ASTRA
ASTRA HÄSSLE

PROJECT NO.	826-01
PRODUCT	Omeprazole
STUDY CODE	SH-OMG-0004
FINAL	
DATE	(year-month-day)

Clinical Study Protocol

OMEPRAZOLE VERSUS ANTI-REFLUX SURGERY IN THE LONG-TERM MANAGEMENT OF PEPTIC ESOPHAGITIS - A 5 YEAR FOLLOW UP STUDY OF PATIENTS PREVIOUSLY STUDIED FOR 5 YEARS
-A NORDIC MULTI-CENTRE STUDY.

COORDINATING INVESTIGATOR:

ASTRA COORDINATOR:

ASTRA STATISTICIAN:

This protocol is accompanied by the following amendments:

1. Date ..... Astra Coordinator/Monitor (initials) .....
2. Date ..... Astra Coordinator/Monitor (initials) .....
3. Date ..... Astra Coordinator/Monitor (initials) .....

CENTRE NO.	PRINCIPAL INVESTIGATOR(S)	ADDRESS OF STUDY SITE
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Names in bold are members of the steering commitee

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1. INTRODUCTION

The Astra I-635 study addressed the efficacy and safety of two treatment modalities in chronic reflux esophagitis; anti-reflux surgery or long term (≤ 5 years) omeprazole treatment. The treatments were compared with respect to the level of symptom control, endoscopic healing of the esophagitis, cost benefit ratio and Quality of Life.

The aims of this open study are to further evaluate the efficacy and safety of these therapeutic modalities by following these patient during an additional 5 year period.

2. OBJECTIVES

2.1. Primary objective

The primary objective is to study the development of gastritis, with particular emphasis on glandular atrophy, during long term omeprazole therapy and the relation to concomitant *Helicobacter pylori* infection.

2.2. Secondary objectives

Secondary objectives are:

- To investigate the long-term control of reflux symptoms, healing of esophagitis and persistence of post fundoplication symptoms.
- To investigate the influence of therapy on Quality of life.
- To further assess the safety profile by the use of laboratory screen variables and the frequency of adverse events.

3. OVERALL STUDY DESIGN

The I-635 study has been run as an open Nordic multi-centre study with two parallel groups, performed at approximately 17 centres in Denmark Finland, Norway and Sweden. The patients were followed-up five years after initial randomisation. The duration of the study will be extended another five years which includes two visits to the clinic and three telephone contacts with the patients to assess the clinical response.

Patients in this study consist of those who have completed and consented to Astra study I-635. The patient population is characterised by having had a previous erosive and/or ulcerative esophagitis initially healed with omeprazole and who either had anti-reflux surgery or received omeprazole, 20 or 40 mg once daily for 5 years. The patients will continue on the same treatment as they were on in study I-635. A summary of the investigational schedule is given in Figure 1.

Year/Visit	0*	1	2	3	4	5
Total/Years	5*	6	7	8	9	10
Physical examination	x*		x			x
Endoscopy	x*		x			x
Symptomatology	x*	x	x	x	x	x
Histopathology	x*		x			x
AE/SAE	x*	x	x	x	x	x
Laboratory	x*		x			x
Gastrin	x*		x			x
QoL	x*	x	x	x	x	x

* last visit in study I-635
Figure 1. Study design

During this additional phase (*i.e.* 5 years), all patients will visit the hospital after another two and five years for assessments according to Figure 1. In the first, third and fourth year, the patients will be contacted by telephone by the hospital staff, for recording of symptoms, Adverse and/or Serious Adverse Events and assessment of Quality of Life.

All patients will be instructed to contact the investigator in the event of symptomatic recurrence (i.e. moderate or severe reflux symptoms for more than three consecutive days). Endoscopy will then be performed and biopsies taken as scheduled. The omeprazole dose will be increased to 40 mg or higher in case of relapse of symptoms with or without esophagitis.

Patients who do not achieve adequate control of reflux symptoms after dose adjustment following a relapse, or who experience Adverse Events during maintenance therapy with 40 mg or higher doses of omeprazole, will be recommended surgical treatment. After surgery these patients will be followed according to the protocol. Patients who relapse after surgery will be offered Losec® or a new operation.

4. PATIENTS

4.1. Number of patients

From the 350 patients that were enrolled in study I-635, all remaining patients at the end of that study will be offered a continuation of the study for an additional 5 years.

4.2. Inclusion criteria

- Previous inclusion into Astra study I-635 and willing to continue for another 5 year period.
- Informed consent obtained.

4.3. Exclusion criteria

- Pregnancy or lactation. Women of childbearing potential must maintain adequate contraception during treatment with omeprazole.
- Women, planning pregnancy within five years.
- Suspected or confirmed malignancy.
- Documented eradication of *Helicobacter pylori*.

4.4. Treatment discontinuations

Patients are free to discontinue their participation in the study at any time, and without prejudice to further treatment. A patient may be withdrawn from the study at any time at the discretion of the investigator.

Patients will be withdrawn from the study in the event of:

- Unacceptable adverse event.
- Violation of inclusion/exclusion criteria, i.e. patients included on wrong assumptions.
- Unwillingness to continue in the study.
- Inability to cope with study protocol.

Incorrectly included patients should be withdrawn from the study.

When a patient decides to discontinue participation in the study, he/she should always be contacted in order to, if possible, obtain information about the reason(s) for discontinuation and any adverse events. Whenever possible, the patient should return for a visit at the clinic at this time of or as soon as possible after withdrawal and the following examinations and assessments should then be done:

- Endoscopy
- Gastric biopsy
- Laboratory screen plus serum samples for gastrin assessments
- Physical examination
- Symptoms
- Recording of adverse events
- Compliance (i.e. number of returned capsules/tablets)
- Recording of any new concomitant drug therapy or any changes to ongoing concomitant drug therapy since last clinic visit.
- Quality of life

5. TREATMENT PLAN

5.1. Description of study drugs

Omeprazole (Losec ® Astra AB, Sweden), 20 or 40 mg will be given orally as enteric-coated granules, dispensed in hard gelatine capsules.

5.2. Dosage regimens of study drugs

Patients receiving omeprazole, will be given 20 mg omeprazole in the morning before breakfast with a glass of water. If the dose is greater than 20 mg the dose can be divided into a morning and an evening dose. Patients with recurrence of symptoms with or without esophagitis during treatment with omeprazole 20 mg will receive treatment with 40 mg omeprazole, or higher if needed (at the discretion of the investigator) given either once daily in the morning before breakfast with a glass of water or divided into two doses (morning and evening dose).

5.3. Other treatment

Other medication which is considered necessary for the patient's welfare may be given at the discretion of the investigator. The administration of all medication (including study drugs) must be recorded in the appropriate sections of the Case Report Form.

Any medication recommended in the treatment of reflux esophagitis will not be allowed during the study.

5.4. Allocation of patient numbers

If the patient agrees to participate in this study, the patient will keep the previously allocated patient number from study I-635.

6. STUDY MEASUREMENTS AND VARIABLES

6.1. Efficacy

6.1.1. CLINICAL MEASUREMENTS

6.1.1.1. Endoscopy

Endoscopy will be performed;

- After 24 and 60 months.
- At any time between visits in patients recurrence of symptoms.

Endoscopic examination in individual patients should, if possible, be performed by the same endoscopist. Patients should fast prior to the visits that include an endoscopy.

The macroscopic appearance of the esophageal mucosa will be scored from 0-4 as follows:

Grade 0 Normal esophageal mucosa, no abnormalities noted.

Grade 1 No macrosopic erosions visible. Erythema, or diffusely red mucosa; edema causing accentuated folds.

Grade 2 Isolated round or linear erosions extending from the squamocolumnar junction upwards in relation to the folds, but not involving the entire circumference.

Grade 3 Confluent erosions involving the entire circumference.

Grade 4 Frank, benign ulcer.

Barrett's esophagus will be defined as intestinal metaplasia in the distal part of esophagus. The position of the squamocolumnar junction (Z-line) and the gastroesophageal (GE) junction will be recorded in cm from the incisors.

The presence of an esophageal stricture will be recorded together with an estimate of its position in cm from the incisors. Strictures will be dilated as required by symptoms.

6.1.1.2. Histology

Esophagus

Multiple pinch biopsies will be obtained only to preclude malignancy and only when considered indicated by endoscopists.

Stomach

Six samples of corpus/fundus biopsies will be taken 10 centimetres below the cardiac mucosa along the major curvature.

The corpus/fundus biopsy specimens will immediately be placed into two separate tubes containing buffered, neutral 3.7% formaldehyde solution (10% formalin). The tubes will be labelled individually with patient number, date and biopsy site and should be sent, accompanied by a single completed Biopsy Report Form, to . The samples will be analysed by .

6.1.1.3. Symptoms

At each visit or during telephone contact, the patients will be questioned in a standardised manner to determine the current severity of reflux symptoms.

Heartburn will be scored as none, mild, moderate or severe.

Regurgitation will be scored as none, mild, moderate or severe.

Odynophagia will be scored as none, mild, moderate or severe.

Dysphagia

None:	No dysphagia; normal diet.
Mild:	Certain solids to be avoided.
Moderate:	Soft foods only.
Severe:	Liquids only.

Flatulence will be scored as none, mild, moderate or severe.

Nausea will be scored as none, mild, moderate or severe.

Postcibal oppression will be scored as none, mild, moderate or severe.

Feeling of distension will be scored as none, mild, moderate or severe.

Postcibal epigastrialgia will be scored as none, mild, moderate or severe.

Nocturnal cough will be scored as none, mild, moderate or severe.

Any changes in the ability to belch and vomit will be recorded.

6.1.1.4. Quality of life

Each year the patients will be sent standardised questionnaires, which they will be asked to complete, regarding their general well-being, lifestyle changes and overall evaluation of symptoms related to gastroesophageal reflux. The scales that will be used are: (GSRS) Gastrointestinal Symptom Rating Scale, (UESS) Ulcer Esophagitis Subjective Symptom Scale and the (PGWB) Psychological General Well-Being (3).

6.1.1.5. Unscheduled visits

Patients reporting recurrence of reflux symptoms which are not controlled by increased dose of omeprazole will be given an extra appointment for endoscopic examination.

Patients with symptomatic recurrence with or without concomitant esophagitis during maintenance treatment with omeprazole 20 mg will be treated with omeprazole 40 mg, or higher if needed, and continue with this daily dose during the remaining maintenance period. Patients who fail to respond should be regarded as failures and recommended surgical treatment. These patients will, subsequent to operation, continue in the study during the remaining five years follow-up period.

A benign esophageal stricture will be dilated when and as required by symptoms. Presence of stricture without concomitant esophagitis will not cause withdrawal from the study if the stricture can be satisfactorily dilated.

6.1.2. CLINICAL AND LABORATORY MEASUREMENTS

6.1.2.1. Medical history and physical examinations

Before entry a physical examination will be performed including patient's age, sex, height and weight, pulse, systolic and diastolic blood pressure. The physical examination will be repeated at 24 months. A general medical history and history of peptic ulcer/esophagitis disease and the current dose of omeprazole will be obtained before entry.

6.1.2.2. Fasting serum gastrin

Blood samples for the measurement of serum gastrin will be taken after an overnight fast at visit 2 and 5. A 5 ml serum sample will be frozen at -20°C and stored at each hospital, clearly labelled with centre and patient numbers. Serum gastrin concentrations will subsequently be quantitated by radioimmunoassay at

.

6.1.2.3. Histopathology

The biopsy specimens will be processed using the paraffin embedding technique, sectioned at 4 µm perpendicularly to the mucosal surface and routinely stained with haematoxylin-eosin. For argyrophil cells, Sevier-Munger silver and for *Helicobacter pylori*, modified Steiner silver will be used. Complementary stainings will be performed if considered necessary.

The biopsies will be histologically graded according to the Sydney system (1).

The main morphological changes in:

- Inflammation
- Activity
- Grading of *Helicobacter pylori*
- Atrophy
- Intestinal metaplasia

will be graded according to the standard Sydney classification into four grades; none (0), mild (1), moderate (2) or severe (3).

Any malignancy found will be reported to the investigator. However due to logistical reasons the reporting time may be long. The local routine procedures for the diagnosis of malignancies must be maintained.

6.1.2.4. Histopathological definitions

The following definition will be used:

Normal mucosa
Contains scattered mononuclear cells and lymphocytes (sometimes forming clusters) and few, scattered plasma cells with or without occasional mast cells and eosinophils. In the corpus, occasional small lymphocyte aggregates may be present at the base of the glands. Granulocytes are absent.

Acute versus chronic gastritis
If neutrophils are the dominant inflammatory cells, gastritis is classified as acute. If there is a concomitant increase in chronic inflammatory cells, gastritis is classified as chronic.

Inflammation
Refers to the amount of inflammatory cells (mostly lymphocytes, plasma cells and macrophages) in the lamina propria.

Activity
Refers to the presence of neutrophil granulocytes in the lamina propria, in the intraepithelial sites or both.

Atrophy
Refers to the loss of normal oxyntic glands. Scores 1-3 indicate respectively, that one third, two thirds or all normal glands have disappeared.

Intestinal metaplasia
Refers to the presence of metaplastic epithelium or glands of intestinal type. Intestinal metaplasia is noted without further differentiation into subclasses. Scores 1-3 indicate respectively, the replacement of epithelium and glands by intestinal metaplasia in one third, two thirds or totally.

Note: Atrophy usually accompanies the presence of intestinal metaplasia. The two parameters are closely correlated.

Helicobacter pylori
Severe colonisation: large numbers of bacteria on the surface and upper pits of more than two-thirds of the mucosal surface examined. Mild colonisation: individual, or small groups of bacteria, covering less than one third of the mucosal surface. Moderate colonisation is classified as being between these two.

Argyrophil, endocrine cells
Will be classified according to Solcia et al (2).

6.2. Safety

6.2.1. LABORATORY MEASUREMENTS

6.2.1.1. Clinical chemistry and haematology

Blood samples (4-10 ml) for laboratory screen will be taken two and five years after study start.

The laboratory screen will include the following variables:

Haematology: Haemoglobin, red and white blood cell count, platelet count

Biochemistry: Serum creatinine, total bilirubin, alkaline phosphates, ASAT and ALAT, NA^{+}, K^{+}, Ca^{++}, triglycerids, cholesterol, S-ferritin, B-folate and S-B_{12}.

Note: If the white blood cell count is considered to represent a clinically relevant leucopenia, a differential count is to be performed.

Normal hospital laboratory procedures will be followed for the analysis of blood samples. Relevant reference ranges from the laboratories to be used in the study must be provided by the investigator prior to the start of the study. Astra must be notified of any subsequent changes.

The last laboratory screen results from study I-635, year 5, will be regarded as baseline data. The investigator will decide whether or not any changes occurring during the study are clinically significant. If a clinically significant abnormal laboratory value is found on any occasion during the study, the treatment is to be kept unchanged according to the study design, if possible, until additional samples have been evaluated. In such situations, the laboratory screen will be repeated for as long as medically indicated. If a patient is withdrawn of any occasion between the scheduled visits, samples of blood and urine should be collected to for laboratory investigations.

Note: A clinically relevant deterioration may constitute an adverse event.

6.2.2. ADVERSE EVENTS (AES)

6.2.2.1. Adverse Event definition

An adverse event is:

- any unintended, unfavourable clinical sign or symptom.

- any new illness or disease or deterioration of existing illness or disease.

- any clinically relevant deterioration in laboratory variable (e.g. haematological, biochemical, hormonal) or other clinical test (e.g. ECG, X-ray).

  whether or not considered treatment related.

Note that the definition could include accidents and the reasons for:

- changes in medication (drug and/or dose).

- medical, nursing and/or pharmacy consultation.

- admission to hospital.

- surgical operations.

Planned hospital admissions and/or surgical operations for an illness or disease which existed before the drug was given or the patient was enrolled in a clinical trial are not to be considered to indicate adverse events.

6.2.2.2. Serious Adverse Event definition

A serious adverse event is an adverse event which results in:

- death.
- permanent or significant disability/incapacity.
- in-patient hospitalisation or prolongation of existing in-patient hospitalisation.

  (Out-patient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema).)

or is

- life-threatening.

  ("Life-threatening" means that the patient was at immediate risk of death from the adverse event as it occurred. "Life-threatening" does not mean that had an adverse event occurred in a more severe form it might have caused death).

- a congenital anomaly or birth defect.

or requires

- medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure.

  (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; other important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Medical and scientific judgement may be required).

An adverse event fulfilling any one or more of these criteria must be reported as a serious adverse event, irrespective of the dose of drug given, and even if it is the result of an interaction or drug abuse.

Cancer will always be reported as a serious adverse event as well as any experience associated with an overdose.

A distinction should be drawn between serious and severe adverse events. A severe adverse event is a major event of its type. A severe adverse event need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but not a serious adverse event. 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 serious adverse event.

6.2.2.3. Procedures for Serious Adverse Event reporting

The investigator must inform the monitor, or other representative of the Astra Company, within **1 working day** by telefax and/or telephone, of any serious adverse event that occurs in the course of the study. The Astra Company must also receive a completed Serious Adverse Event Form within **4 calendar days**. All serious events have to be reported, whether or not considered causally related to the study drug.

6.2.2.4. Procedures for Adverse Event recording

AEs will be recorded as spontaneously reported by the patient and/or reported in response to an open question from the study personnel. Adverse events revealed by observations, physical and laboratory examinations or other diagnostic procedures will also be recorded.

Date when AE started and disappeared, intensity, action taken and outcome will be reported for each AE in the CRF. The intensity will be rated according to the following definitions:

mild	awareness of sign or symptom, but easily tolerated
moderate	discomfort sufficient to cause interference with normal activities
severe	incapacitating, with inability to perform normal activities

For clinical and laboratory findings, date of examination/sampling, action taken and outcome will be reported.

6.3. Compliance with dosage regimens

Patient compliance will be checked by a count of returned study medication each time the patients receive a new supply of study medication. It is the investigator responsibility to assure that the compliance is sufficient enough to make the patient evaluable.

7. SAFETY PROCEDURES

7.1. Procedures in case of medical emergency

The principal investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. Each patient will be supplied a study information card (appendix X).

An emergency may constitute a serious adverse event.

7.2. Procedures in case of pregnancy

A pregnant patient should be withdrawn from the study.
The investigator must follow the course of the pregnancy, and inform Astra about the outcome.

8. DATA MANAGEMENT AND EVALUATION

8.1. Data management

Data entry and editing will be made by Astra Hässle AB. Any questions or missing data will be noted and clarified using the "Data Clarification Form". All clarifications must be verified by the investigators signature on the form. Clarifications must be made and documented for each individual patient. The clean file procedure of Astra Hässle AB will be used.

8.2. Data evaluation and statistical considerations

Statistical analysis will be performed at Astra Hässle AB. All analyses will be performed on an Intention-to-treat basis.

Clinical consequences as symptomatic recurrence, recurrence of esophagitis, surgeries for patients in the maintenance treatment arm and omeprazole treatment for patients in the surgery arm, will be presented in frequency tables and/or by descriptive statistics.

Laboratory variables will be categorised as increased, unchanged or decreased from the first visit in the study to the last visit, and presented in a frequency table. Graphs showing baseline values vs. last visit values will also be presented.

Gastrin values and histopathological assessments will be presented by frequency tables and/or by descriptive statistics. In addition, crosstabulations of baseline assessments vs last assessments of gastritis and anthrophy will be presented.

Presentations of clinical consequences, gastrin values and histopathological assessments will be done for subgroups based on Hp status and treatment modality.

The change from the baseline visit to the last visit in the scores of the Quality of Life questionnaires will be presented using descriptive statistics. The total scores as well as the scores of the individual dimensions of UESS, GSRS and PGWB will be described. Patients discontinuing the study will be included as long as there is a subsequent assessment after baseline.

9. ETHICAL REQUIREMENTS

9.1. Declaration of Helsinki and ethical review

The study will be performed in accordance with the principles stated in the Declaration of Helsinki.

The final study protocol, including the final version of the Patient Information and Consent Form(s) to be used, must be approved by an Ethics Committee before enrolment of any patients into the study. The opinion of the Ethics Committee should be dated and given in writing. A list of those present at the committee meeting (names and positions) should be attached whenever possible. It is the responsibility of the principal investigator to forward to Astra before the start of the study a copy of the approval from the Ethics Committee, clearly identifying by title and date the protocol and other documents submitted for review.

The investigator is responsible for informing the Regulatory Authority and/or Ethics Committee of any serious adverse events and/or amendments to the protocol as per national requirements.

All correspondence with the Ethics Committee should be filed by the investigator and a copy forwarded to Astra.

9.2. Patient information and consent

The investigator will ensure that the patient is given full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue their participation in the study at any time. The patient should be given the opportunity to ask questions and, when possible, time for consideration. The investigator is responsible for obtaining signed or witnessed verbal informed consent from all patients before enrolment.

The Patient Information and Consent Form(s) are enclosed (Appendix 2). If modifications are made according to local requirements, the new version has to be approved by Astra.

A copy of the Patient Information including the Consent Form should be retained by the patient.

9.3. Patient data protection

All data computer-processed at Astra will be identified by patient number only, thereby ensuring that the patient's identity remains unknown to the sponsor.

The patients should be informed in writing that the data will be stored and analysed in a computer, maintaining confidentiality in accordance with national data legislation.

The patients should also be informed in writing that authorised representatives of the company and/or Regulatory Authorities, may require access to those parts of the hospital/practice records relevant to the study, including medical history, for verification of data.

The principal investigator is responsible for keeping a Patient Identification List or Form of all patients randomised, including patient number, full name and last known address.

9.4. Insurance

With respect to any liability directly or indirectly caused by the investigational products in connection with this Clinical Trials, Astra assumes liability by law on behalf of the investigator and his assistants for possible injury to the patient provided the investigator and his assistants have followed the instruction of Astra in accordance with this protocol and any amendments thereto, that the investigational products administered to the patient in this Clinical Trial have been supplied by Astra , and that the investigator and his assistants have in general performed this Clinical Trial in accordance with scientific practice and currently acceptable techniques and know-how.

Astras liability is covered by a liability insurance with

For Sweden:

Astras liability is covered by the or the
and by liability insurance with (Policy

10. HANDLING OF STUDY DRUGS

10.1. Packaging, labelling and storage

The study drugs will be packed at . The patients will be supplied with trial medication for periods of three months during the study, packed in bottles containing 32 capsules of omeprazole 20 or 40 mg.

The bottle label will state study code, "For clinical trial use only", Omeprazole 20 or 40 mg, dosage instruction, expire date, storage instruction, "Keep out of reach of children", Astra Hässle AB and lines for the name of the investigator and the patient number.

Study drugs will be delivered from to the local Astra company, which will be responsible for the distribution to the participating centres.

All study drugs will be kept in a secure place under adequate storage conditions.

11. OTHER STUDY ISSUES

11.1. Study committees

The Coordinating Investigator, national Coordinating Investigators and relevant Astra personnel will together form a group responsible for the implementation and evaluation of the study. The group may co-opted members as needed.

11.2. Monitoring

During the study, the monitor will have regular contact with the investigational site. These contacts will include visits to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, that data are being accurately recorded in the Case Report Forms and to provide information and support to the investigator. The monitor will ensure that drug accountability is being carried out. Source data verification (a comparison of the data in the Case Report Form with the hospital/practice and other records at the investigational site) will also be performed.

The monitor or other Astra personnel will be available between visits, should the investigator need information and advice.

11.3. Training

Standardisation of study procedures between centres in the participating countries will be achieved by international investigators and monitors meetings.

The principal investigator will ensure that appropriate training relevant to the study is given to the medical, nursing and other staff involved, and that any information of relevance to the performance of this study is forwarded to the co-investigators and other staff involved.

11.4. Patient medical records

For every patient, the hospital/practice records should clearly indicate at least:

- that the patient participated in the study, e.g. by including patient identification (enrolment code and/or patient number) and study identification (study code or other).

- diagnosis(es) (past and current; both the diagnosis studied and others, as relevant).

- treatments withdrawn due to participation in the study.

- treatments, including study drug(s), received or changed during the study.

- all visits to the clinic during the study period, including those for study purposes only.

- all serious adverse events.

11.5. Study timetable

First patient in: 1997-04
Last patient in: 1999-05
Last patient out: 2004-05

11.6. Changes to the protocol

No change in the study procedure shall be effected without the mutual agreement of the investigator and Astra. All changes must be documented by signed protocol amendments or a revised protocol.

Changes to the protocol may require notification to/approval by the Ethics Committee and the Regulatory Authorities before implementation. National requirements must be followed.

The Astra coordinator/monitor is responsible for the distribution of an amendment to the principal investigator(s) and those concerned within the company. The principal investigator is responsible for the distribution of an amendment to the Ethics Committee and all staff concerned at his/her centre.

11.7. Study termination

Astra reserves the right to discontinue the study for medical and/or administrative reasons at any time.

12. REFERENCES

1. Price AB. The Sydney System: Histological division,J Gastroenterol Hepatol (1991)6: 209-222.

2. Solcia E, *et. al.* Histopathological classification of non antral gastric endocrine growth in man. Digestion 1988;41:185-200.

3. Dimenäs E, Glise H, et. Al. Well being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand. J. Gastroenterol. 1995;30:1046-1052.

13. SIGNED AGREEMENT TO THE PROTOCOL

13.1. Signature of coordinating investigator

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

Study code: SH-OMG-0004

Centre No:

....
COORDINATING INVESTIGATOR DATE

13.2. Astra signatures

On behalf of Astra, I agree to the terms of this protocol.

Study code: SH-OMG-0004

....
ASTRA COORDINATOR DATE

....
ASTRA STATISTICIAN DATE