Clinical Study Protocol	
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A multicenter, randomized, open-label Phase IV study exploring symptom control rate in co-diagnosed NERD and chronic gastritis patients treated with 8 weeks esomeprazole treatment regimen and 2 weeks esomeprazole treatment regimen

Sponsor: Astrazeneca China

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
Administrative Change No.	**Date of Administrative Change**	**Local Administrative Change No.**	**Date of Local Administrative Change**

PROTOCOL SYNOPSIS

A multicenter, randomized, open-label Phase IV study exploring symptom control rate in co-diagnosed NERD and chronic gastritis patients treated with 8 weeks esomeprazole treatment regimen and 2 weeks esomeprazole treatment regimen

National Co-ordinating Investigator

Study centre(s) and number of subjects planned

The study will have 300 randomized patients from 10 centers in China, with approximate 30 patients per centre.

Study period	Phase of development
Estimated date of first patient enrolled	Phase IV
Estimated date of last patient completed	

Objectives

Primary objective

- To compare the symptom control rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients, as evaluated by GerdQ after 24 weeks maintenance treatment/follow up.

Secondary objective

- To assess time to first relapse, defined as the time to patients first come to see the investigator because of symptom recur and need for treatment after 8 weeks or 2 weeks esomeprazole treatment in the two treatment regimen groups.
- To assess symptom control rate after 8 /16 weeks visits in 24 weeks maintenance treatment/follow up period, as evaluated by GerdQ.

- To assess the symptom relief rate after 8 weeks or 2 weeks esomeprazole treatment in the two different treatment regimen groups.
- In the 8 weeks treatment regimen group, to compare the symptom relief rate after 2 weeks and 8 weeks treatment.
- To compare the number of unscheduled hospital visit between the two different treatment regimen groups.
- To measure patient satisfaction in the two different treatment regimen groups.

Study design

This is a randomized, open-label design. The study is designed to be naturalistic in accordance with how patients are treated in clinical practice in China.

Patients with endoscope diagnosed chronic gastritis (non- atrophic, and mild atrophic gastritis) and GerdQ ≥ 8 will be randomized into two groups.

One group is the 8 weeks treatment regimen group, patients will receive esomeprazole 20 mg qd treatment for 8 weeks, the patients whose symptom relieved (defined as no more than one day with mild symptoms of GERD during the previous 7 days) will have another 24 weeks on-demand maintenance treatment. The 8 weeks treatment regimen is the NERD standard treatment recommended by China GERD consensus (Chinese Medical Association, 2007).

The second group is the 2 weeks treatment regimen group, patients will receive 2 weeks esomeprazole 20 mg qd treatment, if symptom relieved, they will enter 24 weeks follow-up period. During the followed up period, if the patients' symptoms recur and need treatment in the opinion of investigator, they will be given another 2-week esomeprazole 20 mg qd recurrent treatment, and no limitation for the times of recurrent treatment in 24 weeks follow up period.

The patients whose symptom not relieved after 8 weeks treatment in 8 weeks treatment regimen group or 2 weeks treatment in 2 weeks treatment regimen group will be withdrawn from the study and treated according to clinical routines.

There are three scheduled visits (8, 16 and 24 weeks) in 24 weeks' on-demand maintenance treatment/ follow up period. Any unscheduled visits are guided by the patient's symptom recur, need for extra treatment, or the patients' need for medical consultation.

GerdQ will be assessed when the patients enter the study and at 8, 16 and 24 weeks' visit in maintenance treatment/ follow-up period to assess the symptom control in two groups. Controlled patients are defined as patients with all the items ≤1 in A and C category of GerdQ. The symptom control rate will be compared between two treatment regimen groups at the three scheduled visits (8, 16 and 24 weeks in 24 weeks' maintenance treatment/ follow-up period).

Target subject population

Approximately 300 patients (approximately 150 patients per treatment group) with endoscope diagnosed chronic gastritis and GerdQ ≥ 8 will be enrolled in the study and randomized into two different treatment regimen groups.

Investigational product, dosage and mode of administration

8 weeks treatment regimen group:

8 weeks esomeprazole 20 mg tablet qd oral treatment, followed by 24 weeks on-demand maintenance treatment

Comparator, dosage and mode of administration

2 weeks treatment regimen group:

2 weeks esomeprazole 20 mg tablet qd oral treatment, followed by 24 weeks follow up (in 24 weeks follow up period, another 2 weeks recurrent treatment can be indicated by the investigator once the symptoms recur, and no limitation for the times of recurrent treatment).

Duration of treatment

8 weeks treatment regimen group:

Total duration is 32 weeks, including 8 weeks esomeprazole treatment and 24 weeks on-demand maintenance treatment.

2 weeks treatment regimen group:

Total duration is 26 weeks, including 2 weeks esomeprazole treatment and 24 weeks follow-up. During the follow up period, if the patients' symptoms recur and need treatment in the opinion of investigator, they will be given another 2-week esomeprazole 20 mg qd recurrent treatment. There is no limitation for the times of recurrent treatment in the 24-week follow up period.

Outcome variable(s):

Efficacy

Primary outcome variable:

- The symptom control rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group after 24 weeks on-demand maintenance treatment/ follow up. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ.

Secondary outcome variable:

- Time to first relapse, defined as the time to the patients first come to see the investigator because of symptom recur and need for treatment after 8 weeks or 2 weeks treatment in the two treatment regimen groups.

- The symptom control rate after 8 and 16 weeks on-demand maintenance treatment/ follow up in the two different treatment regimen groups. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ.

- The symptom relief rate after 8 weeks or 2 weeks treatment in the two treatment regimen groups (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days).

- In the 8 weeks treatment regimen group, the symptom relief rate after 2 weeks and 8 weeks treatment (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days).

- The number of unscheduled hospital visit in the two treatment regimen groups.

- The proportion of patients satisfied (scores 1-4) or very satisfied (scores 1-2) in the two different treatment regimen groups after 8, 16 and 24 weeks on-demand maintenance treatment/ follow up. Patient satisfaction will be measured using a 7-point scale (completely satisfied-1; very satisfied-2; quite satisfied-3; satisfied-4; dissatisfied-5; very dissatisfied-6; completely dissatisfied-7).

Safety

- Serious adverse events (SAEs), adverse events leading to discontinuation of investigational product (DAEs)

Statistical methods

Analysis on efficacy endpoints will be performed in intention to treat (ITT) population and modified intention to treat (MITT) population. ITT is defined as all randomized subjects who have taken at least one dose of trial treatment. MITT is defined as patients in ITT population whose symptoms relieved after 8 weeks or 2 weeks esomeprazole treatment. In addition, efficacy analysis will also be repeated in per protocol (PP) population. PP population is defined as all ITT subjects without significant protocol violations/deviations.

All treatment comparisons will be done at 2-sided and the nominal level of significance is 5%.

In general, the frequency tables (number and percentage of subjects) will be performed for categorical variables. The descriptive statistics (number, mean, median, standard deviation, minimum and maximum) will be performed for continuous variables. Kaplan-Meier method will be used to assess time to first relapse.

Statistical analysis of the primary endpoint will be based on Fisher's exact test using the modified intention to treat (MITT) population.

Safety endpoints will be summarized by treatment received in the safety population. No inferential statistical analysis will be done for the safety variables. Descriptive statistics for SAEs, DAEs will be performed.

Since we do not have previous data for the symptom control rate in 8 weeks or 2 weeks treatment regimens, the sample size was calculated based on clinical experience. With a total of 170 evaluable patients (85 in each group), the power would be over 80% to detect a difference of 20% in symptom control rate between two treatment regimen groups at two-sided 0.05 significance level using Fisher exact test, assuming the symptom control rate is around 66% in 2 weeks treatment regimen group and 86% in 8 weeks treatment regimen group (based on the relapse rate in the BU-NEG-0005 study). Since the PPI response rate is around 70% and drop off rate will be 20%, so around 300 patients is needed.

TABLE OF CONTENTS PAGE

TITLE PAGE 1
PROTOCOL SYNOPSIS 2
TABLE OF CONTENTS 7
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 11
1. INTRODUCTION 12
1.1 Background 12
1.2 Research hypothesis 13
1.3 Rationale for conducting this study 13
1.4 Benefit/risk and ethical assessment 13
2. STUDY OBJECTIVES 14
2.1 Primary objective 14
2.2 Secondary objectives 14
3. STUDY PLAN AND PROCEDURES 14
3.1 Overall study design and flow chart 15
3.2 Rationale for study design, doses and control groups 19
4. SUBJECT SELECTION CRITERIA 19
4.1 Inclusion criteria 19
4.2 Exclusion criteria 20
5. STUDY CONDUCT 22
5.1 Restrictions during the study 22
5.2 Subject enrolment and randomisation and initiation of investigational product 22
5.2.1 Procedures for randomisation 22
5.3 Procedures for handling subjects incorrectly enrolled or randomised or initiated on investigational product 22
5.4 Blinding and procedures for unblinding the study 23
5.5 Treatments 23
5.5.1 Identity of investigational product(s) 23
5.5.2 Doses and treatment regimens 23
5.5.3 Labelling 24

5.5.4 Storage 25
5.6 Concomitant and post-study treatment(s) 25
5.7 Treatment compliance 25
5.7.1 Accountability 25
5.8 Discontinuation of investigational product 25
5.8.1 Procedures for discontinuation of a subject from investigational product 26
5.9 Withdrawal from study 26
6. COLLECTION OF STUDY VARIABLES 26
6.1 Recording of data 26
6.2 Data collection and enrolment 27
6.2.1 Follow-up procedures 27
6.3 Efficacy 27
6.3.1 Summary of efficacy objectives and variables 28
6.3.2 Derivation or calculation of outcome variable 29
6.4 Safety 30
6.4.1 Definition of adverse events 30
6.4.2 Definitions of serious adverse event 30
6.4.3 Recording of adverse events 31
6.4.4 Reporting of serious adverse events 33
7. BIOLOGICAL SAMPLING PROCEDURES 33
7.1 Volume of blood 33
7.2 Handling, storage and destruction of biological samples 34
8. ETHICAL AND REGULATORY REQUIREMENTS 34
8.1 Ethical conduct of the study 34
8.2 Subject data protection 34
8.3 Ethics Review 34
8.4 Informed consent 34
8.5 Changes to the protocol and informed consent form 35
8.6 Audits and inspections 36
9. STUDY MANAGEMENT BY ASTRAZENECA 36
9.1 Pre-study activities 36
9.2 Training of study site personnel 36
9.3 Monitoring of the study 37
9.3.1 Source data 37
9.4 Study agreements 37

9.4.1 Archiving of study documents 38
9.5 Study timetable and end of study 38
10. DATA MANAGEMENT BY ASTRAZENECA 38
11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA 39
11.1 Calculation or derivation of efficacy variable(s) 39
12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA 39
12.1 Description of analysis sets 39
12.1.1 Efficacy analysis set 39
12.1.2 Safety analysis set 39
12.2 Methods of statistical analyses 39
12.2.1 Analyses of efficacy endpoints 39
12.2.2 Analyses of safety endpoints 40
12.2.3 Interim analyses 40
12.3 Determination of sample size 40
12.4 Data monitoring committee 40
13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR 41
13.1 Medical emergencies and AstraZeneca contacts 41
13.2 Overdose 41
13.3 Pregnancy 42
13.3.1 Maternal exposure 42
14. LIST OF REFERENCES 43

LIST OF TABLES

Table 1 Study Plan 1 (Visits in 8 weeks/2 weeks treatment period) 17
Table 2 Study Plan 2 (Visits in 24 weeks on-demand maintenance treatment/ follow-up period) 18
Table 3 Efficacy objective and endpoints relating to objective 28
Table 4 Volume of blood to be drawn from each subject 33

LIST OF FIGURES

Figure 1 Study flow chart 16

LIST OF APPENDICES

Appendix A Signatures

Appendix B Additional Safety Information

Appendix C GerdQ

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood urea nitrogen
CG	Chronic Gastritis
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GERD	Gastroesophageal reflux disease
GCP	Good Clinical Practice
H_2RA	Histamine type-2 receptor antagonist
ICH	International Conference on Harmonisation
IP	Investigational Product
ITT	Intention to treat
LSLV	Last Subject Last Visit
MITT	Modified intention to treat
National Co-ordinating investigator	National Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities among multicenters nationally.
NERD	Non- erosive reflux disease
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator
PP	Per protocol
PPI	Proton pump inhibitor
SAE	Serious adverse event (see definition in Section 6.4.2).

1. INTRODUCTION

1.1 Background

Gastroesophageal Reflux Disease (GERD) is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications (Vakil N et al 2006). Based on white light endoscopy, GERD is classified into reflux esophagitis (RE), non-erosive reflux disease (NERD) and Barrett's esophagus. NERD is defined by the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy. It is the principal manifestation of GERD, which account for about 60% of GERD patients (Labenz J et al 2004).

Compared to other patients with GERD who have clearly visible manifestations of the disease (RE; Barrett's esophagus), the diagnosis in patients with normal esophageal findings is difficult to establish. 24h pH monitoring, histology and endoscopic features have not led to reliable results (DeVault KR et al 2005; Kiesslich R et al 2004).

According to 2006 Montreal definition (Vakil N et al 2006), GERD can be diagnosed on the basis of typical reflux symptoms, without the need for diagnostic test. In China, although the majority of physicians accept symptom based diagnosis concept, there are still a lot of NERD patients misdiagnosed as chronic gastritis (CG) due to the wide-spread endoscopy. In China clinical practice, most patients without clear endoscopic manifestations are diagnosed as chronic gastritis in endoscopy report. Then many patients with typical reflux symptom and endoscopic chronic gastritis result are misdiagnosed as chronic gastritis. Although physicians know these patients are NERD, they tend to choose chronic gastritis diagnosis, since they think one diagnosis is enough, and follow CG treatment practice (2 weeks treatment regimen) instead of NERD standard treatment (8 weeks treatment regimen), meanwhile CG diagnosis is easier for patients to understand.

However, NERD is chronic and recurrent disease. Many patients require full dose initial Proton pump inhibiter (PPI) treatment and long-term maintenance treatment (8 weeks treatment regimen). Although one or two weeks PPI treatment can temporarily resolve the reflux symptom in NERD patients, the overall symptom control is poor, patients satisfaction is low, hospital visit and recurrent treatment are frequent for such patients.

The present study is conducted to explore the symptom control rate of such NERD patients with 8 weeks treatment regimen and 2 weeks treatment regimen. Our aim is to provide solid data to demonstrate that endoscope diagnosed CG patients with typical reflux symptoms should be co-diagnosed as NERD, only NERD standard treatment (8 weeks treatment regimen) can provide better symptom control, followed by higher patient satisfaction and less hospital visit.

1.2 Research hypothesis

For endoscope diagnosed CG patients with typical reflux symptoms, 8 weeks treatment regimen can provide better symptom control, followed by higher patient satisfaction and less hospital visit.

1.3 Rationale for conducting this study

In China clinical practice, many NERD patients are misdiagnosed as chronic gastritis after endoscopy. Although most physicians accept symptom based diagnosis concept, they tend to choose chronic gastritis diagnosis, since they think one diagnosis is enough, and follow CG treatment practice (2 weeks treatment regimen) instead of NERD standard treatment (8 weeks treatment regimen), meanwhile CG diagnosis is easier for patients to understand.

According to China GERD consensus (Chinese Medical Association 2007), NERD treatment recommends 8 weeks initial PPI treatment followed by personalized on-demand maintenance treatment. Although one or two weeks PPI treatment can temporarily resolve the reflux symptom in NERD patients, the overall symptom control is poor, patients satisfaction is low, and hospital visit is frequent for such patients. Therefore, the objective of this study is to provide solid data to support the recommendation of China GERD consensus, and convince physicians that endoscopic diagnosed CG patients with typical reflux symptoms should be co-diagnosed as NERD, and treated with 8 weeks treatment regimen.

1.4 Benefit/risk and ethical assessment

Preclinical bridging studies with esomeprazole reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction.

In the presence of any alarm symptom (eg, significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered. In non-steroidal anti-inflammatory drugs (NSAID) treated risk patients, subsequent symptom control using on demand treatment is not recommended.

Global randomized, controlled trials (BU-NEG-0005 study) in patients with NERD have shown that esomeprazole 20mg qd taken on demand after 4 weeks initial treatment is an effective and cost-saving treatment regimen in the long-term management of NERD. However, we do not have any local data in Chinese population for the symptom control rate with this cost- effective treatment regimen. On the other hand, a lot of NERD patients are mis-diagnosed as CG and treated irregularly in clinical practice in China. Our current study

will not only provide efficacy data for NERD standard treatment (8 weeks treatment regimen) in Chinese population, but also compare with 2 weeks treatment regimen.

Although one group of NERD patients will receive 2 weeks treatment regimen in this study, we mimic real clinical practice how more than half of NERD patients are treated, and patients will receive another 2 weeks esomeprazole recurrent treatment if they feel symptom recur and go to see physicians during 24 weeks follow-up. There is no limitation for the times of recurrent treatment in the 24-week follow up period.

2. STUDY OBJECTIVES

2.1 Primary objective

- To compare the symptom control rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients, as evaluated by GerdQ after 24 weeks maintenance treatment/follow up.

2.2 Secondary objectives

- To assess time to first relapse, defined as the time to the patients first come to see the investigator because of symptom recur, and need for treatment after 8 weeks or 2 weeks esomeprazole treatment in the two treatment regimen groups.
- To assess symptom control rate after 8 /16 weeks visits in 24 weeks maintenance treatment/follow up period, as evaluated by GerdQ.
- To assess the symptom relief rate after 8 weeks or 2 weeks esomeprazole treatment in the two different treatment regimen groups.
- In the 8 weeks treatment regimen group, to compare the symptom relief rate after 2 weeks and 8 weeks treatment.
- To compare the number of unscheduled hospital visit between the two different treatment regimen groups.
- To measure patient satisfaction in the two different treatment regimen groups.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a randomized, open-label design. The study is designed to be naturalistic in accordance with how patients are treated in clinical practice in China.

Patients with endoscope diagnosed chronic gastritis (non- atrophic, and mild atrophic gastritis) and GerdQ ≥ 8 will be randomized into two groups.

One group is the 8 weeks treatment regimen group, patients will receive esomeprazole 20 mg qd treatment for 8 weeks, the patients whose symptom relieved (defined as no more than one day with mild symptoms of GERD during the previous 7 days) will have another 24 weeks on-demand maintenance treatment. The 8 weeks treatment regimen is the NERD standard treatment recommended by China GERD consensus (Chinese Medical Association 2007).

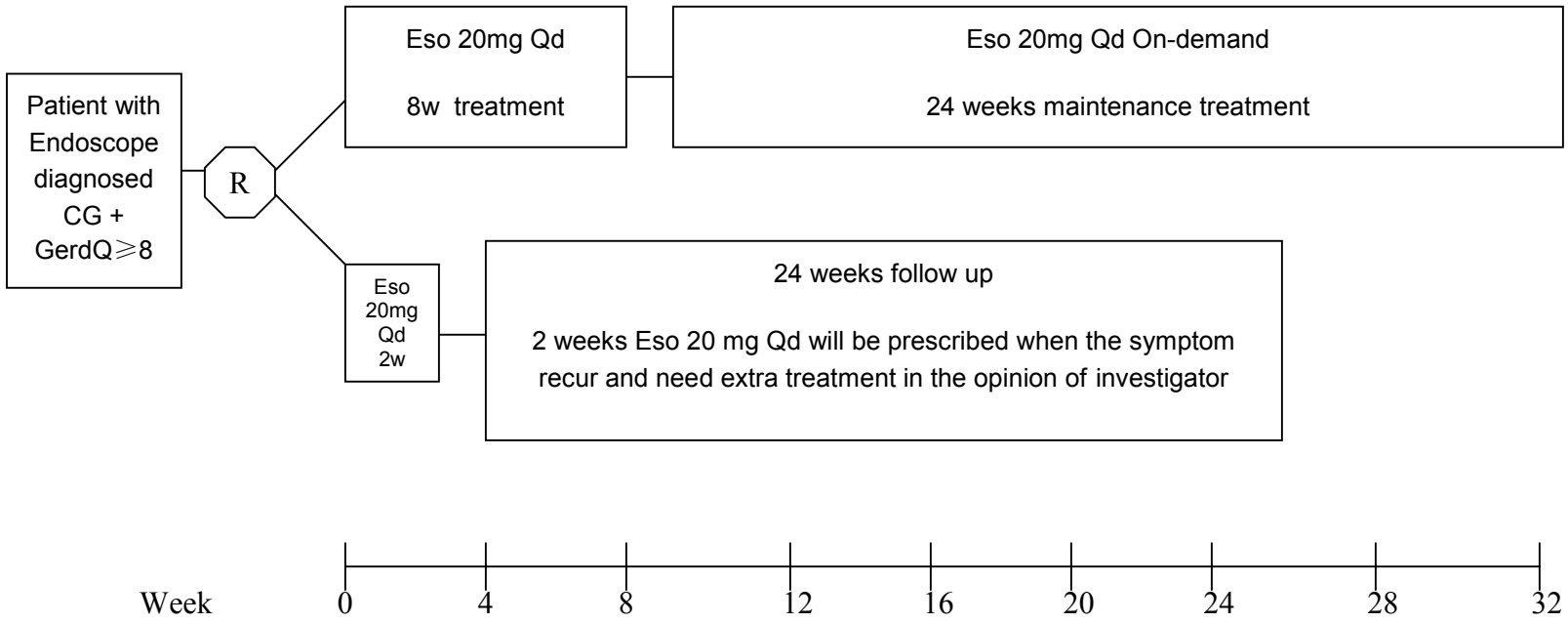
The second group is the 2 weeks treatment regimen group, patients will receive 2 weeks esomeprazole 20 mg qd treatment, if symptom relieved, they will enter 24 weeks follow-up period. During the followed up period, if the patients' symptoms recur and need treatment in the opinion of investigator, they will be given another 2-week esomeprazole 20 mg qd recurrent treatment, and no limitation for the times of recurrent treatment in 24 weeks follow up period.

The patients whose symptom not relieved after 8 weeks treatment in 8 weeks treatment regimen group or 2 weeks treatment in 2 weeks treatment regimen group will be withdrawn from the study and treated according to clinical routines.

There are three scheduled visits (8, 16 and 24 weeks) in 24 weeks' on-demand maintenance treatment/ follow up period. Any unscheduled visits are guided by the patient's symptom recur, need for extra treatment, or the patients' need for medical consultation.

GerdQ will be assessed when the patients enter the study and at 8, 16 and 24 weeks' visit in maintenance treatment/ follow-up period to assess the symptom control in two groups. Controlled patients are defined as patients with all the items ≤1 in A and C category of GerdQ. The symptom control rate will be compared between two treatment regimen groups at the three scheduled visits (8, 16 and 24 weeks in 24 weeks' maintenance treatment/ follow-up period).

Figure 1 Study flow chart



* Only patients whose symptoms relieved after 8 weeks/ 2 weeks treatment will enter 24 weeks maintenance/ follow-up period.

Table 1 Study Plan 1 (Visits in 8 weeks/2 weeks treatment period)

	Pre-entry	8 weeks/ 2 weeks treatment		
	Visit 1[a]	2	3	4
	Week -1	Week 0	Week 2	Week 8[b]
Inclusion & exclusion criteria	X	X		
Informed Consent	X			
Randomisation		X		
Medical history	X			
Demographic data	X			
Urine HCG[c]		X		
Physical examination	X			
Vital signs	X			
Laboratory measurement[d]	X			
Hp infection[d,e]	X			
Concomitant medication	X	X	X	X
Drug dispensing		X	X[b]	
Drug accountability			X	X
GerdQ assessment	X			
SAEs/ DAEs[f] assessment	X[g]→	X→	X→	X→

[a] Once informed consent given, baseline procedures may be completed within 1 week prior to treatment start.
[b] Just for patients in 8 weeks treatment regimen group.

[c] For women of child-bearing potential, a pregnancy test with a negative result must have been made before study.
[d] Laboratory test results in the previous 2 weeks are acceptable, no need to repeat laboratory test at Visit 1.
[e] Hp infection status diagnosed by ^{13}C-urea breath test (UBT), rapid urease test or pathologic test.
[f] Only SAEs and DAEs will be collected.
[g] SAEs will be captured from time of of signature of informed consent. DAEs will be captured from time of first dose of IP.

Table 2 Study Plan 2 (Visits in 24 weeks on-demand maintenance treatment/ follow-up period)

	24-week Maintenance treatment/ follow up			
	5	**6**	**7[a]**	**Unscheduled[b]**
	Week 8±3d	**Week 16±3d**	**Week 24±3d**	
Concomitant medication	X	X	X	X
Drug dispensing	X[c]	X[c]		X
Drug accountability	X	X	X	X
GerdQ assessment	X	X	X	
Patient satisfaction	X	X	X	
SAEs/ DAEs[d] assessment	X→	X→	X	X

[a] If a patient discontinues from the study prior to the Week 24 visit (study completion), every effort should be made to have the patient return for a clinic visit at the time of, or soon after discontinuation to complete all Final Visit procedures.
[b] This includes all unscheduled visits carried out during maintenance treatment/ follow up period due to symptom recur and extra treatment needed. Total unscheduled visits will be compared between two treatment group.
[c] Just for patients in 8 weeks treatment regimen group, only after the first relapse happened. If patients in CG group have symptom relapse at a scheculed visit, drugs will also be dispensed to them.
[d] Only SAEs and DAEs will be collected.

3.2 Rationale for study design, doses and control groups

This study has a controlled design allowing us to evaluate efficacy in two different esomeprazole treatment regimens in patients with co-diagnosed NERD and CG. The randomized design ensures the unbiased baseline characteristics of the subjects in the two groups. The open-label design is chosen because the duration of treatment and the treatment regimen in maintenance/ follow up phase are different in the two groups.

Based on Nexium® product package insert, for symptomatic treatment of GERD, the indicated dose is 20 mg once daily in patients without esophagitis. Once symptoms have resolved, subsequent symptom control can be achieved using an on demand regimen taking 20 mg once daily, when needed. 2007 China GERD consensus (Chinese Medical Association, 2007) recommends 8 weeks initial PPI treatment followed by personalized maintenance treatment for NERD patients. Therefore, esomeprazole 20 mg qd 8 weeks treatment followed by 24 weeks on-demand maintenance treatment is considered as NERD standard treatment in the present study. On the other hand, a lot of NERD patients are misdiagnosed as CG and treated irregularly in China clinical practice. Therefore, our study will not only evaluate the efficacy of 8 weeks treatment regimen, but also compare with 2 weeks treatment regimen.

According to 2006 Montreal definition (Vakil N et al 2006), NERD can be diagnosed on the basis of typical reflux symptoms. The newly published Diamond study (Jones R et al 2009) already demonstrated that GerdQ is a simple and effective symptom-based assessment tool for GERD diagnosis and management. Therefore, in the present study, GerdQ is not only used as diagnostic criteria for NERD in screening phase, but also an assessment tool for patients' symptom control status in maintenance/ follow-up phase.

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

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

2. Males and females aged 18 to 75 years

3. Heartburn and/or regurgitation symptoms last for at least 3 months

4. Endoscopic diagnosed as chronic gastritis (non-atrophic, and mild atrophic gastritis) within 2 weeks prior to randomization

5. GerdQ score ≥8

4.2 Exclusion criteria

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

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

2. Previous enrolment or randomisation in the present study

3. Participation in another clinical study with an investigational product during the last 3 month

4. Endoscopic visible reflux esophagitis, esophageal varices, Barrett's esophagus, malignancy or peptic ulcer

5. Patients with Hp positive result and are eager to take Hp eradication therapy will be excluded. If Hp positive, patients could take Hp eradication therapy after the study completion

6. Presence of any alarm features within the last 6 months, such as:

   - Unintentional weight loss >3 kg in the previous 3 months
   - Haematemesis, melaena or per-rectum blood loss in the previous year
   - Progressive dysphagia
   - Anaemia
   - Any other symptom suggestive of malignancy

7. Previous PPI or H_2RA therapy in the last 2 weeks before enrollment

8. Known intolerance/allergy to PPIs

9. History of esophageal, gastric or duodenal surgery

10. History of chronic condition (eg, osteoarthritis or rheumatoid arthritis) that requires long-term daily NSAID treatment

11. History of severe liver disease, including (but not limited to) cirrhosis and acute or chronic hepatitis

12. Liver enzymes (AST, ALT, or alkaline phosphatase) twice the upper limit of normal at baseline examination

13. Severe renal disease, including chronic renal disease or impaired renal function as manifested by any of the following: serum creatinine greater than 2.0 mg/dL or markedly abnormal urine protein at baseline examinations

14. Current or historical evidence (within 3 months) of the following diseases/conditions:

    - Signs and symptoms of gastric outlet obstruction (eg, abdominal distension, or multiple episodes of vomiting)
    - Zollinger-Ellison syndrome
    - Gastric or duodenal ulcers within the last 3 months
    - Pancreatitis
    - Severe cardiovascular, pulmonary disease or diabetes mellitus
    - Cerebral vascular disease, such as cerebral ischemia, infarction, hemorrhage, or embolus

15. Pregnancy or lactation (must have a negative urine pregnancy test at baseline). Women of childbearing potential must maintain effective contraception during the study period as judged by the investigator

16. Current treatment with phenytoin, warfarin (or other vitamin K antagonists), ketoconazole, itraconazole, cisapride and systemic corticosteroids

17. Any condition, which, in the opinion of the investigator, may interfere with the evaluation of the study objectives

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

PPI other than esomeprazole and H_2RA are not allowed during the study.

5.2 Subject enrolment and randomisation and initiation of investigational product

The Principal Investigator will:

1. Screen endoscope diagnosed CG patients with GerdQ questionnaire. The patients with GerdQ ≥ 8 are potential subjects.

2. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

3. Assign potential subject a unique enrolment number, beginning with 'E#'.

4. Determine subject eligibility. See Sections 4.1 and 4.2

5. Assign eligible subject unique randomisation code (subject number), beginning with '#'. The subjects will be randomized into two treatment groups, one is 8 weeks treatment regimen group, the other is 2 weeks treatment regimen group.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

5.2.1 Procedures for randomisation

The randomization will be performed by a computer equally for the two treatment regimens. Each centre will be provided with sealed treatment code envelopes corresponding to a list of patient randomization numbers. Randomization numbers will be assigned strictly sequentially as subjects become eligible for randomization.When a subject is allocated to a specified randomization number, the corresponding code envelope will be opened to identify the allocated treatment regimen (8 weeks or 2 weeks treatment regimen).

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

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

Where subjects that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

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

5.4 Blinding and procedures for unblinding the study

Blinding was not performed in this study (reasons given in Section 3.2).

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Esomeprazole	20 mg tablets	Astrazeneca AB, Sweden

All investigational products should be kept in a secure place under appropriate storage conditions. Esomeprazole is stored at room temperature, <30ºC.

5.5.2 Doses and treatment regimens

Patients will be randomized into below two groups at the Visit 2.

8 weeks treatment regimen group:

Patients will receive 8 weeks esomeprazole 20 mg qd treatment, if symptom relieved (defined as no more than one day with mild symptoms of GERD during the previous 7 days), they will receive another 24 weeks on-demand maintenance treatment. The first drug dispensing during maintenance phase is the time of first relapse, which is defined as patients' symptom recur, go to consult investigators and need treatment in the opinion of investigator. The following on-demand drugs will be dispensed at Visit 5 and 6 if the first relapse happened before Visit 5. Patients will be instructed to "Take one tablet daily if needed for relief of your reflux symptoms for at least 3-5 days. Stop taking the tablets when your symptom is adequately controlled."

During 24 weeks on-demand maintenance treatment period, 14 tablets esomeprazole will be dispensed at each scheduled visit. If it is not enough before next scheduled visit, patients can

go to the study center to get extra drugs. If they do not have symptoms recur, and just come to get on-demand drugs, it is not considered as unscheduled visit.

2 weeks treatment regimen group:

Patients will receive 2 weeks esomeprazole 20 mg qd treatment, if symptom relieved, they will enter 24 weeks follow-up period. During the followed up period, if the patients' symptom recur and need treatment in the opinion of investigator, they will be given another 2-week esomeprazole 20 mg qd recurrent treatment. There is no limitation for the times of recurrent treatment in the 24-week follow up period.

Study medication should be taken once daily in the morning with a glass of water.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- Study code
- Enrolment code
- Number of product
- Dosage form, route of administration, number of doses
- Visit no
- For clinical study use only
- Dosing directions
- Dr……(to be filled in by hospital staff)
- Expiry date: dd-mm-yy
- Store at room temperature <30°C
- Keep out of reach of children
- AstraZeneca Pharmaceuticals,

5.5.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions, room temperature < 30°C.

5.6 Concomitant and post-study treatment(s)

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form. On enrolment into the study, patients should stop any current GERD/anti-reflux medication for at least 2 weeks.

Following completion of the study, patients will be treated at the discretion of the investigator.

5.7 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of the Case Report Form (CRF).

5.7.1 Accountability

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

Subject compliance with study drug dosing will be determined by tablet count. At Visit 2 and 3, 5, 6 (Visit 3, 5, 6 only for 8 weeks treatment regimen group) and unscheduled visit, the subject will be dispensed the study medication. The subject will be asked to bring all unused medication at the subsequent visit. The investigator, or delegate, will count and record the amounts of the remaining study drug in the CRF. The investigator, or delegate, will ask the subjects about discrepancies in the drug count or the study drug prescribed, and the explanation will be recorded in the CRF.

At Visit 7 or at premature withdrawal, the subjects will be asked to return all remaining investigational products dispensed at the prior visit, to the investigator. Study site personnel will account for all received study drugs and return all unused study drugs to Astrazeneca for destruction.

Documentation of amounts of study drugs delivered, returned and destroyed and how these procedures are carried out will be made.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol
- Development of any study exclusion criteria

Patients with persisting symptoms after the 8 weeks treatment in 8 weeks treatment regimen group or 2 weeks treatment in 2 weeks treatment regimen group will be withdrawn from the study and treated according to the clinical routines.

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); diary cards, questionnaires and study drug should be returned by the subject. If possible, the subject should return for a clinic visit at the time of or soon after discontinuation of the study to have the following assessments made:

- SAEs and DAEs assessments
- Concomitant medication review
- GerdQ assessment
- Patient satisfaction assessment
- Drug accountability

5.9 Withdrawal from study

Subject will be withdrawn from study if discontinuation of investigational product.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The investigator will ensure that data are recorded on the paper Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed paper Case Report Forms. A copy of the completed paper Case Report Forms will be archived at the study site.

6.2 Data collection and enrolment

At enrolment, below data will be collected:

- Age, sex and race
- Standard/significant medical and surgical history
- Physical examination and vital signs
- Blood sample for standard clinical chemistry and haematology, urine sample for urinalysis
  - Clinical chemistry: AST, ALT, creatinine, BUN
  - Haematology: Haemoglobin, leukocyte and thrombocyte counts
  - Urinalysis: pH, protein, erythrocyte, leukocyte and additional urine analyses.
- Pregnancy test
- GerdQ score
- Hp infection status (diagnosed with ^{13}C-urea breath test (UBT), rapid urease test or pathologic test)
- Concomitant medication

6.2.1 Follow-up procedures

Refer to Study Plan (Table 1 and Table 2) what procedures will be made at each specific follow-up visit.

6.3 Efficacy

The appropriateness of the efficacy measurements and variables in this study are addressed in Section 3.2.

6.3.1 Summary of efficacy objectives and variables

Table 3 shows how the efficacy endpoint of this study relates to the study objective.

Table 3 Efficacy objective and endpoints relating to objective

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
Primary Objective	**Primary variable**	
To compare the symptom control rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients, as evaluated by GerdQ after 24 weeks maintenance treatment/follow up.	The symptom control rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group after 24 weeks on-demand maintenance treatment/ follow up. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ. (ITT, MITT and PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients controlled, Fisher's exact test.
Secondary Objective	**Secondary variable**	
To assess time to first relapse.	Time to first relapse, defined as the time to the patients first come to see the investigator because of symptom recur and need for treatment after 8 weeks or 2 weeks treatment in the two treatment regimen groups. (MITT and PP)	Median and percentiles of time to relapse, if appropriate. Treatment group comparison using Log-Rank test.
To assess symptom control rate after 8 /16 weeks visits in 24 weeks maintenance treatment/follow up period, as evaluated by GerdQ.	The symptom control rate after 8 and 16 weeks on-demand maintenance treatment/ follow up in the two different treatment regimen groups. Controlled patients are defined as patients with all items ≤1in A and C category of GerdQ. (ITT, MITT and PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients controlled, Fisher's exact test.

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
To assess the symptom relief rate after 8 weeks or 2 weeks esomeprazole treatment in the two different treatment regimen groups.	The symptom relief rate after 8 weeks or 2 weeks treatment in the two treatment regimen groups (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days). (ITT)	Summary statistics (number and percentage of patients in each category).
In the 8 weeks treatment regimen group, to compare the symptom relief rate after 2 weeks and 8 weeks treatment	In the 8 weeks treatment regimen group, the symptom relief rate after 2 weeks and 8 weeks treatment (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days). (ITT)	Summary statistics (number and percentage of patients in each category).
To compare the number of unscheduled hospital visit between the two different treatment regimen groups.	The number of unscheduled hospital visit in the two treatment regimen groups. (MITT and PP)	Descriptive statistics (number, mean, median, standard deviation, minimum and maximum). Treatment group comparison of unscheduled hospital visit, two sample t-test.
To measure patient satisfaction in the two different treatment regimen groups.	The proportion of patients satisfied (scores 1-4) or very satisfied (scores 1-2) in the two different treatment regimen groups after 8, 16 and 24 weeks on-demand maintenance treatment/ follow up. (MITT and PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients satisfied and very satisfied, Fisher's Exact test.

6.3.2 Derivation or calculation of outcome variable

Symptom control rate is calculated as the proportion of patients whose symptom controlled at the Week 8, 16 and 24 visits in maintenance treatment or follow-up phase. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ.

Time to first relapse is defined as after 8 weeks / 2 weeks treatment, the time to the patients first come to see the investigator because of symptom recur, and need for treatment. The on-

demand drugs in the 8 weeks treatment regimen group will be dispensed after the first relapse. The average time to first relapse in the two groups will be compared.

Symptom relief is defined as patients with no more than one day mild symptoms of GERD during the previous 7 days. Symptom relief rate is calculated as the proportion of patients whose symptom relieved after 8 weeks and 2 weeks treatment.

Unscheduled hospital visit is calculated as the number of unscheduled hospital visit in 8 weeks treatment regimen and 2 weeks treatment regimen groups.

Patient satisfaction will be measured using a 7-point scale (completely satisfied-1; very satisfied-2; quite satisfied-3; satisfied-4; dissatisfied-5; very dissatisfied-6; completely dissatisfied-7). The patient will fill out the scale at Week 8, 16 and 24 visits in maintenance treatment or follow-up period. The proportion of patients satisfied (scores 1-4) or very satisfied (scores 1-2) will be calculated.

6.4 Safety

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

6.4.1 Definition of adverse events

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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs. Regarding non-serious AEs, in this study only non-serious AEs leading to discontinuation of IP (DAEs) will be collected.

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening

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

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of SAEs/ DAEs

Time period for collection of SAEs/ DAEs

SAEs will be captured from time of signature of informed consent. DAEs will be captured from time of first dose of IP, throughout the treatment period and including the follow-up period in 2 weeks treatment regimen group.

Follow-up of unresolved SAEs/ DAEs

Any SAEs and DAEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing SAEs/DAEs at the end of the study, if judged necessary.

Variables

The following variables will be collect for each SAE and DAE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity (mild, moderate, severe) or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*

- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

SAEs/ DAEs based on signs and symptoms

All SAEs and DAEs spontaneously reported by the subject or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and

there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

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

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 4 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	4	1	4
	Haematology	2	1	2
Total		6	2	6

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of according to local laboratory standardized process after analyses.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics Review

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

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

AstraZeneca will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the National Co-ordinating Investigator and AstraZeneca.

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

The amendment should be approved by each Ethics Committee before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, 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 will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilised.

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

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

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual 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 medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

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

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

10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by AstraZeneca Data Management Centre staff.

When the completed paper Case Report Forms have been scanned and indexed, the data are entered into the study database and proofread.

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

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

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

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

The calculation or derivation of efficacy variable(s) is described in section 6.3.2.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

Efficacy endpoints will be analyzed by randomized treatment and safety endpoints will be analyzed by the actual treatment received. MITT population will be used as the primary analysis population to observe the symptom control rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group after 24 weeks maintenance treatment/ follow up.

12.1.1 Efficacy analysis set

Analysis on efficacy endpoints will be performed for intention to treat (ITT) population and modified intention to treat (MITT) population. ITT is defined as all randomized subjects who have taken at least one dose of trial treatment. MITT is defined as patients in ITT population whose symptoms relieved after 8 weeks or 2 weeks esomeprazole treatment. Efficacy analysis will also be repeated in per protocol (PP) population defined as all ITT subjects without significant protocol violations/deviations. Detailed criteria and identification of the Per Protocol population will be decided in the statistical analysis plan prior to database lock.

12.1.2 Safety analysis set

Analysis on safety endpoints will be performed for subjects who take at least one dose of the trial treatment and for whom post-dose data have been collected.

12.2 Methods of statistical analyses

In general, the descriptive statistics (number, mean, median, standard deviation, minimum and maximum) will be performed for continuous variables. The frequency tables (number and percentage of subjects) will be performed for categorical variables. All statistical tests will be two-sided with the 5% level of significance.

12.2.1 Analyses of efficacy endpoints

Analysis on efficacy endpoints will be performed for ITT, MITT and PP population.

Fisher's exact test will be used to assess statistical difference in symptom control rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group. Differences between treatment groups in the proportion of patients very satisfied (scores 1-2) and satisfied (scores 1-4) will also be analyzed using Fisher's exact test. Symptom relief after 8 weeks or 2 weeks treatment will be summarized with number and percentage of patients in each category.

The number of unscheduled hospital visit was compared between treatments using two-sample t-test. Kaplan-Meier method will be used to assess time to first relapse and a log-rank test to provide a comparison of treatment groups.

12.2.2 Analyses of safety endpoints

Analysis on safety endpoints will be performed for patients who take at least one dose of the trial treatment and for whom post-dose data have been collected. Efficacy endpoints will be analyzed by randomized treatment and safety endpoints will be analyzed by treatment received.

12.2.3 Interim analyses

No interim analysis will be performed for this trial.

12.3 Determination of sample size

The primary objective of this study is to compare the symptom control rate in 8 weeks treatment regimen group, and 2 weeks treatment regimen group after 24 weeks maintenance treatment/ follow-up. Since we do not have previous data for the symptom control rate in the two treatment regimens, the sample size was calculated based on clinical experience. With a total of 170 evaluable patients, 85 in the 8 weeks treatment regimen group and 85 in the 2 weeks treatment regimen group, the power would be over 80% to detect a difference of 20% in symptom control rate between two treatment groups at two-sided 0.05 significance level using Fisher exact test, assuming the symptom control rate is around 66% in 2 weeks treatment regimen group and 86% in 8 weeks treatment regimen group (based on data from BU-NEG-0005 study). Considering the PPI response rate is around 70% and drop off rate will be 20%, around 300 patients are needed to be randomised.

12.4 Data monitoring committee

Not applicable in this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician/other physician at the AstraZeneca Research and Development.

Name	Role in the study	Address & telephone number	

13.2 Overdose

Data are limited but single doses of 80 mg esomeprazole oral was uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within**

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

For esomeprazole, limited clinical data on exposed pregnancies are available. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition, or postnatal development. Caution should be exercised when prescribing to pregnant women. Therefore, women participate in the present study must be either non-pregnant or postmenopausal or using a reliable form of contraception.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

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. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

14. LIST OF REFERENCES

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Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A multicenter, randomized, open-label Phase IV study exploring symptom control rate in co-diagnosed NERD and chronic gastritis patients treated with 8 weeks esomeprazole treatment regimen and 2 weeks esomeprazole treatment regimen

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

_____ _____

Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

A multicenter, randomized, open-label Phase IV study exploring symptom control rate in co-diagnosed NERD and chronic gastritis patients treated with 8 weeks esomeprazole treatment regimen and 2 weeks esomeprazole treatment regimen

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AstraZeneca Research and Development site representative

Date
(Day Month Year)

Clinical Study Protocol Appendix B

Drug Substance	Esomeprazole
Study Code	D9612L00127
Edition Number	1.0

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

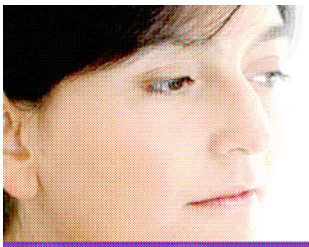
- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Esomeprazole
Study Code	D9612L00127
Edition Number	1.0

Appendix C
GerdQ



GerdQ

Please answer all the questions below. The answers will assist your doctor in finding the best treatment choice to ensure that your life gets back to normal.

Think about *the past seven days...*

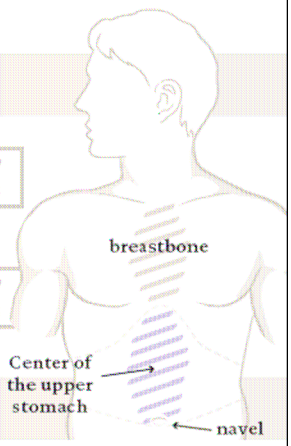
Tick only one box per question

A

Symptoms differ from person to person

1. **How often** did you have a burning feeling behind your breastbone (heartburn)? — 0 DAYS | 1 DAY | 2–3 DAYS | 4–7 DAYS

2. **How often** did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)? — 0 DAYS | 1 DAY | 2–3 DAYS | 4–7 DAYS



B

1. **How often** did you have a pain in the center of the upper stomach? — 0 DAYS | 1 DAY | 2–3 DAYS | 4–7 DAYS

2. **How often** did you have nausea? — 0 DAYS | 1 DAY | 2–3 DAYS | 4–7 DAYS

C

It is important for your doctor to fully understand how your daily life is affected by your symptoms

1. **How often** did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation? — 0 DAYS | 1 DAY | 2–3 DAYS | 4–7 DAYS

2. **How often** did you take additional medication for your heartburn and/or regurgitation other than what the physician told you to take? (such as Tums, Rolaids, Maalox?) — 0 DAYS | 1 DAY | 2–3 DAYS | 4–7 DAYS

Please discuss with your doctor any ways GERD impacts your life

Name _____ *Date* _____

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Esomeprazole
Study Code	D9612L00127
Date	
Protocol Dated	

A multicenter, randomized, open-label Phase IV study exploring symptom control rate in co-diagnosed NERD and chronic gastritis patients treated with 8 weeks esomeprazole treatment regimen and 2 weeks esomeprazole treatment regimen

Sponsor:

Astrazeneca China

Centres affected by the Amendment:

This amendment affects all centres in the study.

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

Add "To compare the success rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients" as secondary objective. Secondary variables are updated accordingly, "The success rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group after 24 weeks on-demand maintenance treatment/ follow up. Success is defined as patients who relieved after 8 weeks or 2 weeks esomeprazole treatment, and also get symptom controlled after 24 weeks maintenance treatment/follow up period." is added.

The number of drug dispensed during 24 weeks on-demand maintenance treatment period is changed from14 tablets to 28 tablets esomeprazole.

Per Protocol population was differentiated as ITT-PP and MITT-PP, defined as all subjects without significant protocol violations/deviations out of ITT, and MITT population respectively.

Section of protocol affected:

2.2 Secondary objectives

Previous text:

2.2 Secondary objectives

- To assess time to first relapse, defined as the time to the patients first come to see the investigator because of symptom recur, and need for treatment after 8 weeks or 2 weeks esomeprazole treatment in the two treatment regimen groups.
- To assess symptom control rate after 8 /16 weeks visits in 24 weeks maintenance treatment/follow up period, as evaluated by GerdQ.
- To assess the symptom relief rate after 8 weeks or 2 weeks esomeprazole treatment in the two different treatment regimen groups.
- In the 8 weeks treatment regimen group, to compare the symptom relief rate after 2 weeks and 8 weeks treatment.
- To compare the number of unscheduled hospital visit between the two different treatment regimen groups.
- To measure patient satisfaction in the two different treatment regimen groups.

Revised text:

2.2 Secondary objectives

- To compare the success rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients. Success is defined as patients who relieved after 8 weeks or 2 weeks esomeprazole treatment, and also get symptom controlled after 24 weeks maintenance treatment/follow up period.
- To assess time to first relapse, defined as the time to the patients first come to see the investigator because of symptom recur, and need for treatment after 8 weeks or 2 weeks esomeprazole treatment in the two treatment regimen groups.
- To assess symptom control rate after 8 /16 weeks visits in 24 weeks maintenance treatment/follow up period, as evaluated by GerdQ.
- To assess the symptom relief rate after 8 weeks or 2 weeks esomeprazole treatment in the two different treatment regimen groups.

- In the 8 weeks treatment regimen group, to compare the symptom relief rate after 2 weeks and 8 weeks treatment.
- To compare the number of unscheduled hospital visit between the two different treatment regimen groups.
- To measure patient satisfaction in the two different treatment regimen groups.

Reason for Amendment:

Relief rate is to evaluate the efficacy of initial 8 week or 2 week treatment, and symptom control rate is to evaluate the efficacy of 24 weeks maintenance treatment/follow up period. Now success rate is added to evaluate the efficacy of whole treatment regimen, it is the combination of relief and control.

Section of protocol affected:

5.5.2 Doses and treatment regimens

Previous text:

8 weeks treatment regimen group:

During 24 weeks on-demand maintenance treatment period, 14 tablets esomeprazole will be dispensed at each scheduled visit. If it is not enough before next scheduled visit, patients can go to the study center to get extra drugs. If they do not have symptoms recur, and just come to get on-demand drugs, it is not considered as unscheduled visit.

Revised text:

8 weeks treatment regimen group:

During 24 weeks on-demand maintenance treatment period, 28 tablets esomeprazole will be dispensed at each scheduled visit. If it is not enough before next scheduled visit, patients can go to the study center to get extra drugs. If they do not have symptoms recur, and just come to get on-demand drugs, it is not considered as unscheduled visit.

Reason for Amendment:

During study operation, we found some patients in 8 week treatment regimen group did not go to the study center to get extra drugs when their drugs used up. They only went to the study center until their symptom recurred. To ensure these patients have drugs and really with on-demand treatment, we decided to increase the number of drugs dispensed at each scheduled visit.

Persons who initiated the Amendment:

Study physician

Section of protocol affected:

6.3.1 Summary of efficacy objectives and variables

Previous text:

Table 1 Efficacy objective and endpoints relating to objective

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
Primary Objective	**Primary variable**	
To compare the symptom control rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients, as evaluated by GerdQ after 24 weeks maintenance treatment/follow up.	The symptom control rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group after 24 weeks on-demand maintenance treatment/ follow up. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ. (ITT, MITT and PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients controlled, Fisher's exact test.
Secondary Objective	**Secondary variable**	
To assess time to first relapse.	Time to first relapse, defined as the time to the patients first come to see the investigator because of symptom recur and need for treatment after 8 weeks or 2 weeks treatment in the two treatment regimen groups. (MITT and PP)	Median and percentiles of time to relapse, if appropriate. Treatment group comparison using Log-Rank test.
To assess symptom control rate after 8 /16 weeks visits in 24 weeks maintenance treatment/follow up period, as evaluated by GerdQ.	The symptom control rate after 8 and 16 weeks on-demand maintenance treatment/ follow up in the two different treatment regimen groups. Controlled patients are defined as patients with all items ≤1in A and C category of GerdQ. (ITT, MITT and PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients controlled, Fisher's exact test.

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
To assess the symptom relief rate after 8 weeks or 2 weeks esomeprazole treatment in the two different treatment regimen groups.	The symptom relief rate after 8 weeks or 2 weeks treatment in the two treatment regimen groups (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days). (ITT)	Summary statistics (number and percentage of patients in each category).
In the 8 weeks treatment regimen group, to compare the symptom relief rate after 2 weeks and 8 weeks treatment	In the 8 weeks treatment regimen group, the symptom relief rate after 2 weeks and 8 weeks treatment (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days). (ITT)	Summary statistics (number and percentage of patients in each category).
To compare the number of unscheduled hospital visit between the two different treatment regimen groups.	The number of unscheduled hospital visit in the two treatment regimen groups. (MITT and PP)	Descriptive statistics (number, mean, median, standard deviation, minimum and maximum). Treatment group comparison of unscheduled hospital visit, two sample t-test.
To measure patient satisfaction in the two different treatment regimen groups.	The proportion of patients satisfied (scores 1-4) or very satisfied (scores 1-2) in the two different treatment regimen groups after 8, 16 and 24 weeks on-demand maintenance treatment/ follow up. (MITT and PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients satisfied and very satisfied, Fisher's Exact test.

Revised text:

Table 2 Efficacy objective and endpoints relating to objective

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
Primary Objective	**Primary variable**	

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
To compare the symptom control rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients, as evaluated by GerdQ after 24 weeks maintenance treatment/follow up.	The symptom control rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group after 24 weeks on-demand maintenance treatment/ follow up. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ. (MITT and MITT-PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients controlled, Fisher's exact test.
Secondary Objective	**Secondary variable**	
To compare the success rate between 8 weeks esomeprazole treatment regimen group and 2 weeks esomeprazole treatment regimen group in co-diagnosed NERD and chronic gastritis patients.	The success rate in 8 weeks treatment regimen group, compared with 2 weeks treatment regimen group after 24 weeks on-demand maintenance treatment/ follow up. Success is defined as patients who relieved after 8 weeks or 2 weeks esomeprazole treatment, and also get symptom controlled after 24 weeks maintenance treatment/follow up period. (ITT, ITT-PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients succeeded, Fisher's exact test.
To assess time to first relapse.	Time to first relapse, defined as the time to the patients first come to see the investigator because of symptom recur and need for treatment after 8 weeks or 2 weeks treatment in the two treatment regimen groups. (MITT and MITT-PP)	Median and percentiles of time to relapse, if appropriate. Treatment group comparison using Log-Rank test.

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
To assess symptom control rate after 8 /16 weeks visits in 24 weeks maintenance treatment/follow up period, as evaluated by GerdQ.	The symptom control rate after 8 and 16 weeks on-demand maintenance treatment/ follow up in the two different treatment regimen groups. Controlled patients are defined as patients with all items ≤1in A and C category of GerdQ. (MITT and MITT-PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients controlled, Fisher's exact test.
To assess the symptom relief rate after 8 weeks or 2 weeks esomeprazole treatment in the two different treatment regimen groups.	The symptom relief rate after 8 weeks or 2 weeks treatment in the two treatment regimen groups (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days). (ITT,ITT- PP)	Summary statistics (number and percentage of patients in each category).
In the 8 weeks treatment regimen group, to compare the symptom relief rate after 2 weeks and 8 weeks treatment	In the 8 weeks treatment regimen group, the symptom relief rate after 2 weeks and 8 weeks treatment (Symptoms relief are defined as no more than one day with mild symptoms of GERD during the previous 7 days). (ITT, ITT-PP)	Summary statistics (number and percentage of patients in each category).
To compare the number of unscheduled hospital visit between the two different treatment regimen groups.	The number of unscheduled hospital visit in the two treatment regimen groups. (MITT and MITT-PP)	Descriptive statistics (number, mean, median, standard deviation, minimum and maximum). Treatment group comparison of unscheduled hospital visit, two sample t-test.

Objective	Summary variables for analysis (including timepoint and population)	Statistical analysis methods or presentation of data
To measure patient satisfaction in the two different treatment regimen groups.	The proportion of patients satisfied (scores 1-4) or very satisfied (scores 1-2) in the two different treatment regimen groups after 8, 16 and 24 weeks on-demand maintenance treatment/ follow up. Patient satisfaction will be measured 7-point scale (completely satisfied-1; very satisfied-2; quite satisfied-3; satisfied-4; dissatisfied-5; very dissatisfied-6; completely dissatisfied-7) (MITT and MITT-PP)	Summary statistics (number and percentage of patients in each category). Treatment group comparison of proportion of patients satisfied and very satisfied, Fisher's Exact test.

Reason for Amendment:

Relief rate is to evaluate the efficacy of initial 8 week or 2 week treatment, and symptom control rate is to evaluate the efficacy of 24 weeks maintenance treatment/follow up period. Now success rate is added to evaluate the efficacy of whole treatment regimen, it is the combination of relief and control.

Persons who initiated the Amendment:

Study physician

Section of protocol affected:

6.3.2 Derivation or calculation of outcome variable

Previous text:

Symptom control rate is calculated as the proportion of patients whose symptom controlled at the Week 8, 16 and 24 visits in maintenance treatment or follow-up phase. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ.

Time to first relapse is defined as after 8 weeks / 2 weeks treatment, the time to the patients first come to see the investigator because of symptom recur, and need for treatment. The on-demand drugs in the 8 weeks treatment regimen group will be dispensed after the first relapse. The average time to first relapse in the two groups will be compared.

Symptom relief is defined as patients with no more than one day mild symptoms of GERD

during the previous 7 days. Symptom relief rate is calculated as the proportion of patients whose symptom relieved after 8 weeks and 2 weeks treatment.

Unscheduled hospital visit is calculated as the number of unscheduled hospital visit in 8 weeks treatment regimen and 2 weeks treatment regimen groups.

Patient satisfaction will be measured using a 7-point scale (completely satisfied-1; very satisfied-2; quite satisfied-3; satisfied-4; dissatisfied-5; very dissatisfied-6; completely dissatisfied-7). The patient will fill out the scale at Week 8, 16 and 24 visits in maintenance treatment or follow-up period. The proportion of patients satisfied (scores 1-4) or very satisfied (scores 1-2) will be calculated.

Revised text:

Success is defined as patients who relieved after 8 weeks or 2 weeks esomeprazole treatment, and also get symptom controlled after 24 weeks maintenance treatment/follow up period.

Symptom control rate is calculated as the proportion of patients whose symptom controlled at the Week 8, 16 and 24 visits in maintenance treatment or follow-up phase. Controlled patients are defined as patients with all items ≤1 in A and C category of GerdQ.

Time to first relapse is defined as after 8 weeks / 2 weeks treatment, the time to the patients first come to see the investigator because of symptom recur, and need for treatment. The on-demand drugs in the 8 weeks treatment regimen group will be dispensed after the first relapse. The average time to first relapse in the two groups will be compared.

Symptom relief is defined as patients with no more than one day mild symptoms of GERD during the previous 7 days. Symptom relief rate is calculated as the proportion of patients whose symptom relieved after 8 weeks and 2 weeks treatment.

Unscheduled hospital visit is calculated as the number of unscheduled hospital visit in 8 weeks treatment regimen and 2 weeks treatment regimen groups.

Patient satisfaction will be measured using a 7-point scale (completely satisfied-1; very satisfied-2; quite satisfied-3; satisfied-4; dissatisfied-5; very dissatisfied-6; completely dissatisfied-7). The patient will fill out the scale at Week 8, 16 and 24 visits in maintenance treatment or follow-up period. The proportion of patients satisfied (scores 1-4) or very satisfied (scores 1-2) will be calculated.

Reason for Amendment:

Relief rate is to evaluate the efficacy of initial 8 week or 2 week treatment, and symptom control rate is to evaluate the efficacy of 24 weeks maintenance treatment/follow up period. Now success rate is added to evaluate the efficacy of whole treatment regimen, it is the combination of relief and control.

Section of protocol affected:

12.1.1 Efficacy analysis set

Previous text:

Analysis on efficacy endpoints will be performed for intention to treat (ITT) population and modified intention to treat (MITT) population. ITT is defined as all randomized subjects who have taken at least one dose of trial treatment. MITT is defined as patients in ITT population whose symptoms relieved after 8 weeks or 2 weeks esomeprazole treatment. Efficacy analysis will also be repeated in per protocol (PP) population defined as all ITT subjects without significant protocol violations/deviations. Detailed criteria and identification of the Per Protocol population will be decided in the statistical analysis plan prior to database lock.

Revised text:

Analysis on efficacy endpoints will be performed for intention to treat (ITT) population, modified intention to treat (MITT) population and per protocol (PP) population, with MITT as the primary analysis population.

ITT is defined as all randomized subjects who have taken at least one dose of trial treatment. MITT is defined as patients in ITT population whose symptoms relieved after 8 weeks or 2 weeks esomeprazole treatment. Efficacy analysis will also be repeated in per protocol (PP) population including ITT-PP and MITT-PP population, defined as all subjects without significant protocol violations/deviations out of ITT and MITT population respectively. Detailed criteria and identification of the Per Protocol population will be decided in the statistical analysis plan prior to database lock.

Reason for Amendment:

Relief rate is to evaluate the efficacy of initial 8 week or 2 week treatment, and symptom control rate is to evaluate the efficacy of 24 weeks maintenance treatment/follow up period. Now success rate is added to evaluate the efficacy of whole treatment regimen, it is the combination of relief and control.

The calculation of relief rate and success rate should be based on ITT population, and symptom control rate on MITT population. Correspondingly, it will make more sense to differentiate PP population as ITT-PP and MITT-PP.

Persons who initiated the Amendment:

Study statistician