Clinical Study Protocol

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The primary symptoms of GERD in Chinese outpatients in Gastroenterology department: A cross-sectional investigation

Sponsor:

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

The primary symptoms of GERD in Chinese outpatients in Gastroenterology department: A cross-sectional investigation

Principal Investigator

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Study site(s) and number of subjects planned

One site

Study period	
Estimated date of first subject enrolled	Aug 2015
Estimated date of last subject completed	Sep 2018

Study design

Cross-sectional investigation

Objectives

Primary Objective:	**Outcome Measure:**
To define the primary symptom of GERD in Chinese outpatients in Gastroenterology department	*The primary symptoms of GERD in Chinese outpatients in Gastroenterology department defined by 24-hour impedance-pH monitoring, upper endoscopy or proton pump inhibitor test.*

Secondary Objective:	**Outcome Measure :**
1. To investigate the symptom distribution of paitents who present with symptoms originated from upper gastrointestinal tract and have pathologic esophageal reflux established by 24-hour impedance-pH monitoring, upper endoscopy, or proton pump inihibitor test. *2. To evaluate the life quality of patients with atypical GERD symptoms (symptoms except heartburning and regurgitation)* *3. To investigate the diagnostic value of proton pump inhibitor trial to diagnose GERD with atypical reflux symptoms* *4. To investigate the predictive value of Gerd Q to diagnose GERD with atypical reflux symptoms with heartburn or regurgitation*	*1. The percentage of each symptom of GERD in the symptom questionnaire in Chinese outpatients in Gastroenterology department* *2. The measurement of SF-36 questionnaire of GERD patients with atypical symptoms before PPI test* *3. The sensitivity and specificity of positive PPI test in patients with atypical reflux symptom* *4. The concordance rate of Gerd Q with 24-hour pH monitoring in GERD patients with atypical reflux symptoms with heartburn or regurgitation*

Target subject population

Consecutive patients aged 18–65 years who go to the gastroenterology clinic presented with upper gastrointestinal discomfort, such as the following symptoms: heartburn, regurgitation, dysphagia, substernal pain, epigastric pain,epigastric burning, early satiety, postprandial fullness.

Duration of treatment

4-8 weeks

Investigational product, dosage and mode of administration

Esomeprazole, 20mg bid, p.o

4-8 weeks

Statistical methods

Assuming the prevalence of GERD is 30%, 400 completed patients provides a precision (half width of 95% CI) of 0.045 for the estimate of two-sided 95% confidence interval of the primary endpoint. All patients underwent upper endoscopy or an ambulatory 24-h pH monitoring. Pathologic esopheal acid reflux was defined as the percentage total time for which a pH value < 4 was >4.2 % in the distal esophagus. Then, patients were treated with esomeprazole 20 mg twice daily for 28 days. The symptom scores were measured by the frequency score multiplied by the severity scores of the predominant symptom before and at the end of the treatment, and the " PPI test " was defined as positive if the overall scores of the predominant dyspeptic symptom in the fourth week decreased by >50 % compared with those of the baseline.

GERD is defined by either 24-hour impedance-pH monitoring or positive PPI test or positive result from endoscopy. The percentage of each symptom of GERD in the symptom questionnaire in Chinese outpatients in Gastroenterology department will be calculated. The symptom of the highest percentage will be the primary symptom.

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1. INTRODUCTION

1.1 Background and rationale for conducting this study

Gastroesophageal reflux disease (GERD) is a condition which develops when the reflux of stomach contents cause troublesome symptoms and/or complication. It is one of the most common gastrointestinal diseases in the West countries and imposes a heavy burden on the population. It was reported that the prevalence of GERD has increased greatly since 1995, particularly in North America and East Asia. GERD has been believed to be a major risk factor for esophageal adenocarcinoma, especially in Barrett's esophagus. Thus it is important to confirm the diagnosis of GERD and give the subsequent therapy for the patient to lower down the risk for esophageal adenocarcinoma.

According to the global consensus issued in 2006, GERD could be diagnosed simply by typical reflux symptoms.Heartburn and acid regurgitaiton are the primary symptoms of gatroesophageal reflux disease. These two symptoms are derived from the studies performed in western countries. And using the 24-hour esophageal pH monitoring as “gold standard”, the sensitivity and specificity of reflux symptoms are moderate. The current prevalence of heartubrn and/or regurgitation in China was 6.2% weekly and there is an increasing trend in the prevalence of GERD. It is reported that the prevalence of GERD is much lower in China than that in other western countries.. This might be due to the diet culture in China, where a lower fat intake is introduced. Another common reason is about the understanding of GERD symptoms. The primary symptom of GERD is heartburn as confirmed in the Montreal consensus, which is defined as the burning sensation in the retrosternal area. However, there is no equivalent word for heartburn in Chinese, many Chinese pateints came to the hospital with the complaint of “burning in the stomache”, thus the questionaire which focus on the

heartburn symptoms would underestimate the prevalence of GERD. The last and also the most important reason might lie in that the symptoms which indicate reflux were different in Chinese population. In other words, heartburn might not be the primary reflux symptom in China. For example, more symptoms oiginated from the upper gastrointestinal tract was described as reflux symptom when patients went to see docotors in China. According to the investigation in our own center, about one third of dyspepsia patients without reflux syptoms presented pathologic esophageal acid reflux in our clinic. Thus heartburn was not understood as well as in other western countries, the symptoms of GERD might distribute differently in China compared to other western countries. So it is necessary to investigate the primary symptoms and spectrum of GERD in Chinese population in order to better define and diagnose GERD.

1.2 Rationale for study design, doses and control groups

The symptom spectrum of GERD has been studied in the western population using the 24-hour esophageal pH monitoring as the gold standard, heartburn and regurgitation has been advocated as the primary symptoms of GERD according to these studies. However, the current studies on GERD in China referred to these western studies and took it for granted that heartburn and regurgitation were also the primary symptoms of GERD. Our clinical practise indicated that a lot of Chinese patients who came to the hospital seeking for therapy of symptoms originated from the upper GI tract including epigastric pain, epigastric burning sensation et al turned out to be GERD. Thus the primary symptoms of GERD might differ from that in the western counties. It is necessary to find out the primary symptoms and symptoms spectrum in Chinese population, which might be useful in our clinical management.

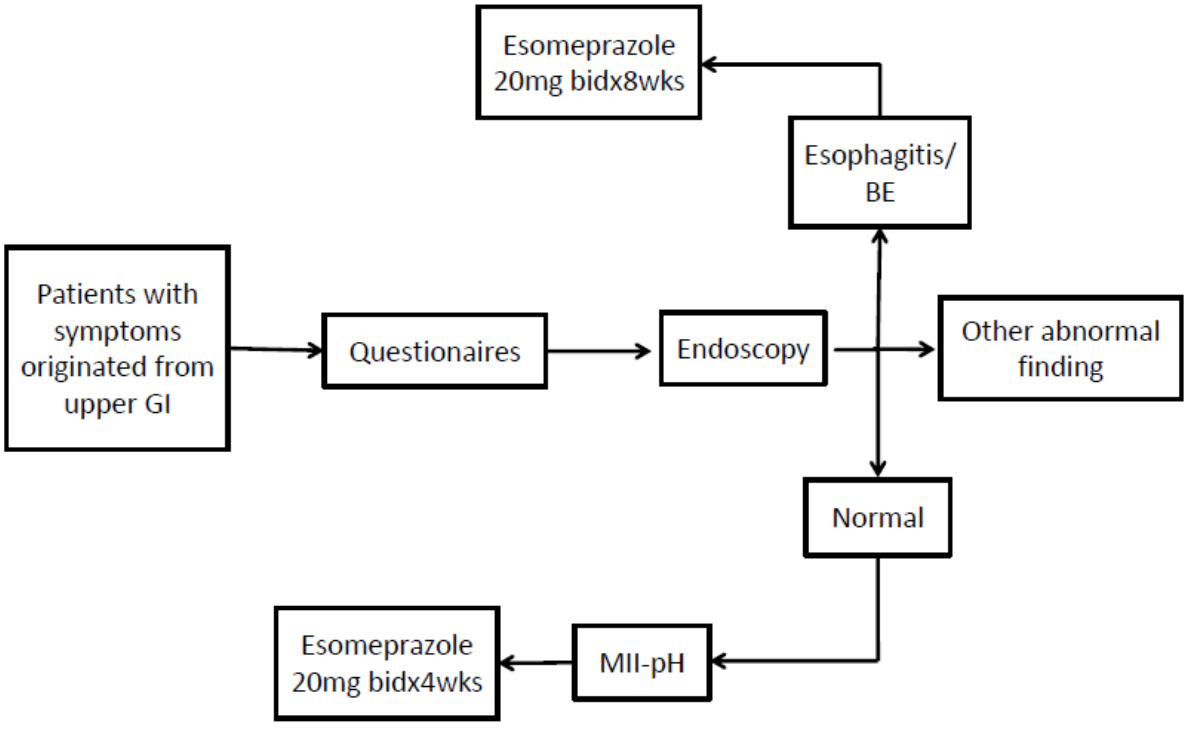
All the included patients who do not have positive finding during 24 hour esophageal pH monitoring would be administered with esomeprazole 20mg bid for 4 weeks which would be a complement for GERD diagnosis of pH monitoring.

Benefit/risk and ethical assessment

The study might be helpful in the understanding of symptom spectrum of GERD in Chinese population and promote the GERD study in China. There won't be any risk and ethical issue in the current study.

1.3 Study Design

Figure 1 Study flow chat



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To define the primary symptom of GERD in Chinese outpatients in Gastroenterology department	*The primary symptoms of GERD in Chinese outpatients in Gastroenterology department defined by 24-hour impedance-pH monitoring,upper endoscopy or proton pump inhibitor test.*

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure :**
1. To investigate the symptom distribution of paitents who present with symptoms originated from upper gastrointestinal tract and have pathologic esophageal reflux established by 24-hour impedance-pH monitoring, upper endoscopy or proton pump inihibitor test. *2. To evaluate the life quality of patients with atypical GERD symptoms (symptoms except heartburning and regurgitation)* *3. To investigate the diagnostic value of proton pump inhibitor trial to diagnose GERD with atypical reflux symptoms* *4. To investigate the predictive value of Gerd Q to diagnose GERD with atypical reflux symptoms with heartburn or regurgitation*	*1. The percentage of each symptom of GERD in the symptom questionnaire in Chinese outpatients in Gastroenterology* *department* *2. The measurement of SF-36 questionnaire of GERD patients with atypical symptoms before PPI test* *3. The sensitivity and specificity of positive PPI test in patients with atypical reflux symptom* *4. The concordance rate of Gerd Q with 24-hour pH monitoring in GERD patients with atypical reflux symptoms with heartburn or regurgitation*

2.3 Safety objectives

NA

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

The study will be done in the outpatient clinic, department of Gastroenterology, first affiliated hospital, sun yet-sen university.

3.1 Inclusion criteria

1. Consecutive patients aged 18–65 years who go to the gastroenterology clinic presented with upper gastrointestinal discomfort, such as the following symptoms: heartburn, regurgitation, dysphagia, substernal pain, epigastric pain, epigastric burning, early satiety, postprandial fullness.

2. The previous symptoms should last for at least 3 months.

3. The frequency of the previous symptoms should be at least 3 days per weekwith at least moderate.

4. All the previous symptoms would be evaluated in the questionaires (see attachment).

3.2 Exclusion criteria

1.Patients with gastric or duodenal ulcers, upper GI neoplasms on upper endoscopy

2.Patients with severe cardiac or pulmonary diseases, diabetes or rheumatic diseases

3.Patients with a history of operations in the upper GI tract

4.Patients with renal failure or abnormal liver function

5. Patients with use of non-steroidal anti-inflammatory drugs (NSAIDs)

6. Patients who are allergy to esomeprazole

7. Pregnancy or lactating mother

3.3 Subject enrolment and randomization

Consecutive patients who met the inclusion criteria in the Gastroenterology clinic in the first affiliated hospital will be enrolled in the study. There will not be any randomization in the study.

3.4 Methods for assigning treatment groups

All the patients who were endoscopy negative, with esophagatitis or Barrett's esophagus would be given esomeprazole 20mg bid for 4- 8 weeks.

3.5 Methods for ensuring blinding

Not applicable. This is a cross-sectional study.

3.6 Criteria for withdrawal

Patients would be withdraw from the current study if their symptoms do not meet the inclusion criteria, they could no tolerate any procedure of the study, they could not finish the esomeprazole therapy part.

3.7 Discontinuation of the study

Those patients who had not symptom relief after four weeks of esomeprazole would discontinue this study.

4. STUDY PLAN AND TIMING OF PROCEDURES

The study includes screening and treatment period. The screen period would be 7 days, during this stage all the procedure including questionaires, upper endoscopy and MII-pH monitoring need to be finished. The treatment period would be 4 to 8 weeks according to the findings under upper endoscopy. For patients with esophagitits, this period would be 8 weeks; for patients with normal findings, this period would be 4 weeks.

Table 1 Study Plan detailing the procedures for patients with esophagitis

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit window Days –7 to 0 for Visit 1 ±0 day for Visit 2 ±1 day for Visits 3 and 4 ±5 days starting at Visi t 5	**Screening**						
Week		**0**	**1**	**2**	**4**	**8**	**12**
Day	**-**	**0**	**7**	**14**	**28**	**56**	**84**
Written informed consent *(including tissue samples, pharmacogenetics*)	X						
Demographics	X						
Physical examination, height, and weight	X						
Medical/surgical history	X						
Inclusion/exclusion criteria	X	X					
Treatment dispensed/returned		X					X
Concomitant medication	X	X	X	X	X	X	X
GERD questionaire		X	X	X	X	X	X

Table 2 Study Plan detailing the procedures for endoscopy negative patients

Visit	**1**	**2**	**3**	**4**	**5**	**6**
Visit window Days –7 to 0 for Visit 1 ±0 day for Visit 2 ±1 day for Visits 3 and 4 ±5 days starting at Visit 5	**Screening**					
Week		**0**	**1**	**2**	**4**	**8**
Day	**-**	**0**	**7**	**14**	**28**	**56**
Written informed consent *(including tissue samples, pharmacogenetics*)	X					
Demographics	X					
Physical examination, height, and weight	X					
Medical/surgical history	X					
Inclusion/exclusion criteria	X	X				
Treatment dispensed/returned		X				
Concomitant medication	X	X	X	X	X	X
GERD questionaire		X	X	X	X	X

4.1 Enrolment/screening period

Seven days

4.2 Treatment period

Four to eight weeks

4.3 Follow-up period

Four weeks

5. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

5.1 Definition

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

The term AE is used to include both serious and non-serious AEs.

Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (i.e., 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/incapacity or substantial disruption of the ability to conduct normal life functions
- 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.

Adverse Drug Reaction (ADR)

An ADR is a response to a medicinal product which is noxious and unintended. A response in this context means that a causal relationship between the medicinal product and an AE is at least a reasonable possibility.

5.2 Reporting of Serious Adverse Events

Investigators are responsible for meeting all regulatory reporting requirements.

The investigator should report SAEs associated with AstraZeneca study drug Esomerprozole to AstraZeneca Patient Safety data entry site within 24 hours of initial awareness, whether or not considered causally related to the AstraZeneca investigational product.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigator should inform AstraZeneca of any follow-up information on a previously reported SAE within one calendar day when he or she becomes aware of it.

5.3 Reporting of Non-serious Adverse Drug Reactions

All non-serious ADRs which are suspected to be related to AstraZeneca investigational Product should be reported to AstraZeneca.

If any non-serious ADR occurs in the course of the study, the investigator should report it to AstraZeneca Patient Safety data entry site within 24 hours of initial awareness.

AstraZeneca Patient Safety data entry site contact information:

E-mail: AEMailboxClinicalTrialTCS@astrazeneca.com

6. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

Esomeprazole MUPS, 20 mg, bid, Astrazeneca, 4- 8 weeks

7. STATISTICAL ANALYSES

7.1 Sample size estimate

Assuming the prevalence of GERD is 30%, 400 completed patients provides a precision (half width of 95% CI) of 0.045 for the estimate of two-sided 95% confidence interval of the primary endpoint..

7.2 Definitions of analysis sets

7.2.1 Efficacy analysis set

All the patients complete the study per protocol.

7.3 Outcome measures for analyses

Pathologic esopheal acid reflux was defined as the percentage total time for which a pH value < 4 was >4.2 % in the distal esophagus. Then, patients were treated with esomeprazole 20 mg twice daily for 28 days. The symptom scores were measured by the frequency score multiplied by the severity scores of the predominant symptom before and at the end of the treatment, and the " PPI test " was defined as positive if the overall scores of the predominant dyspeptic symptom in the fourth week decreased by >50 % compared with those of the baseline. GERD is defined by 24-hour impedance-pH monitoring, upper endoscopy or positive PPI test.

7.4 Methods for statistical analyses

7.4.1 Analysis of the primary variable(s)

The percentage of each symptom of GERD in the symptom questionnaire in Chinese outpatients in Gastroenterology department will be calculated. The symptom of the highest percentage will be the primary symptom.

7.4.2 Analysis of the secondary variable(s)

The percentage of each symptom of GERD in the symptom questionnaire in Chinese outpatients in Gastroenterology department will be calculated.

The life quality of GERD patients with atypical symptoms before PPI test will be measured via SF-36 questionnaire.

Receiver operating characteristic (ROC) curves will be constructed to identify the sensitivity and speicificity of either GERD Q or 4-week PPI test against positive 24-hour pH monitoring or positive endoscopy result in GERD patients with atypical reflux symptoms

8. DATA COLLECTION

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator as specified in the Clinical Study Agreement.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), First Affiliated Hospital of Sun Yat-sen University should be prospectively notified. The study records must be transferred to a designee acceptable to First Affiliated Hospital of Sun Yat-sen University, such as another investigator, another institution, or to an independent third party arranged by First Affiliated Hospital of Sun Yat-sen University. The investigator must obtain written permission from

First Affiliated Hospital of Sun Yat-sen University before disposing of any records, even if retention requirements have been met.

9. ETHICS

9.1 Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

9.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to study sites.

9.3 Subject information and Informed consent

All parties will ensure protection of subject personal data and will not include subject names on any forms, reports, publications, or in any other disclosures, except where required by laws.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB/IEC before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

10. LIST OF REFERENCES

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