adjusted, but is not to exceed 40 mg daily whilst awaiting the surgery. Visit 5 and 6 will only be attended by subjects randomized to surgery.

- Endoscopy with biopsy sampling will be performed at visit 8, 12, 16, 33 and 39. A 24 hour pH metry and SAP will be performed at visit 7 and 16. Endoscopy will be performed at extra visits in case of symptomatic relapse or early discontinuation. A 24 hr pH metry and SAP should be performed in case of dose adjustments (prior to).

- Symptoms will be assessed at each visit except at visit 5 and the telephone visits (visit 30, 32, 34, 36, 38). Laboratory screen will be done at visit 8, 12, 16, 33 and 39 and at early discontinuation visits.

- Patient reported outcomes (PRO) will be assessed by QOLRAD and GSRS at visits 4, 8, 10, 12, 14, 16, 31, 33, 35, 37 and 39 and at early discontinuation visits.

- Body weight will be assessed at visits 4, 8, 12, 16, 33, 39 and at extra visits and at early discontinuation visits.

- All serious adverse events and those adverse events causing premature discontinuation of study drug and/or study will be recorded at each visit except visit 1 and 5 (surgery visit).

During the 10-year study period subjects in both treatment arms having (moderate-severe) recurrent GERD symptoms on at least **3 consecutive days** will be instructed to contact the clinic. The subject will be asked to answer the questions regarding treatment failure and follow the instructions for each treatment arm. In case of dose adjustments, the increased dosage must be taken for 8 weeks before a second dose adjustment is made. A 24 hr pH metry and SAP should be made prior to dose adjustment (only applicable to an adjustment to a higher dose). If the subject is symptom-free and satisfied after this treatment period with an increased dose, a reduction to the previous lower dose should be aimed at. At least one attempt to return to the previous lower dose should be made. After two periods of dose increase due to recurrence of symptoms, the investigator can decide which dose is required to maintain symptoms under control for the remaining study period, but the dose cannot exceed 40 mg o.d. or 20 mg b.i.d.

In case of subjects who are satisfied with their treatment, but with temporarily (at least **3 consecutive days**) moderate-severe GERD symptoms, the subject will be offered an endoscopy and:

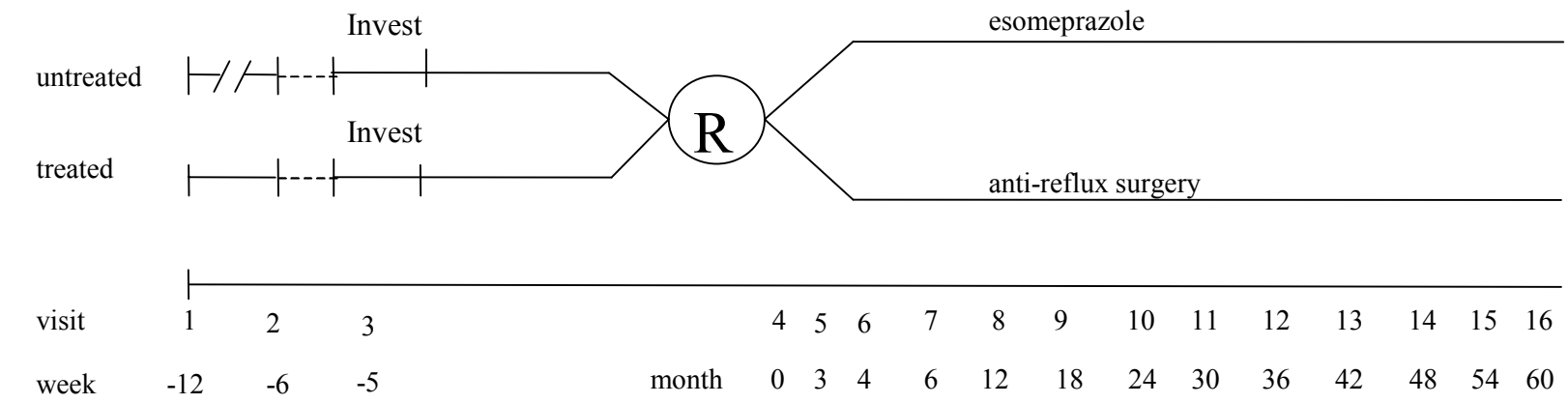
- Subjects in the medical arm will then receive treatment with esomeprazole 40 mg o.d. for 2-12 weeks according to endoscopic findings and symptomatology. After treatment the subject in the medical arm will continue the study with esomeprazole at a dose which is required to maintain symptoms under control but does not exceed 40 mg daily.

- Subjects in the surgical arm are allowed to have symptomatic treatment (antacids) and will continue the study.

Visits 5 and 6 are only relevant to subjects randomized to surgery.

Interim analyses are planned 3 years (visit 12) and 5 years (visit 16) after last subject randomized (medical arm) or operated (surgical arm) on, to evaluate efficacy and tolerability.

Figure 1 Study flow chart



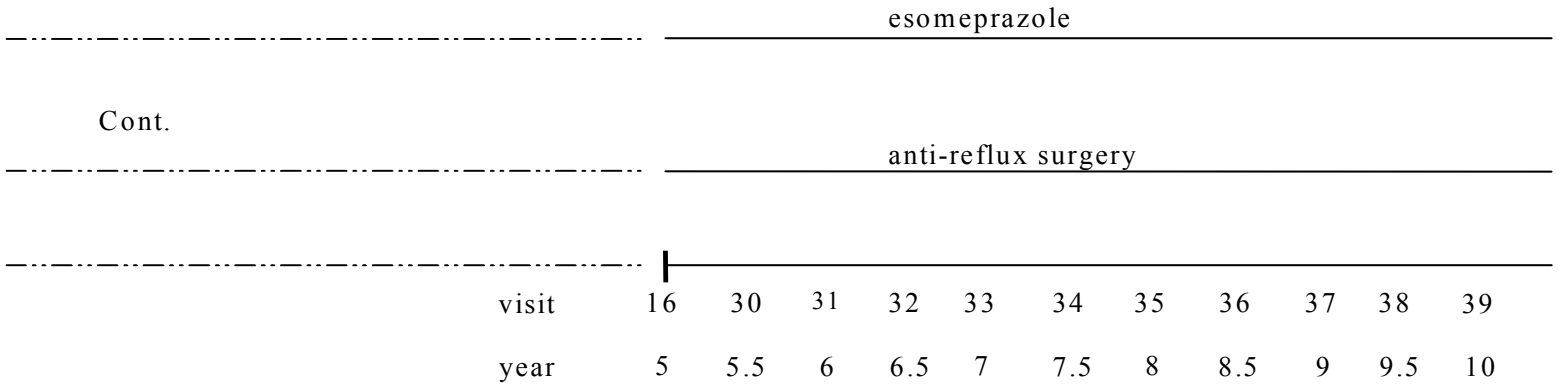


Table 1 Study plan (For more outlined study plans see appendix L)

Visit Nos. **Week/month Assessments**	**1** **-12 w**	**2[6]** **-6 w ±1w**	**3[7]** **-5 w**	**4** **0**	**5[2]** **<3m**	**6[2,12]** **<4 m**	**7** **6m ±2w**	**8** **12 m ±2w**	**9** **18 m ±2w**	**10** **24 m ±2w**	**11** **30m ±2w**	**12** **36 m ±2w**	**13** **42 m ±2w**	**14** **48 m ±2w**	**15** **54 m ±2w**	**16** **60 m ±2w**	**Extra visit**	**Discont. visit[17]**
Endoscopy incl. biopsies Hp status	X[4]		X[8]	X[10]				X				X				X	X[15]	X
24 hr pH metry, manometry & SAP[1]	X[5]		X[9]				X									X	X[16]	X
Surgery[2]					X													
Post-operative symptoms[2]						X												
QOLRAD, GSRS				X				X		X		X		X		X		X
Symptoms	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory screen	X[5]		X[9]					X				X				X		X
Medical, surgical hist., demograph.	X																	
Vital signs incl. body weight	X			X[11]				X[11]				X[11]				X[11]	X[11]	X[11]
Inclusion and exclusion criteria	X			X														
Dispense study drug	X			X	X		X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]		X[14]	
Randomization				X														
Compliance			X	X	X	X[13]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]
Written Informed consent and Subj. information	X																	
Adverse events[3]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

1 If pH monitoring was less than 18 hours, pH metry should be repeated. Manometry should be done by all subjects only on the first occasion of pH metry

2 Only for subjects randomized to surgery.
3 All SAE and those AE causing premature discontinuation of study drug and/or study.
4
5 Only for subjects who were untreated with PPI prior to study enrolment and if an appointment for pH metry was scheduled within 2 weeks from visit 1.
6 Withholding of medical treatment
7 7 days after visit 2
8 Only for subjects who were treated with PPI prior to study enrolment or if too few biopsy specimens were taken from untreated subjects at visit 1.
9 For all subjects unless pH metry and laboratory screen was done at visit 1 for untreated subjects.
10 Only for subjects with RE LA grade C or D at visits 1 or 3.
11 Only body weight
12 30 days after visit 5 (surgery)
13 Only for subjects in the surgical arm receiving esomeprazole
14 Only for subjects in the medical arm
15 In case of administration of healing dose (esomeprazole 40 mg o.d.)
16 In case of dose adjustment
17 In case of premature discontinuation after randomization (visit 4)

Table 2 Study plan prolongation

Visit Nos.	**16[a]**	**30[b]**	**31**	**32[b]**	**33**	**34[b]**	**35**	**36[b]**	**37**	**38[b]**	**39**	**Extra visit**	**Discont. Visit[h]**
Year	**5 ±6w**	**5.5 ±6w**	**6 ±6w**	**6.6 ±6w**	**7 ±6w**	**7.5 ±6w**	**8 ±6w**	**8.5 ±6w**	**9 ±6w**	**9.5 ±6w**	**10 ±6w**		**17**
	X												
Endoscopy incl. biopsies Hp status	X				X						X	X[f]	X
24 hr pH metry, manometry & SAP[c]												X[g]	X
QOLRAD, GSRS	X		X		X		X		X		X		X
Symptoms	X		X		X		X		X		X	X	X
Laboratory screen	X				X						X		X
Body weight	X				X						X	X	X
Dispense study drug[d]	X		X		X		X		X			X	
Compliance[d]	X		X		X		X		X		X	X	X
Concomitant Medication	X		X		X		X		X		X	X	X
AE[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent and blood sample for genetic research (optional)[i]	X												

a Last Visit in the 5-year LOTUS study
b Telephone Visit (hospital visit optional)
c If pH monitoring was less than 18 hours, pH metry should be repeated
d Only for Subjects in the medical arm
e All SAE and those AE causing premature discontinuation of study drug and/or study
f In case of administration of healing dose (esomeprazole 40mg o.d)
g In case of increased dose
h In case of premature discontinuation
i See appendix O

3.2 Rationale for study design, doses and control groups

This study is designed to investigate the efficacy and tolerability of long-term treatment with esomeprazole compared to anti-reflux surgery i.e. laparoscopic fundoplication.

The 12-week run-in period allows for the treatment of reflux esophagitis, enables the initial tolerability to esomeprazole to be controlled and allows for the collection of baseline data.

Dose adjustment not exceeding 40 mg daily will be allowed. Esomeprazole 40 mg o.d. has been chosen for during the run-in period. This dose has been shown to be the most effective in the healing of reflux esophagitis (Richter JE et al 2001).

Laparoscopic fundoplication is the surgical method chosen to be the comparator to long-term medical treatment (for surgical details see Section 3.4.2).

The duration of the study is 10 years. The target population is adult subjects with chronic gastroesophageal reflux disease in need for either long-term medical treatment or surgical treatment. All subjects should be eligible for surgery. The subjects will be randomized to either medical treatment or anti-reflux surgery.

3.2.1 Risk/benefit and ethical assessment

The prolongation is a an additional 5-year follow-up of a 5-year comparison between esomeprazole and laparoscopic reflux surgery in patients with severe GERD.

The subjects health will be monitored during regular visits to the investigator. There have not been any findings in the ongoing study that indicate any safety concerns.

In the prolongation the subjects will be followed up with regular visits to the investigator. The benefit to the patient is mainly the possibility of regular long term health/therapy controls of a life-long severe disease with risk for complications

3.3 Selection of study population

3.3.1 Study selection record

The investigator must keep a record of subjects who were considered for enrolment but never enrolled. This information is necessary to establish that the patient population was selected without bias. This record will be kept at the centre and will not be entered into any database at AstraZeneca.

3.3.2 Inclusion criteria (at enrolment)

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

1. Provision of written informed consent

2. Male or female 18-70 years of age.

3. Ability to complete the Quality of Life questionnaires

4. Subjects with a history of chronic (> 6 months) reflux esophagitis (endoscopically verified) or a history of chronic (> 6 months) symptomatic GERD with pathological

24 hour pH metry according to local standards and in need for long-term treatment with acid suppressive therapy.

5. Subjects considered suitable for surgical treatment and long-term management with esomeprazole.

3.3.3 Inclusion criteria (at randomization)

For randomization in the study subjects must fulfil all of the following criteria

6. Subjects considered suitable for surgical treatment and long-term management with esomeprazole.

7. None or mild symptoms of GERD at the end of the run-in period.

8. Subjects should not have more than LA grade B endoscopic-visualized mucosal breaks at the last endoscopy prior to randomization.

3.3.4 Exclusion criteria

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

1. History of esophageal, gastric or duodenal surgery predicted to influence negatively on subsequent treatment within the study.

2. Subjects with **current** or **historical** evidence of the following diseases/conditions:

   - Zollinger-Ellison syndrome
   - The primary esophageal disorders; achalasia, scleroderma and primary esophageal spasms
   - Inflammatory bowel disease.
   - Dysplastic changes in a columnar lined esophagus.
   - Any condition associated with abnormal absorption in the GI tract.
   - Significant cardiovascular, pulmonary, pancreatic, renal or liver diseases as judged by the investigator to interfere with the evaluation of the study.
   - Malignant disease except of minor superficial skin disease.
   - Current unstable diabetes mellitus. Stable diabetics controlled on diet, oral agents or insulin are acceptable.
   - Cerebral vascular disease, such as cerebral ischemia, infarction, haemorrhage or embolus as judged by the investigator.

3. Contraindication to the study drug, e.g. known or suspected allergy to esomeprazole and any other constituents of the formulation. Known hypersensitivity to substituted benzimidazole.

4. Pregnancy or lactation.

5. Child-bearing potential (female subjects must be post-menopausal, surgically sterilized or using medically accepted contraceptive measures during the study period as judged by the investigator.

6. Any significant "alarm symptoms" such as unintentional weight loss, recurrent vomiting, recurrent dysphagia, anaemia, haematemesis, melaena, jaundice or any other sign indicating serious or malignant disease.

7. Need for concomitant therapy with:

   - per oral anticholinergics and other drugs having anticholinergic co-effects such as tricyclic and tetracyclic antidepressive drugs
   - motility activators (prokinetic drugs) – except for operated subjects between visit 5 and visit 6 for treatment of post-operative intestinal paralysis.
   - prostaglandin analogues
   - NSAIDs (except for intermittent usage)
   - ASA (except for 165 mg daily or less for cardiovascular prophylaxis and for intermittent usage)
   - anticoagulants
   - PPI (other than study medication),
   - H_2RA

8. Use of any other investigational compound or participation in another clinical trial within 28 days prior to entry of the study.

9. Previous participation in this study.

10. Alcohol and/or drug abuse or any condition associated with poor compliance, including expected non-cooperation, as judged by the investigator.

11. Requirement of an interpreter.

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, at the discretion of the investigator(s). A subject may, however, continue the study under exceptional circumstances (e.g. if continuation of study treatment or follow-up actions are necessary for the subjects safety and well-being, and the continuation of the study is not expected to be associated with any risk or discomfort for the subject). Specific reasons for discontinuing a subject from this study are:

1. Withdrawal of informed consent
2. Unwillingness to continue the study or lost to follow-up.
3. Any unacceptable adverse event, including laboratory result or physical findings, as judged by the investigator
4. Any "alarm symptoms" which, in the investigator's judgement, requires treatment outside this protocol.
5. Continuous need for/intake of drugs listed under Section 3.3.4 criteria 7.
6. Protocol non-compliance as judged by the investigator
7. Classified as treatment failure
8. Pregnancy
9. Incorrect enrolment or randomization of subject
10. Other reason specified by the investigator.

3.3.5.2 Voluntary discontinuation by a subject

Subjects are free to discontinue their participation in the study at any time, without prejudice to further treatment. Subjects who discontinue from the study should always be asked about the reason(s) for their discontinuation and about the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up, questionnaires (e.g., for PRO assessments) and investigational products should be returned by the subject.

3.3.5.3 Incorrectly enrolled or randomized subjects

Incorrectly enrolled or randomized subjects will be discontinued from further study treatment and assessments.

3.3.5.4 Procedures for discontinuation

The subject should return for a clinic visit at the time of, or soon after discontinuation with maintained medication (medical arm) for the following assessments:

Discontinuation before randomization:

- All SAE and those AE causing premature discontinuation of study drug and/or study
- The reason for discontinuation

Discontinuation after randomization:

- Endoscopy including biopsies and *Hp* status
- Laboratory screening
- Body weight
- All SAE and those AE causing premature discontinuation of study drug and/or study
- Patient reported outcomes
- Symptoms
- 24 hour pH metry and SAP
- The reason for discontinuation

Procedures for discontinuation from genetic aspects of the study
See Appendix O for description of procedures for discontinuation from the genetic part of the Clinical Study.

After completion or discontinuation of the study the subjects will be treated according to clinical practise for GERD.

3.3.6 Restrictions

Not applicable

3.4 Treatments

3.4.1 Investigational products

3.4.1.1 Identity of investigational product and comparators

Generic name: esomeprazole

Dosage form: tablet

Strength: 20 mg

Manufacturer's name: AstraZeneca Pharmaceutical Production

Type of packaging: plastic bottle

Run-in period: 100 tablets/bottle, white label

5-year study period: 100 tablets/bottle, white label

5-year study period increased dose: 100 tablets/bottle, white label

Healing dose/ dose adjustment: 100 tablets/bottle, white label

5 to 10-year study period: 100 tablets/bottle, white label

3.4.1.2 Labelling

Note: Only one label will be used from January 2007 and onwards. This label the "**5 to 10-year study period**" label will replace the "5-year study period", "5-year study period increased dose" and "Healing dose/ dose adjustment" label.

5 to 10-year study period

AstraZeneca

100 tablets esomeprazole 20 mg, oral

Study/order ref.: SH-NEG-0003-XXX

Randomisation code: (to be filled in by hospital staff)

E-code: (to be filled in by hospital staff)

For the treatment of gastroesophageal reflux disease

Take …….. Tablet/tablets in the morning and …… tablet/tablets in the evening with water

Prescribed by: Dr: (to be filled in by hospital staff)

Visit no: (to be filled in by hospital staff)

Visit date: (to be filled in by hospital staff)

Expiry date: YYYY-MM-DD

For clinical study use only

Store at room temperature (below 25 °C)

Keep out of reach of children

(LOTUS)

3.4.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions.

3.4.1.4 Accountability

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

3.4.2 Doses and treatment regimens

The medication arm of the study design includes the following:

- esomeprazole
- oral administration
- the start dose is 20 mg once daily and may be adjusted not to exceed 40 mg total daily dose and be swallowed together with a glass of water.

The surgical arm of the study design includes the following:

The surgical procedure is laparoscopic fundoplication. The surgical procedure to be used is laparoscopic total fundoplication and reconstruction of the hiatus. A per-operative record should be filled in and sent by the monitor to AstraZeneca R&D Mölndal for datahandling. The procedure should be done by or supervised by an experienced surgeon. Surgery should be performed within three months of randomization. The subject is allowed to be treated with esomeprazole 20 mg o.d or 40 mg o.d awaiting the surgery.

3.4.3 Method of assigning subjects to treatment groups

Individual treatment codes, indicating the treatment allocation for each randomized subject, will be provided by AstraZeneca.

The subjects will be randomized into either esomeprazole or anti-reflux surgery.

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

3.4.4 Blinding and procedures for breaking the blind

3.4.4.1 Methods for ensuring blinding

Not applicable, as this is an open study. See Section 3.2.

3.4.4.2 Methods for breaking the blind

Not applicable

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

Subjects entering this study have most likely been on long-term treatment with various anti- acid secretion therapy (i.e. PPI, H_2RA). During the 12 week run-in period the subject must undergo the “Investigational week” including endoscopy with biopsy sampling, 24 hr pH-metry, manometry, SAP and laboratory measurements. In order to get relevant pH measurements the study medication (esomeprazole 40 mg o.d.) must be stopped at least 7 consecutive days before the 24 hr pH-metry at visit 3. Subjects randomized to anti-reflux surgery should be treated with

esomeprazole (20 mg o.d. to 40 mg daily) before surgery (within three months from randomization).

Motility activators (prokinetic drugs) e.g. metoclopramide are allowed for operated subjects between visit 5 and visit 6 for treatment of post-operative intestinal paralysis.

In case of an ulceration/erosion in the fundoplication within 3 months post surgery, subjects are allowed to be treated with esomeprazole 40 mg o.d. for 2-12 weeks. Subjects in the surgical arm are instructed to take antacid/alginate medication if they experience dyspeptic symptoms after surgery. If the subject has need for additional medication he/she shall contact the investigator who may dispense 1 bottle of esomeprazole 20 mg to be taken on demand, not more than one tablet daily. Unused medication is to be returned on the following visit (visit 7) and drug accountability is to be recorded in the CRF. After visit 7 no such medication is allowed. Subjects in the surgical arm, who develop a gastric or duodenal ulcer due to intermittent usage of NSAID are allowed to be treated with esomeprazole 40 mg o.d. for 2 weeks.

Concerning *Hp* eradication please see Section 3.1.

Antacids and alginates are allowed during the study.

Other medication which is 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, antacids and alginates) must be recorded in the appropriate sections of the case report form (CRF).

Not allowed concomitant medication

The following drugs are not allowed during the course of the study. NB including OTC drugs.

- per oral anticholinergics and other drugs having anticholinergic co-effects such as tricyclic and tetracyclic antidepressive drugs
- motility activators (prokinetic drugs) - except for operated subjects between visit 5 and visit 6 for treatment of post-operative intestinal paralysis.
- prostaglandin analogues
- NSAIDs (except for intermittent usage e.g. 2 weeks twice yearly, prn ≤3 days per week)
- ASA (except for 165 mg less daily for cardiovascular prophylaxis)
- anticoagulants are not allowed 2 weeks prior to endoscopy
- PPI (other than study medication/for surgical arm please see above in Section 3.4.5)

- H_2RA
- *Hp* eradication therapy during the run-in period

3.4.6 Treatment compliance

Subjects will be instructed to return all unused study drugs at each visit. Returned tablets will be calculated and documented in the CRF.

4. STUDY MEASUREMENTS AND ENDPOINTS

4.1 Primary endpoint

The primary endpoint of the study is time to treatment failure, defined as

- Time to treatment failure where **treatment failure** is defined as;

a/ In the medical arm:

Need for treatment other than esomeprazole for control of symptoms of reflux disease:

In order to allow for a stringent assessment of treatment failure ask the following the question:

"Do you have sufficient control of your heartburn and acid regurgitation?"

If the answer is **No,** continue with:

"Do you need other regular drug treatment to control your symptoms?"

If the answer to this question is **Yes** and the dose of esomeprazole is 20 mg once daily, then the dose is to be increased to 40 mg once daily. The subject will be treated with the increased dosage for 8 weeks before a second dose adjustment can be made.

If the answer to this question is **Yes** and the dose is esomeprazole 40 mg once daily, then the dose is to be changed to 20 mg twice daily. The subject will be treated with the changed dosage for 8 weeks before being classified as a treatment failure if sufficient symptom control has not been achieved.

If the answer to this question is **Yes** and the dose is 20 mg twice daily, then the subject is a **treatment failure and will be withdrawn.**

b/ In the surgical arm**:**

Need for medical treatment for control of symptoms from reflux disease:

In order to allow for a stringent assessment of treatment failure ask the following question:

"Do you have sufficient control of your heartburn and acid regurgitation?"

If the answer is **No,** continue with:

"Do you need other regular drug treatment to control your symptoms?"

If the answer to this question is **Yes** the subject has to be classified as a **treatment failure and will be withdrawn.**

Furthermore, the subject will also be regarded as a **treatment failure** if the following occurs;

- Post-operative - post-fundoplication complaints requiring further medical actions to control symptom burden.
- Per-operative death
- Post-operative death within 30 days after surgery
- Dysphagia requiring further treatment. In case of esophageal stenosis, one dilatation is allowed.

4.2 Screening and demographic measurements

At visit 1, demographic data e.g. date of birth, gender and race as well as body weight and height will be recorded. Smoking and drinking habits will also be recorded.

The investigator will carry out an eligibility check to ensure that the subject has no medical abnormalities which might disqualify him/her from enrolment. Medical and surgical history including details about GERD will be obtained and a complete physical examination will be done. The physical examination will include: general appearance, cardiovascular, lungs and abdomen and vital signs (pulse, blood pressure and body weight).

4.3 Efficacy measurements and endpoints

An endoscopic examination of esophagus, stomach and duodenum, will be done in each subject. Biopsy specimens will be taken in antrum, corpus, the cardiac region (grasping the Z-line) and in esophagus (see Section 4.3.4.1 and App. H). The presence of *Hp* will be assessed by biopsy examination.

4.3.1 Summary of efficacy objectives and endpoints

Table 3 shows how the efficacy endpoints of this study relate to the study objectives.

Table 3 Efficacy objectives and endpoints relating to each objective

Objective	Endpoint(s)	Summary statistic for analysis (incl. timepoint and population)	Planned analysis	Significance of results
Primary				
4.1, 4.3.2 To compare treatments with regard to treatment failure	Number of days, treatment failure (yes/no)	Median number of days ITT population	Logrank test, and survival curves	Longer time to treatment failure indicates a more efficient treatment
Other				
4.3.3 Histopathological findings	Histological assessments .	All histological presentations will be performed for the safety population and ITT population.	No formal statistical comparison	
4.3.4 Periodic prevalence of endoscopic and symptomatic recurrences	Endoscopic relapse (LA grade C-D) between scheduled endoscopies. Symptomatic relapse between scheduled visits	Mean number of relapses per time period (subject year). ITT population	Descriptive descriptive	
4.3.4 Point prevalence of endoscopic and symptomatic recurrences	Endoscopic relapse (LA C-D) at scheduled endoscopies. Symptomatic relapse at scheduled visits.	Mean number of relapses per scheduled endoscopy visit. ITT population		
4.3.5 GI symptoms assoc. with GERD over time	Symptom assessments at clinical visits	Proportion of subjects with no symptoms ITT population	descriptive	
4.3.6 Per-operative events	Per-operative event assessments during the operation	Proportion of subjects randomized to surgery with per-operative symptoms ITT population	descriptive	
4.3.7 Post-operative symptoms and events	Post-operative symptom assessments during the first 30 post-operative days	Proportion of subjects randomized to surgery with post-operative symptoms ITT population	descriptive	
4.3.8 24 hr intragastric and intraesophageal pH	% of time with intragastric and intraesophageal pH≤4	ITT population	Descriptive	
4.3.8 Symptom Association Probability (SAP)	Association between symptoms and reflux episodes	ITT population	Descriptive	

The methods for collecting efficacy data are presented below.

4.3.2 Time to treatment failure

4.3.2.1 Methods of assessment

The number of days from start of treatment after randomization to treatment failure or, in case of no treatment failure, from start of treatment after randomization to last visit in the study.

4.3.2.2 Calculation or derivation of endpoint

Not applicable

4.3.3 Histopathological changes

4.3.3.1 Methods of assessment

Histopathological changes will be assessed by observing the biopsy specimens taken during endoscopy. The biopsy specimens will be sent to a central laboratory with courier. The Central laboratory will send all biopsies for analyses to the pathologist, . A short diagnostic report will be sent to the investigator by fax or email. In addition, the grading of the histological parameters and a full report will be sent to AstraZeneca.

In case of endoscopic suspicion of malignancy, additional biopsies, outside of this protocol should be taken and sent to the local pathology department of each hospital or institute.

Biopsy sampling, handling and logistics will be found in Appendix H.

4.3.3.2 Calculation or derivation of endpoints

Not applicable

4.3.4 Endoscopic and symptomatic relapse

4.3.4.1 Methods of assessment

The method of assessment of endoscopic recurrences will be endoscopy. The endoscopic examination of esophagus, cardiac region, stomach, and duodenum will be done in each subject. The subject should be fasting at least 12 hours prior to endoscopy. Endoscopic findings will be classified according to the Los Angeles classification grade A to D.

Grade A One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds

Grade B One (or more) mucosal break more than 5 mm, that does not extend between the tops of two mucosal folds

Grade C One (or more) mucosal break that is continuous between the tops of of two mucosal folds but which involves less than 75% of the circumference.

Grade D One (or more) mucosal break, which involves at least 75% of the esophageal circumference.

Biopsies will be taken in the antrum, the corpus, the cardiac region (grasping the Z-line) and esophagus. 2 biopsy specimens (3 from the Z-line) will be taken from each location (see also Section 4.3.3.1 and appendix H). The biopsies will be preserved and stored, according to local procedures for a maximum time of 15 years after the end of the study for future analysis.

The presence of a stricture and/or columnar lined esophagus (CLE) will be separately recorded and the extent of CLE assessed.Video endoscope should be used. Biopsy sampling in the esophagus may be taken with antegrade or retrograde technique and should be recorded in the CRF.

4.3.4.2 Calculation or derivation of endpoint

Endoscopic relapse is defined as an endoscopic finding of LA grade C to D. Symptomatic relapse has occurred when a subject has recurrent GERD symptoms (moderate-severe, see below) over 3 consecutive days before the clinical visit.

4.3.5 Gastrointestinal symptoms associated with GERD over time

4.3.5.1 Methods of assessment

GERD symptoms

The method of assessment of symptoms will be a questionnaire in the CRF. At each visit, the presence of symptoms will be assessed retrospectively by the investigator in a standardized manner. The definition for each symptom is:

- heartburn	a burning feeling, rising from the stomach or lower part of the chest up towards the neck
- acid regurgitation	flow of sour or bitter fluid into the mouth
- dysphagia	difficulties in swallowing

Other GI symptoms

- epigastric pain	Pain centred in the upper abdomen
-flatulence	The presence of excessive amounts of air or gases in the stomach or intestine, leading to distension of the organs
- bloating	A tightness located in the upper abdomen; it should be distinguished from visible abdominal distension
- diarrhoea	abnormal frequency and liquidity of faecal discharges.

and will be classified as:

none:

mild:	awareness of symptoms, but easily tolerated
moderate:	discomfort sufficient to cause interference with normal activities
severe:	incapacitating, with inability to perform normal activities
-Ability to vomit	The forcible expulsion of the contents of the stomach through the mouth
-Ability to belch	Eructation, the noisy voiding of gas from the stomach through the mouth

4.3.5.2 Calculation or derivation of endpoint

Not applicable.

4.3.6 Per-operative events

4.3.6.1 Methods of assessment

The assessment of per-operative complications will be made in a standardized manner and recorded in the CRF:

- Bleeding
- Perforation
- Pneumothorax
- CO_2 retention
- Emphysema
- Other complications

Total operation time, completion of surgical procedure, type of fundoplication and if crural repair was done or not will be recorded in the CRF.

4.3.6.2 Calculation or derivation of endpoint

Not applicable.

4.3.7 Post-operative symptoms and events

4.3.7.1 Methods of assessment

The method of assessment of short term (< 30 days) post-operative lapse and symptoms will be made by the investigator in a standardized manner and recorded in the CRF at visit 6 for operated subjects to ensure a smooth post-operative recovery.

- Post-operative hospital stay (days).
- Abdominal infection.
- Other abdominal complications.
- Pulmonary infection.
- Other pulmonary complications.
- Bleeding
- Other complications
- In hospital post-operative death
- Other post-operative symptoms

4.3.7.2 Calculation or derivation of endpoint

Not applicable.

4.3.8 24 hour pH metry, manometry and SAP

4.3.8.1 Methods of assessment

<u>24 hour pH metry</u>

Intra-esophageal and intra-gastric acid exposure as assessed by 24 hr pH metry, where Intra-esophageal pH monitoring is mandatory. The 24 hr pH -monitoring will be initiated at visit 1 or visit 3 to document the subject's reflux pattern. Each investigational centre will use their standard equipment for ambulatory pH -recording, including standard analysis software. Manometry will be made in all subjects at the first pH metry occasion according to local standards. After at least four hours of fasting and topical anaesthesia of the nostril, the pH -electrode (preferably a 2 way channel will be positioned, 1 in the distal esophagus and 1 in the proximal stomach, with the esophageal recording tip 5 cm above the oral margin of the lower esophageal sphincter, the location which is determined by manometry). The electrode will be connected to a data recorder.

During the recording time the subject will be at home or at work and will be instructed to live as normal as possible including participating in normal daily activities and taking meals. Acidic food, beverages and intake of alcohol are not allowed. Furthermore, the subjects will be told not to take

any medication that interferes with the recording, such as acid reducing compounds and PPIs. However, at visit 7 and 16 the subjects randomized to medical treatment should continue their treatment during the pH metry.

After 24 hours the subject will return to the laboratory, the data will be downloaded to the host computer and the data from the recorder will be analysed by the software program. A visual check of the pH-curve will be carried out to discover electrode drift or interference in the recording.

The fraction of time during which pH ≤ 4 for the total, upright and supine periods will be calculated from the pH data. If the pH -monitoring is inadequate for technical reasons or is discontinued within 18 hours, the recording should be repeated. Results will be recorded in the CRF. The data will be sent to AstraZeneca.

Symptom Association Probability (SAP)

Esophageal acid exposure and symptom reflux event correlation will be evaluated, this assessment is called Symptom Association Probability (SAP). SAP will be calculated according to Shi G et al 1995, or Weusten B et al 1994. Subjects with a positive SAP will be considered as having GERD.

4.3.8.2 Calculation or derivation of endpoint

Not applicable

4.4 Safety measurements and endpoints

In this study will long-term treatment of esomeprazole be compared to anti-reflux surgery in the control of gastroesophageal reflux disease. The study is designed to study histological findings and changes in laboratory variables and not adjusted for non-serious reporting. The time between visits is too long to receive quality data for non-serious adverse events. The following safety variables will be recorded during the study:

- Histopathological changes in the squamous epithelium of the distal esophagus, the mucosa of the z-line and of the gastric mucosa as assessed by the use of the Sydney classification system (see Section 4.3.3 and appendix H)
- Changes in the laboratory screen variables (including serum gastrin, serum chromogranin A, Vitamin B_{12} and homocysteine)
- All serious adverse events and those adverse events causing premature discontinuation of study drug and/or study.

4.4.1 Summary of safety objectives and endpoints

Table 4 shows how the safety endpoints of this study relate to the study objectives.

Table 4 Safety objectives and endpoints relating to each objective

Objective	Endpoints	Summary statistic for analysis (including timepoint and population)	Planned analysis	Significance of results
4.4.3 Laboratory screen variables	Laboratory assessments	- Descriptive presentation of laboratory results for each sample occasion. - Number of subjects with values below, within and above the reference range, over time. - Median changes between baseline and the last visit for each laboratory variable. - Graphs showing last visit values versus the baseline values for each laboratory variable. -All clinical laboratory presentations will be made for the safety population.	No formal statistical comparison.	The result will contribute to the determination of the adverse drug reaction pattern and frequency during long-term treatment with esomeprazole.
4.4.2 SAE and AE	Occurrence and nature (seriousness intensity and action taken to study drug due to AE) of all SAEs and AEs causing premature discontinuation of study drug and /or study.	-Frequency of subjects with SAEs and AEs leading to discontinuation of study drug and/or study. -AE pattern (e.g. by system organ classification) - SAEs and discontinuations due to AE will be presented for the safety population	No formal statistical comparison.	The result will contribute to the determination of the adverse drug reaction pattern and frequency during long-term treatment with esomeprazole.

The methods for collecting safety data are described below

4.4.2 Adverse Events

4.4.2.1 Definitions

The definitions of adverse events (AEs), serious adverse events (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 adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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 serious adverse event is an AE occurring during any study phase (i.e., 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-subject 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 (i.e., 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?” For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix F.

Other significant adverse event

An AstraZeneca expert will identify OAEs 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 haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative will be written and included in the Clinical Study Report.

4.4.2.2 Recording of adverse events

SAEs and AEs causing premature discontinuation of study drug and/or study will be recorded retrospectively by the investigator in the Case Report Form at visit 2 and the following visits. If any SAE or AE causing premature discontinuation of study drug and/or study are ongoing at the subjects last visit in the study, they must be followed up after 2 to 4 weeks and thereafter as long as medically indicated. This can be done either as an extra visit to the clinic or by written or verbal contact with the subject.

Spontaneously reported SAEs and AEs causing premature discontinuation of study drug and/or study, objective findings and observations, and SAE and AEs causing premature discontinuation of study drug and/or study 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), outcome, maximum intensity, seriousness, and action taken with regard to investigational product and if the AE caused subject to discontinue the study will be recorded. Maximum intensity will be rated according to the following scale:

1 = Mild - awareness of sign or symptom, but easily tolerated

2 = Moderate - discomfort sufficient to cause interference with normal activities

3 = Severe - incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.4.2.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea, but not a SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Abnormal test results from laboratory investigations or endoscopy investigations (including biopsies) that meet any criteria of an SAE must be reported in accordance with the SAE reporting procedures (see Section 4.4.2.3).

Symptoms included in the efficacy variables

- Section 4.3.5.1 GERD symptoms (i.e. heartburn, acid regurgitation, dysphagia)
- Section 4.3.5.1. other GI symptoms (i.e. epigastric pain, flatulence, bloating, ability to vomit, ability to belch, diarrhoea)
- Section 4.3.7. Post-operative symptoms (i.e. post-operative hospital stay, abdominal infection, other abdominal complications, pulmonary complications, cardiac complications, other complications, in hospital post-operative death, other post-operative symptoms)

will only be recorded as AEs if they result in discontinuation of the study drug and/or study. If a sign or symptom meets any of the criteria of an SAE according to the definition (see Section 4.4.2.1) it must be reported as SAE.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4. 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.

Adverse events will be classified by AstraZeneca staff according to the terminology of the Medical Dictionary for Regulatory Activities (MedRA).

4.4.2.3 Reporting of serious adverse events

Investigator reporting

When the investigator becomes aware of a SAE during the course of the study, the SAE must be reported to the local monitor or other AstraZeneca/Contract Research Organization representative within one (1) day and a completed written SAE report must be sent within four (4) calendar days. Follow-up information should be reported by the investigator within one (1) day and in writing within four (4) calendar days.

All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the case report form. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

4.4.3 Laboratory safety measurements and variables

4.4.3.1 Methods of assessment

A laboratory screen, which includes haematology, clinical chemistry and urine analysis will be performed. A laboratory screen will also be done in case of premature discontinuation from the study. The visit 3 laboratory screen, or visit 1 for untreated subjects, is to be regarded as baseline data. The subjects should be fasting at least 12 hours before sampling.

The laboratory variables are

Haematology

Haemoglobin, MCV, leukocytes, thrombocytes

Clinical chemistry

Creatinine, ASAT, ALAT, Alk. Phosphatase, total bilirubin, Sodium, Potassium, TIBC, s-Fe, ferritin, triglycerides, b-ery-folate, Cholesterol (LDL, HDL, LDL/HDL), Zinc, Calcium (albumin corr), D-vitamins, Gastrin, Chromogranin A, Homocysteine, Vitamin B_{12}

Urine analysis

Protein, glucose, WBC, RBC

Haematology, clinical chemistry and urine will be analysed by a central laboratory. An accredited central laboratory will be chosen for sample collection, labelling, storage and shipment. This information will become available at a later date. Instructions for sampling, preparation of samples, request forms, labels and materials for collection and shipping of samples will be provided by the central laboratory.

4.4.3.2 Calculation or derivation of endpoints

Not applicable

4.5 Quality of Life measurements and endpoints

4.5.1 Summary of Quality of Life objectives and endpoints

Table 5 shows how the Quality of Life endpoints of this study relate to the study objectives.

Table 5 Quality of Life objectives and endpoints relating to each objective

Objective	Endpoint(s)	Summary statistic for analysis (including timepoint and population)	Planned analysis	Significance of results
Patient reported outcomes (PRO)	GSRS and QoLRAD questionnaires at clinical visits	Mean change from baseline for each prespecified dimension ITT population	Descriptive, for treatment comparisons baseline assessment will be used as covariate	

The methods for collecting Quality of Life data are presented below

4.5.2 Patient reported outcomes

Symptoms of heartburn and acid regurgitation impact the everyday life of subjects and consequently their Health Related Quality of Life (HRQL) . HRQL is a subjective multidimensional concept used to measure treatment efficacy. Hence, HRQL has become a significant endpoint when evaluating the effectiveness of treatments in clinical trials, in particular for conditions that lack objective markers of disease activity. For these conditions, adequate symptom control may best be defined as sustained reduction of symptoms to a level that does not cause significant impairment in HRQL (Dent J et al 1999).

4.5.2.1 Methods of assessment

The evaluation of patient-based outcomes in this study focuses on reflux symptoms and the impact thereof on subjects' daily life. Therefore, a symptom questionnaire, the Gastrointestinal Symptom Rating Scale (GSRS), will be used together with a disease-specific HRQL-questionnaire, the Quality Of Life in Reflux And Dyspepsia (QOLRAD), which was specifically developed for subjects with symptoms of reflux and dyspepsia. GSRS

The GSRS covers 15 GI symptoms and uses a 7-graded Likert scale to rate each symptom. The GSRS contains five dimensions depicting Indigestion (item no 6, 7, 8, 9), Diarrhoea (item no 11, 12, 14), Constipation (item no 10, 13, 15), Abdominal pain (item no 1, 4, 5) and Reflux (item no 2, 3). In the GSRS, the lower the value, the less are the perceived GI symptoms, (Appendix I). The reliability and validity of the GSRS have previously been documented (Revicki DA et al 1998) and there are norm values available for a healthy population (Dimenäs E et al 1996). The GSRS has previously been used to assess symptom relief during treatment with omeprazole in subjects with GERD (Havelund T et al 1999).

QOLRAD

The impact of heartburn and acid regurgitation will be assessed using the QOLRAD questionnaire **(**Appendix J). The questionnaire consists of 25 items combined into the dimensions Emotional distress (item no 12, 14, 15, 17, 19, 22), Sleep dysfunction (item no 8, 10, 11, 18, 21), Vitality (item no 1, 4, 7), Food/drink problems (item no 3, 5, 9, 13, 16, 20) and Physical/social functioning(item no 2, 6, 23, 24, 25). The questions are rated on a 7-graded Likert scale, the lower the value, the more severe is the impact on the daily functioning. The QOLRAD has been extensively documented in international studies in subjects with heartburn with regards to reliability (Pickard AS et al 2004), validity (Wiklund IK et al 1998) and responsiveness (Talley NJ et al 2001). Previous studies have revealed that a change of 0.5 represents a minimum important change in the QOLRAD (Wiklund IK et al 2000)

The translations of the questionnaires into other languages have been done according to proposed guidelines involving several independent translators.

Based on previous studies, the Reflux and the Indigestion dimension in the GSRS questionnaire have been selected as treatment outcomes. In the QOLRAD a beneficial impact on symptom relief is expected in terms of the Sleep and Food /Drink dimensions. Subjects with GERD have previously reported acid-related sleep disturbances. For the prespecified dimensions, the mean change from baseline to end of the study will be assessed.

The questionnaires are self-administered and the subject will be asked to complete the questionnaires at Visit 4, 8, 10, 12, 14, 16, 31, 33, 35, 37 and 39 and in case of early discontinuation from the study.

Appropriate procedures for minimizing bias and enhancing compliance will be followed throughout the study. To ensure this, a study co-ordinator at each site will be responsible for the PRO evaluation and a standardized procedure for the administration of the questionnaires

will be applied. The subject will complete the questionnaires independently. Each site will have a designated quiet space in the clinic for subjects to complete the questionnaire at each appropriate visit. The questionnaires will be completed **prior** to other examinations, before there are substantial professional encounters with transmission of information, such as disease status. Such information may influence the answers that subjects provide on questionnaires.

A manual describing the HRQL questionnaires and instruction manuals on the standardized administration and other practical issues will be provided to all involved study personnel. The manual will include guidelines for handling issues that can arise with the PRO assessment, including answers to questions that are commonly asked. Careful training will be given to study personnel to ensure the data quality through the standardised administration of the questionnaires. Group training sessions for all involved will be held at each site. In addition, clinical study monitors will be trained to evaluate the quality of the PRO assessments and alert sites to possible problems in this component of the trial.

4.5.2.2 Derivation or calculation of endpoint

For each dimension in QOLRAD and GSRS respectively, the average score will be calculated. Dimensions for the respective questionnaires are defined in the previous Section. The procedure adopted to handle missing values in questionnaires is defined in Section 6.2.1.

5. DATA MANAGEMENT

The AstraZeneca monitor will continuously check and collect all CRFs. Corrections or additions in the CRFs must be initialled and dated by qualified study personnel. Any remaining questions or missing data will be noted on Data Clarification Forms (DCFs), which will be sent to the investigator. It is the investigator's obligation to complete and return them to AstraZeneca as soon as possible.

Data Management at AstraZeneca in each respective country will perform data entry and validation continuously and promptly during the study. The data will be entered into an Oracle database using RAMOS as the data entry application. When data have been entered into the database, proof reading will be performed to ensure that the entered data are correct and complete according to the CRF.

Adverse events will be classified according to the terminology of the MedRA. Concomitant medication will be classified according to the WHO Drug Dictionary and the Anatomical Therapeutic system (ATC).

It is the responsibility of the investigator to complete Serious Adverse Event Forms (part of the CRF) when applicable. It is the AstraZeneca monitor's responsibility to ensure that any Serious Adverse Event Form is completed.

All data editing and data validation activities will be performed by investigators, monitors and data management staff. All data editing and data validation procedures have to be carried out

and the AstraZeneca "clean file" procedure have to be completed. Clean file is defined as a status where the data in the CRFs, the database and the reference values are complete and logical according to the study protocol, general guidelines and data entry instructions. The contents of the database must correspond to that of the CRF together with Data Edit Documents, DQFs, general guidelines and data entry instructions.

Reporting of genotypic results

Results from any genetic research performed will be reported separately from the clinical study report. AstraZeneca will not provide individual genotype results to subjects, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The subject's DNA will not be used for any purpose other than those described in the study protocol.

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Determination of sample size

The true rate of treatment successes (i.e. subjects who have not experienced treatment insufficiency within 5 years) is assumed to be at least 70% for both treatments. With 275 subjects on each treatment the true difference between treatment is, with a probability of 95%, not going to differ by more than 8 percentage points from the observed difference.

6.2 Statistical evaluation

6.2.1 Methods of statistical analysis

A comprehensive Statistical Analysis Plan will be prepared before unblinding the data, or in instances where the data are not blinded, database lock.

Both Intention To Treat (ITT) and Per Protocol (PP) analyses will be made for the primary variable. Secondary variables will be analysed for the ITT population only. In the ITT analyses all randomized subjects will be included, except subjects who are randomized into medical treatment and who have taken no dose of study drug, or subjects who are randomized to laparoscopic fundoplication and who refuse to undergo the operation. The PP population will include subjects with no major protocol violations, including the violation of entry criteria (the nature and reasons for these protocol violations will be defined and documented before

database lock). Subjects eligible for safety evaluation are those who take at least one dose of the study drug and for whom post-dose information is available.

The two treatment groups will be compared regarding the primary endpoint using Life Table methods for graphic presentation and a logrank test for statistical inference.

For each GSRS and QOLRAD dimension, the individual score at each assessment is calculated as the average score for the items included in the dimension. If there are missing items in the questionnaires, the mean of the completed items in one dimension will be imputed to substitute the missing item provided that more than 50% of the items in one dimension are completed.

6.2.2 Study endpoint

The primary endpoint of the study is time to treatment failure, defined as

- Time to treatment failure where **treatment failure** is defined as:

a/ In the medical arm:

Need for treatment other than esomeprazole for control of symptoms of reflux disease:

In order to allow for a stringent assessment of treatment failure ask the following question:

"Do you have sufficient control of your heartburn and acid regurgitation?"

If the answer is **No,** continue with:

"Do you need other regular drug treatment to control your symptoms?"

If the answer to this question is **Yes** and the dose of esomeprazole is 20 mg once daily, then the dose is to be increased to 40 mg once daily. The subject will be treated with the increased dosage for 8 weeks before a second dose adjustment can be made.

If the answer to this question is **Yes** and the dose is esomeprazole 40 mg once daily, then the dose is to be changed to 20 mg twice daily. The subject will be treated with the changed dosage for 8 weeks before being classified as a treatment failure if sufficient symptom control has not been achieved.

If the answer to this question is **Yes** and the dose is 20 mg twice daily, then the subject is a **treatment failure and will be withdrawn.**

b/ In the surgical arm**:**

Need for medical treatment for control of symptoms from reflux disease:

In order to allow for a stringent assessment of treatment failure ask the following question:

"Do you have sufficient control of your heartburn and acid regurgitation?"

If the answer is **No,** continue with:

"Do you need other regular drug treatment to control your symptoms?"

If the answer to this question is **Yes,** the subject has to be classified as a **treatment failure and will be withdrawn.**

If the answer to this question is **Yes** and one dilatation has been done, then the subject is a **treatment failure and will be withdrawn.**

Furthermore the subject will also be regarded as a **treatment failure** if the following occurs;

- Post-operative - post-fundoplication complaints requiring further medical actions to control symptom burden
- Per-operative death
- Post-operative death within 30 days after surgery
- Dysphagia requiring further treatment. In case of esophageal stenosis, one dilatation is allowed.

6.2.3 Statistical analyses

The two treatment groups will be compared regarding the primary endpoint using Life Table methods for graphic presentation and a log rank test (two-sided) for statistical inference. In both the ITT and the PP analyses data will be censored in case of discontinuation due to reasons other than treatment failure. Post-operative complications, histopathology, endoscopy and symptoms are summarized using frequency tables.

For subjects randomized to the surgery group, post-operative complications during the first month after surgery will be assessed descriptively. Quantitative data on post-operative complications will be tabulated with Mean, SD, min and max. For post-operative complications data with nominal or ordinal outcome, the number of subjects and relative frequency distribution will be presented.

Histopathological changes will be assessed by frequency tabulation by treatment group and visit.

The number of endoscopic and/or symptomatic relapses at clinical visits will be presented by visit and treatment group with frequency tables. Mean, SD, min and max, both combined and separately.

Number of endoscopic and/or symptomatic relapses between visits will be presented by time period (subject year) and treatment group with frequency tables. Mean, SD, min and max, both combined and separately.

GI symptoms associated with GERD over time will be presented by visit and treatment in frequency tables and as number and proportion of subjects with no symptoms.

The percentage of 24 hr intragastric pH $\leq$ 4 will be presented using descriptive methods (Mean, SD) by visit and treatment group.

Symptom Association Probability (SAP) will be presented using descriptive methods (Mean, SD) by visit and treatment group.

Safety analyses

The laboratory data will be presented in terms of median, Mean and SD for the baseline value, the last visit value and the change from baseline to last visit. A cross-table showing the number of subjects with the values below, within and above the normal range at baseline versus the same classification at the last visit will be provided for each laboratory variable. Graphs showing last visit values versus the baseline values and descriptive presentation over time will be presented for each treatment group and each laboratory variable.

Serious adverse events and AEs causing premature discontinuation of study drug and/or study will be presented descriptively.

6.2.4 Interim analyses

Interim analyses are planned 3 years (visit 12) and 5 years (visit 16) after last subject randomized. The purpose the interim analyses are to evaluate efficacy and tolerability.

6.3 Data or safety monitoring committee

The Steering committee will evaluate SAE every 6 months or upon request and report to the Global Drug Safety Physician.

7. STUDY MANAGEMENT

7.1 Monitoring

Before the study begins, a representative of AstraZeneca will visit the investigational site to

- determine the adequacy of the facilities

- 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.

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the investigational 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 case report forms (CRFs), and that investigational product accountability checks are being performed
- perform source data verification (a comparison of the data in the CRFs with the subject's 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 (e.g., 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.

7.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) 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, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca 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. Histopathological training will be held at investigators meetings.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the international principal investigator(s) and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol must be notified to or approved by each IEC or IRB, and in many countries also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular centre's Written Informed Consent Form, then AstraZeneca and the centre's IEC or IRB must be notified. Approval of the revised Written Informed Consent Form by AstraZeneca and by the IEC or IRB is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her IEC or IRB, 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 study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this study agreement shall prevail.

7.6 Genetic sampling and storage

7.6.1 Collection of samples for genetic research

Subjects will provide a blood sample as per visit schedule.

A single venous blood sample (approximately 10 mL) will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection. No personal identifiers (subject name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the subject consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate Section of the CRF.

7.6.2 Sample processing and shipping

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory within one month of collection and must remain frozen at all times.

Where possible samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that samples arrive within working hours. A requisition sheet, detailing the protocol study number, centre number, enrolment code and/or randomisation code and date of sample collection, should accompany the shipment

7.6.3 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labelled with the study number and subject number. Only the investigator will be able to link the blood sample to the individual subject. The sample and data will not be labelled with a personal identifier. The link between the subject enrolment/randomisation code and the DNA number will be maintained.

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at . The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. Access to the link file will require written authorisation from the Project Team Leader.

7.6.4 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to esomeprazole and/or susceptibility to or prognosis of gastroesophageal reflux disease (GERD) under investigation in this protocol. The results of the genetic research will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on esomeprazole to generate hypotheses to be tested in future studies.

7.7 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 6):

Table 6 Volume of blood to be drawn from each subject

Assessment		Sample volume (ml)	N of samples	Total volume (ml)
Safety	Clinical chemistry	Approx. 28.5	Approx. 6	Approx. 171
	Haematology	Approx. 4.5	Approx. 6	Approx. 27
Genotyping (optional)		Approx 10	1	Approx. 10
Total				Approx. 208

7.8 Study timetable and termination

First subject in (FSI) Q4 2001

Last subject in (LSI) Q4 2002

Last subject out (LSO) Q3 2013

Planned duration of the study

End of study is defined as date of final database lock, which is the time point after which no patient will be exposed to study related activities. The study prolongation is expected to start in Q1 2007, and to be completed in Q4 2013

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favourable opinion in writing by an IEC or IRB as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any subject into the study.

The principal investigator(s) is responsible for informing the IEC or IRB of any amendment to the protocol in accordance with local requirements. In addition, the IEC or IRB must approve all advertising used to recruit subjects for the study. The IEC or IRB must reapprove the protocol annually, as local regulations require.

Either the investigator(s) or AstraZeneca must submit progress reports to the IEC or IRB according to local regulations and guidelines. The principal investigator(s) must also provide

the IEC or IRB with any reports of serious adverse events from the study site as local regulations require.

Where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any subject participates in this genetic research.

8.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki (see Appendix C), Good Clinical Practice, and applicable regulatory requirements.

Subjects included into this study have a chronically troublesome disease in need of therapy. They are considered suitable for anti-reflux surgery and for long-term treatment with PPI. Even if the subject had not been included in this study, one of these two treatment options would have been chosen. Anti-reflux surgery is associated with post-operative morbidity during the convalescent period as well as a risk of post-operative complications. By including a subject into this study the investigator confirms that this has been taken into account and that according to his judgement the benefits the subject receives from the operation outweighs this risk.

The additional risk the subject is exposed to by participating in the study is associated with some assessments not included in routine clinical practise (4 extra endoscopies with biopsies). Biopsy taking is generally associated with minimal bleeding and only causes bleeding of clinical importance in extremely rare cases. Benefits of participating are long-term follow-up by a clinical specialist with special interest in GERD subjects, including additional assessments of symptoms and objective findings at specified intervals, as well as the opportunity to contact the doctor when needed throughout the study period.

8.3 Subject information and 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 and the prolongation, including the following:

- Collection of blood samples
- Collection of urine samples
- Physical examination

- Endoscopic examinations with biopsy sampling
- 24 hr ambulatory pH metry, manometry and SAP
- Completion of rating scales and questionnaires
- Withholding medical treatment for 2 weeks during run-in phase
- Intake of investigational product (5-year prolongation)

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

A sample Written Informed Consent Form is enclosed (Appendix B). If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

The genetic research is optional and the subject may participate in the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue the genetic aspect of the study at any time.

If modifications are made in the informed consent (non-genetic component) and/or informed consent (genetic component) according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Subject data protection

The Written Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. Subjects in this database will be identified by initials or subject number only. The Written Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IEC or IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

9. EMERGENCY PROCEDURES

9.1 AstraZeneca emergency contact procedure

Due to the nature of the population participating in this study (GERD subjects) no immediate emergency concerns related to the disease, drug or the assessments can be foreseen. Any

emergency situation should be managed and handled by the participating clinics after their local emergency protocols.

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study.

9.3 Procedures in case of overdose

There is no experience to date with deliberate overdose. Data are limited but single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

9.4 Procedures in case of pregnancy

Since esomeprazole is a new drug, there is no/limited information on its effects in humans on the unborn baby. Data available from animal studies to date do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Consequently, women must be either post-menopausal, permanently surgically sterilized or, if of childbearing potential, using a reliable form of contraception prior to and during participation in the study. A subject who during the trial intends to or actually becomes pregnant should contact the investigator. The investigator must notify AstraZeneca and withdraw the subject from the study. Pregnancy itself is not regarded as an adverse event 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.

10. REFERENCES

Carlsson R et al 1998
Carlsson R, Dent J, Watts R, Riley S, Sheikh R et al. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies. Euro J Gastroenterol Hepatol 1998; 10:119-24.

Dent J et al 1999
Dent J, Brun J, Fenwick AM, Fennerty MB, Janssens J, Karhilas PJ, Lauritsen K, Reynolds JC, Shaw M, Talley NJ. An evidence-based appraisal of reflux disease management - the Genval Workshop Report. Gut 1999; 44 (suppl 2):1-16.

Dimenäs E et al 1996
Dimenäs E, Carlsson G, Glise H, Israelsson B, Wiklund I. Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. Scand J Gastroenterol 1996;31 suppl 221:8-13.

Havelund T et al 1999
Havelund T, Lind T, Wiklund H, Glise H, Hernqvist H, Lauritsen K et al. Quality of life in patients with heartburn but without esophagitis: effects of treatment with omeprazole. Am J Gastroenterol 1999; 94:1782-89.

Heading RC 1989
Heading RC. Epidemiology of esophageal reflux disease. Scand J Gastroenterol 1989; 24 (suppl 168):33-37.

Jones RH et al 1995
Jones RH, Hungin PAS, Phillips J et al. Gastroesophageal reflux disease in primary care in Europe: clinical presentation and endoscopic findings. Eur J Gen P 1995; 1:149-55.

Johnson F et al 1987
Johnson F, Joelsson B, Gudmundsson K et al. Symptoms and endoscopic findings in the diagnosis of gastroesophageal reflux disease. Scand J Gastroenterol 1987; 22:714-18.

Lundell L 2000
Lundell L. Antireflux surgery in the laparoscopic era. Ed. Holloway RH. Clinical Gastroenterology in Reflux Disease. Baillière Tindall. 2000; 45(2) :793-810.

Lundell L et al 2000
Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Thor K, Lamm M, Blomqvist A, Hatlebakk JG, Janatuinen E, Levander K, Nyström P, Wiklund I. Nordic GORD Study Group. Long-term management of gastro-oesophageal reflux disease with omeprazole or open antireflux surgery: results of a prospective, randomized clinical trial. Eur J Gastroenterol Hepatol 2000; 12:879-87.

Pickard AS et al 2004
Pickard AS, Johnson JA, Sadowski D, Grace E. Health-related quality of life in GERD: reliability of a new diseases-specific measure. Qual Life Res. In press.

Revicki DA et al 1998
Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. Qual Life Res 1998; 7:75-83.

Richter JE et al 2001
Richter JE. Kahrilas PJ. Johanson J. Maton P. Breiter JR. Hwang C. Marino V. Hamelin B. Levine JG. Esomeprazole Study Investigators. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am. J of Gastroenterol. 2001, 96(3):656-65.

Lind T et al 1997
Lind T, Havelund T, Carlsson R, Anker-Hansen O, Glise H et al. Heartburn without oesophagitis: Efficacy of omeprazole therapy and features determining therapeutic response. Scand J Gastroenterol 1997; 32:974-9.

Shi G et al 1995
Shi G, Bruley des Varannes S, Scarpignato C, Le Rhun M, Galmiche, J-P. Reflux related symptoms in patients with normal oesophageal exposure to acid. GUT 1995; 37:457-464

Solcia E et al 2000
Solcia E, Villani L, Luinetti O, Trespi E, Strada E, Tinelli C, Fiocca R. Altered intercellular Virchows Arch 2000; 436: 207-16.

Spechler SJ 1992
Spechler SJ. Epidemiology and natural history of gastroesophageal reflux disease. Digestion 1992; 55 (suppl 1):24-29.

Talley NJ et al 2001
Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. Am J Gastroenterol. Submitted.

Weusten B et al 1994

Weusten B, Roelofs J, Akkermans L, Van Berge-Henegouwen G, Smout A. The symptom – association probability; An improved method for symptom analysis of 24 hour esophageal pH data. Gastroenterology 1994; 107: 1741-1745.

Wiklund IK et al 1998

Wiklund IK, Junghard O, Grace E, Talley NJ, Kamm M, Veldhuyzen van Zanten S, Paré P, Chiba N, Leddin DS, Bigard M-A, Colin R, Schoenfeld P. Quality of Life in reflux and

dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire(QOLRAD). Eur J Surg 1998; Suppl 583:41-40.

Wiklund IK et al 2000

Wiklund IK, Fullerton S, Junghard O, Talley NJ. Interpretability and meaningfulness of quality of life changes in patients with heartburn. Gastroenterology 2000; 118 (Suppl 2, Part 2): A220.