Clinical Study Protocol

Drug Substance	D961H
Study Code	D961HC00002
Date	
Edition	1

A multicentre, randomised, double-blind, parallel-group, comparative study to compare the efficacy and safety of D961H 20 mg and 40 mg once daily oral administration with omeprazole 20 mg once daily oral administration in patients with reflux esophagitis

Sponsor:

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

Amendment No.	Date of Amendment

Administrative Change No.	Date of Administrative Change

PROTOCOL SYNOPSIS

A multicentre, randomised, double-blind, parallel-group, comparative study to compare the efficacy and safety of D961H 20 mg and 40 mg once daily oral administration with omeprazole 20 mg once daily oral administration in patients with reflux esophagitis

Investigator

[redacted]

Study centre(s) and number of subjects planned

This study will be conducted in approximately 555 randomised subjects recruited from about 70 centres [redacted]

Study period		**Phase of development**
Estimated date of first subject enrolled	December 2007	Phase III (Therapeutic confirmatory)
Estimated date of last subject completed	March 2009	

Objectives

Primary objective

The primary objective of this study is to evaluate the efficacy of D961H 20 mg once daily (D20) and 40 mg once daily (D40) for 8 weeks on healing of RE in patients with reflux esophagitis (RE) in comparison with omeprazole 20 mg once daily (O20) by assessment of presence/absence of RE at Week 8 according to the Los Angeles (LA) classification (Lundell LR, et al., 1999).

Secondary objectives

The secondary objectives are as follows:

- To evaluate the efficacy of D20 and D40 on healing of RE in comparison with O20 by assessment of presence/absence of RE at Week 4 according to the LA classification.

- To evaluate the efficacy of D20 and D40 on gastroesophageal reflux disease (GERD) symptoms in comparison withO20 by assessment of presence/absence and severity of the patient-reported symptoms.

- To evaluate the effect of D20, D40 and O20 on the health related quality of life (HRQOL) by assessment of HRQOL using "Quality of Life in Reflux and Dyspepsia patients (QOLRAD)".

- To evaluate the safety and tolerability of D20, D40 and O20 by assessment of adverse events (AEs), laboratory test values and vital signs (blood pressure and pulse rate).

Study design

This is a multicentre, randomised, double-blind, double dummy, parallel-3 group study on the patients with RE.

Target subject population

Male and female patients aged 20 years or over with RE endoscopically verified Grade A, B, C or D by LA classification within 1 week prior to initiation of the investigational product administration. At least 100 patients with grade C or D RE according to LA classification will be enrolled.

Investigational product, dosage and mode of administration

In this study, the following products will be used.

- D961H capsule 20 mg

  One capsule of D961H capsule 20 mg and 2 tablets of omeprazole tablet placebo will be orally administered once daily after breakfast for a maximum of 8 weeks in patients randomised into the D20 group.

- D961H capsule 40 mg
  One capsule of D961H capsule 40 mg and 2 tablets of omeprazole tablet placebo will be orally administered once daily after breakfast for a maximum of 8 weeks in patients randomised into the D40 group.

Comparator, dosage and mode of administration

- Omeprazole tablet 10 mg
  Two tablets of omeprazole tablet 10 mg and 1 capsule of D961H capsule placebo will be orally administered once daily after breakfast for a maximum of 8 weeks in patients randomised into the O20 group.

Duration of treatment

A maximum of 8 weeks

Outcome variables

– **Efficacy**

– **Primary outcome variable:**

- Presence/absence of RE at Week 8 according to LA classification

– **Secondary outcome variables:**

[Healing of RE]
- Presence/absence of RE at Week 4 according to LA classification.

[GERD symptoms]
- Time to sustained resolution of each GERD symptom (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of that symptom).
- Time to sustained resolution of all GERD symptoms (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of all symptoms).
- The proportion of subjects without each GERD symptom during the 7 days preceding visits at Week 1, 2, 4 and 8.
- The proportion of subjects without each GERD symptom or with 'Mild' GERD symptoms up to 1 day during the 7 days preceding visit at Week 1, 2, 4 and 8.

[Patient reported outcomes (PROs)]
- QOLRAD

– **Safety**

- AEs

- Laboratory test values

- Vital signs (blood pressure, pulse rate)

Statistical methods

The healing rate of RE at Week 8 and its two-sided 95% confidence interval will be calculated for each group. The difference in healing rates between the D40 group and O20 group (D40 group – O20 group) and that between the D20 group and O20 group (D20 group – O20 group) as well as respective two-sided 95% confidence intervals will be obtained. It is concluded that the non-inferiority of D40 to O20 is verified if the lower limit of the two-sided 95% confidence interval of the difference between D40 group and O20 group exceeds -10%. If the non-inferiority of D40 to O20 is verified, verification of the non-inferiority of D20 to O20 will be investigated similarly. The healing rates at Week 8 will be compared between D40 group and O20 group and between D20 group and O20 group using Cochran-Mantel-Haenszel test

stratified by the baseline LA classification or CYP2C19 genotype. In these comparisons, the significant level will not be adjusted.

For safety variables, quantitative data will be summarised for each treatment group using descriptive statistics and qualitative data will be summarised for each treatment group using a frequency table.

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[redacted] [redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.7.1.1)
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamic pyruvic transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
CK (CPK)	Creatine kinase (Creatine phosphokinase)
COX-2	Cyclooxygenase-2
CYP	Cytochrome P450
D20	D961H 20 mg once daily
D40	D961H 40 mg once daily
ECRF	electronic Case Report Form
EGD	Esophagogastroduodenoscopy
EM	Extensive Metaboliser
FAS	Full Analysis Set
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
γ-GTP	γ-Glutamyltranspeptidase
HIV	Human Immunodeficiency Virus
Hp	*Helicobacter pylori*
HRQOL	Health related quality of life
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
Investigator(s)	Principal investigators and sub-investigators in this protocol
LA	Los Angeles
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
O20	Omeprazole 20 mg once daily

Abbreviation or special term	Explanation
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.7.1.1).
PM	Poor Metaboliser
PPS	Per Protocol set
PRO	Patient reported outcomes
Principal investigator	A person responsible for the conduct of a clinical study at a study site. Every study site has a principal investigator.
QOLRAD	Quality of Life in Reflux and Dyspepsia
RE	Reflux esophagitis
SAE	Serious adverse event (see definition in Section 4.7.1.1).
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Reflux esophagitis (RE) is a disease that causes mucosal damage in the esophagus due to reflux of gastric acid. The incidence of RE is sharply increasing in Japan along with the aging of society, Westernization of dietary life and increase in the prevalence of obesity. Marked adverse influence on the health-related quality of life (HRQOL) is observed in the patients with RE due to the symptoms of epigastric pain and acid regurgitation including the heartburn that is the primary symptom of gastric acid reflux.

For the treatment of this disease in Japan, H_2 receptor antagonist was approved in 1982. Subsequently in 1991, proton pump inhibitor (PPI) whose action to inhibit gastric acid secretion is superior to H_2 receptor antagonist was approved. Omeprazole is a PPI that is extensively used in clinical practice in Japan and abroad. Its efficacy and safety have been evidenced in the initial treatment of RE as well as in the maintenance treatment against the recurrence and relapse after the initial treatment.

D961H (generic name: esomeprazole) is a PPI and is the S-enantiomer of racemate omeprazole. Its features are as follows:

- The metabolic rate by cytochrome P450 (CYP) isoform, CYP2C19, is lower than that of omeprazole the impact of genetic effect is less pronounced than for omeprazole.
- The first pass effect in the liver is less than omeprazole.
- The inter-individual variation in antisecretory effect is less than omeprazole.

D961H has a low systemic toxicity after repeated oral administration to rats and dogs. All findings noted have also been seen after treatment with omeprazole. Results of the reproductive and genetic toxicity tests for D961H did not indicate a risk to humans. Exposure to D961H in animals in the toxicology studies was sufficient to support an adequate margin of safety for clinical use.

In overseas clinical studies to assess pharmacokinetics, D961H was rapidly absorbed with maximal plasma concentration (C_{max}) reached within 1 to 2 hours after oral administration to humans. A bioavailability was 64% after a single dose of 40 mg and 89% after repeated dosing of 40 mg. The elimination half-life ($t_{½}$) in CYP2C19 extensive metaboliser (EM) was 0.9 hours after a single dose and 1.3 hours after repeated dosing. The metabolic rate of D961H was decreased in patients with severe liver dysfunction, but not decreased in those with mild or moderate liver dysfunction.

Results from overseas clinical studies to examine the drug interaction suggested that D961H inhibit CYP2C19, but not CYP3A4.

In overseas clinical studies to assess the efficacy and safety of D961H, results from Phase I studies (approximately 860 subjects), indicated a more pronounce and sustained acid inhibition than the corresponding dosed of omeprazole. Four initial treatment (up to 8 weeks) studies (SH-QBE-0013/172, SH-QBE-0016/173, SH-QBE-0017/174, SH-QBE-0052/222) were conducted in patients with RE and two maintenance treatment studies (SH-QBE-0014/177, SH-QBE-0015/178) were conducted in patients who had complete healing of their RE in one of the initial treatment studies. In the initial treatment studies, 6709 patients were randomised, and D961H 20 mg once daily and/or 40 mg once daily were compared with omeprazole 20 mg once daily. D961H 40 mg given once daily resulted in higher healing rates than did omeprazole 20 mg once daily for the healing of RE after both 4 and 8 weeks of treatment and the Life Table estimated difference after 8 weeks was significant in study SH-QBE-0013/172 ($p<0.001$) and in study SH QBE 0052/222 ($p=0.0001$). D961H 20 mg and 40 mg once daily provided high healing rates of RE at Week 8 (D961H 20 mg: 89.9-90.6%; D961H 40 mg: 92.2-94.1%). In the maintenance treatment studies, 693 patients were randomised, and 3 doses of D961H - 10 mg, 20 mg, and 40 mg - were compared with placebo. All doses of D961H effectively maintained healing across all grades of Los Angeles (LA) classification (Lundell LR, et al., 1999) of RE and controlled heartburn and other symptoms of GERD (Maintenance of RE Life Table estimated healing rates at Month 6, SH-QBE-0014/177: D961H 10 mg 54.2% [$p<0.001$], 20 mg 78.7% [$p<0.001$], 40 mg 87.9% [$p<0.001$], placebo 29.1%; SH-QBE-0015/178: D961H 10 mg 57.1% [$p<0.001$], 20 mg 93.2% [$p<0.001$], 40 mg 93.6% [$p<0.001$], placebo 29.0%). On the other hand, the frequency of adverse events (AEs) in comparative studies with omeprazole of initial treatment on the healing effect of RE (SH-QBE-0013/172, SH-QBE-0016/173, SH-QBE-0017/174, SH-QBE-0052/222) and placebo controlled studies of maintenance treatment on the maintenance effect of healed RE (SH-QBE-0014/177, SH-QBE-0015/178) were almost the same between D961H and omeprazole group, and D961H and placebo group. In addition, the profile of reported AEs for the maintenance treatment up to 1 year was similar to that seen in the initial treatment. The laboratory variables, such as haemoglobin, serum iron, serum vitamin B_{12}, did not indicate any significant changes over time. Also, the subsequent post-marketing surveillance data in overseas have been the same as safety data resulted from these clinical studies.

In Japan, Phase I single dose study (SH-QBE-0094) and repeated dosing study (SH-QBE-0098) with healthy adult males were conducted. The safety and pharmacokinetics for D961H 10 mg, 20 mg and 40 mg were assessed in the single dose study, and 24-hour intragastric pH monitoring after 5-day administration was conducted in the repeated dosing study to assess the antisecretory effect of D961H. Both the single dose and the repeated dosing were well tolerated. Prospectively compared with data from the study with Caucasian (SH-QBE-0095), the level of pharmacokinetic profiles and antisecretory effect were similar to that in Japanese who has the same genotype as Caucasian. The safety profiles of D961H 10 mg, 20 mg and 40 mg in Caucasian were similar to the one in Japanese.

Based on the above results, the significant efficacy and safety of D961H are also expected in Japan for acid-related gastrointestinal diseases as well as omeprazole.

Approval status of D961H in overseas

D961H for oral use has been approved in more than 95 countries as of August 2006, and its indications are:

- healing of erosive RE and long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD) (adults and 12-18 year old children)
- in combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* (Hp) and treatment of concurrent duodenal ulcers
- treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug (NSAID) therapy
- healing of gastric ulcers associated with NSAID therapy, including selective cyclooxygenase 2 (COX-2) inhibitors
- prevention of gastric and duodenal ulcers associated with NSAID therapy, including selective COX-2 inhibitors, in patients at risk
- treatment of pathological gastric acid hypersecretory conditions including Zollinger-Ellison Syndrome

1.2 Rationale

D961H is the S-enantiomer of racemate omeprazole. Omeprazole has a pronounce and sustained antisecretory effect and has been confirmed as the useful drug for acid-related diseases such as RE. The results of clinical studies conducted abroad indicated that D961H has the same or more clinical effect on RE in comparison with omeprazole, and D961H has been approved abroad for the indication of healing and maintenance treatment of RE same as omeprazole. The results of Phase I clinical studies (SH-QBE-0094, SH-QBE-0098) conducted in Japan showed that D961H was well tolerated. Prospectively compared with data from the study with Caucasian (SHQBE-0095), the level of pharmacokinetic profiles and antisecretory effect were similar to that in Japanese who has the same genotype as Caucasian. The safety profiles in Caucasian were also similar to the one in Japanese. Based on the above results, the significant efficacy and safety of D961H are also expected in Japan for RE. Accordingly, it was considered valid to conduct this clinical study to verify the healing effect as well as safety of D961H in RE using omeprazole as the comparator because omeprazole is extensively used in the initial treatment and maintenance treatment of this target disease and its efficacy and safety have been verified. As in the case of omeprazole, D961H is metabolised by CYP2C19 but D961H is characterised in that the proportion metabolised by CYP2C19 is lower and the influence of genotype is less in comparison with omeprazole. In this regard, it was decided to conduct a genetic test in this clinical study to also investigate the influence of CYP2C19 genotype on the healing effect of D961H and omeprazole in RE.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate the efficacy of D961H 20 mg once daily (D20) and 40 mg once daily (D40) for 8 weeks on healing of RE in patients with reflux esophagitis (RE) in comparison with omeprazole 20 mg once daily (O20) by assessment of presence/absence of RE at Week 8 according to the LA classification.

2.2 Secondary objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of D20 and D40 on healing of RE in comparison with O20 by assessment of presence/absence of RE at Week 4 according to the LA classification.

- To evaluate the efficacy of D20 and D40 on GERD symptoms in comparison with O20 by assessment of presence/absence and severity of the patient-reported symptoms.

- To evaluate the effect of D20, D40 and O20 on HRQOL by assessment of HRQOL using “Quality of Life in Reflux and Dyspepsia patients (QOLRAD)”.

- To evaluate the safety and tolerability of D20, D40 and O20 by assessment of adverse events (AEs), laboratory test values and vital signs (blood pressure and pulse rate).

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

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

This is a multicentre, randomised, double-blind, double dummy, parallel-three group study to evaluate the efficacy and safety of D20, D40 and O20 in patients with RE.

The subjects with RE endoscopically verified grade A, B, C or D by LA classification at the time of screening, that is, within 1 week prior to initiation of the investigational product administration, will be classified based on the LA classification in grade A/B and C/D, and will be randomised to D20 group, D40 group or O20 group at the ratio of 1:1:1 in each group.

Esophagogastroduodenoscopy (EGD) will be done at Week 4 and 8 to find whether RE is healed or not. If the healing is observed at Week 4 in a subject, the subject will complete the study at the time point. The maximum duration of investigational product administration

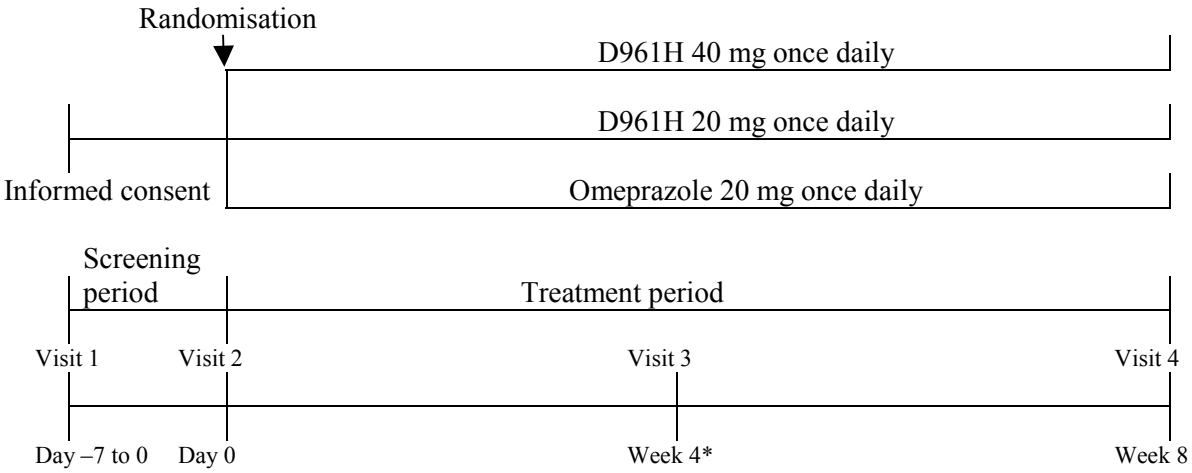
period is 8 weeks. In addition to checking the safety throughout the study period (from the day of informed consent to the day of the last scheduled visit or withdrawal), the GERD symptoms are assessed by subjects themselves using the patient diary. Furthermore, HRQOL is assessed using QOLRAD.

A patient whose RE is healed in this study may be enrolled in the follow-on clinical study (D961HC00006) in which the efficacy and safety of D961H will be assessed on the maintenance of healed RE after the informed consent and the eligibility assessment.

All EGD images of all patients allocated the investigational products during the study period will be reviewed by the central evaluation committee (see Section 6.7) established by AstraZeneca K.K. under the blinded conditions as needed.

Figure 1 and Table 1 present the study flow chart and the schedule of the study.

Figure 1 Study flow chart



* If healing of RE is confirmed in a subject by EGD, the study will be completed in the subject at the time point.

Table 1 Study plan

	Screening		Study Treatment	
		Randomisation		
Visit	**1**	**2**	**3** **Week 4**	**4 (or at discontinuation)** **Week 8**
Days after Visit 2	**-7 to 0**	**0**	**28**	**56**
Time window (days)	**-**	**-**	**±4**	**±4**
Informed consent [1)]	X			
Inclusion/exclusion criteria	X	X		
Demographic data	X			
Medical/surgical history	X			
Underlying diseases	X	X		
Physical examination	X	X	X	X
Vital signs	X		X	X
Clinical laboratory tests [2)]	X		X	X
Pregnancy test (urine) [3)]	X			
Hp test (IgG antibody)	X[6)]			
Genetic test for CYP2C19	X[6)]			
QOLRAD (HRQOL)		X	X[8)]	X[8)]
EGD [4)]	X[7)]		X[9)]	X
Randomisation		X		
Dispense Patient Diary		X	X	
Review/Collect Patient Diary			X	X
Dispense investigational products		X	X	
Review/Collect returned investigational products			X	X
Review treatment compliance			X	X
Check concomitant medications	◄	―	―	►
AEs [5)]	◄	―	―	►

1) Within 3 weeks (21 days) before visit 2 (randomisation).
2) Central laboratory is used for laboratory tests. If the results of test conducted within 2 weeks before randomisation at the laboratory test department of each participating medical institution are available, the

eligibility may be checked using these test values even if obtained before the informed consent. However, the baseline laboratory test values should be determined within 1 week before randomisation at the central laboratory.
3) Conducted in pre-menopausal females with a child-bearing potential.
4) Conducted in fasting condition.
5) As to serious adverse events (SAEs) and AEs resulting in discontinuation, all those that occur after informed consent are recorded in the electronic case report form (eCRF). As to the AEs other than serious or resulting in discontinuation, those that occur from the start of investigational product administration to the day of the last scheduled visit or withdrawal are recorded in eCRF.
6) If it is not possible to conduct it at the time of screening, the test may be conducted at any visit during the treatment period until the discontinuation or completion of this study.
7) If the results of test conducted within 1 week before randomisation are available, these data may be used with the consent of subject even if obtained before informed consent.
8) The subject fills in QOLRAD after receiving EGD.
9) When the healing of RE is verified by EGD, this study is completed.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

Rationale for doses

The relationship between gastric acid inhibitory effect and healing of RE has been demonstrated. In the Japanese Phase I repeated dosing study (SH-QBE-0098), acid inhibitory effects of D961H 10 mg, 20 mg and 40 mg were investigated, and the results showed that there was a great inter-individual variability of acid inhibitory effect of D961H 10 mg, and acid suppression by D961H 10 mg was not sufficient enough especially in homozygote EM. In the overseas studies (SH-QBE-0013/072, SH-QBE-016/173, SH-QBE-0017/174, SH-QBE-0052/222) of initial treatment for RE, the healing rates of RE with D961H 20 mg, 40 mg and O20 mg were investigated. The results showed that in the patients with mild RE classified in grade A or B according to LA classification there is no difference among these dosing groups in the healing rate after 8 weeks from the first administration, but in the patients with severe RE classified in grade C or D the healing rate of D96H 40 mg group is higher than that of D961H 20 mg and omeprazole 20 mg. According to the results of Japanese Phase I study and overseas studies, we considered that an optimal therapeutic dose for Japanese patients with RE would be within the overseas approved dose range, D961H 20-40 mg.

Rationale for setting the length of treatment period

Based on the approved duration of treatment with omeprazole or other PPIs for RE in Japan (8 weeks) as well as the approved duration of treatment with D961H for RE in overseas (4-8 weeks), the treatment period was set to be a maximum of 8 weeks for this study.

Rationale for selecting comparator groups

Omeprazole 20 mg once daily that demonstrates excellent clinical effect on RE and that is extensively used in the daily treatment is selected as the comparator group.

Rationale for a genetic test

As D961H is mainly metabolised by CYP2C19 whose polymorphism is known, the genotype of CYP2C19 is considered to influence the efficacy and safety of D961H. It was decided to

conduct a genetic test in order to evaluate the influence of CYP2C19 genotype on the healing effect of D961H.

Rationale for an Hp test

According to the Hp infection diagnosis and treatment guideline (revised in 2003) by the Japanese Society for Helicobacter Research, GERD including RE is cited as one of the "diseases investigated for the significance of Hp eradication". There is a report (Kuipers EJ, et al., 1996) that the eradication is necessary because PPI aggravated the atrophy of stomach mucosa in Hp-positive GERD patients under long-term treatment with PPI. However, since this report is not supported by Food and Drug Administration, no conclusion has been reached up to present. On the other hand, it was anticipated that Hp eradication could lead to GERD aggravation and Barrett's esophagus increase, increasing the incidence of lower esophageal adenoma (Labenz J, et al., 1997). However, such possibility is considered negligible at present (Befrits R, et al., 2000, Moayyedi P, et al., 2001, Sugiyama T, 2003). Accordingly, further investigation on the relation of Hp infection and eradication to RE is considered necessary. Therefore, it was decided to collect information on the presence or absence of Hp infection in this study.

Rationale for HRQOL

Not only to heal RE but to enhance the degree of satisfaction with the treatment are becoming the important points in the treatment of RE. In this regard, it was decided to collect HRQOL data using QOLRAD (Pace F, et al., 2005) that is extensively used in clinical studies in patients with GERD including RE as self-administered HRQOL investigation card specific to the disease.

Rationale for assessment of GERD symptoms

RE is a disease that causes mucosal damage in the esophagus due to reflux of gastric acid and associated with the symptoms of acid regurgitation, epigastric pain and dysphagia including the heartburn that is the primary symptom of gastric acid reflux. Therefore, it was decided to obtain relevant data to evaluate the GERD symptoms in detail from the patient diary [redacted]

3.2.2 Risk/benefit and ethical assessment

D961H is a proton pump inhibitor (PPI) and is the S-enantiomer of racemate omeprazole.

Omeprazole was approved in Japan on 18 January 1991 for the indication for gastric ulcer, duodenal ulcer, anastomotic ulcer, RE, and Zollinger-Ellison syndrome at a dose of 10 to 20 mg given once daily. Omeprazole has been widely used in the clinical practice and the efficacy and safety of the drug have been well established.

Meanwhile, D961H has not been approved in Japan but it has been approved in more than 95 overseas countries, mainly for the treatment of GERD. The evaluation of the postmarketing surveillance data, after more than 397 million delivered treatment courses (as of 10 August 2006), has not revealed any unexpected safety issues.

In Japan, the tolerability of repeated administration of placebo (18 subjects), D961H 10 mg (24), 20 mg (24) and 40 mg (24) once daily for 5 days was examined in 90 healthy Japanese subjects (SH-QBE-0098). Two AEs (pharyngeal discomfort and epigastric discomfort) were observed in 40 mg group, and one AE (a common cold) was observed in 20 mg group. As all three AEs were of mild intensity and assessed as not related to D961H, it was judged that there is no safety concern about conducting the study.

3.3 Selection of study population

3.3.1 Study selection record

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

3.3.2 Inclusion criteria

For inclusion in the treatment period (subject registration) subjects must fulfil all of the following criteria:

1. Provision of written informed consent (including written informed consent to a genetic test)

2. Male or female with endoscopically verified RE classified into LA classification Grade A, B, C or D within 1 week before randomisation

3. Patients who are able to answer QOLRAD and Patient Diary.

Rationale for inclusion criteria

1. Established as the part of ethics requirements in accordance with 'Good Clinical Practice (GCP).

2. In general, RE is diagnosed by EGD. Since LA classification is the commonly used diagnostic criterion of EGD in the world, and LA classification Grade A to D is classified as RE, the criterion was decided to be used in this study.

3. Established because the answer to QOLRAD and Patient Diary by the patients is necessary for the evaluation of the secondary objectives.

3.3.3 Exclusion criteria

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

1. Male or female aged less than 20 years at the time of informed consent.

2. Patients with current or historical evidence of the following gastrointestinal diseases/conditions:

- Esophageal stricture
- Primary esophageal motility disorder(s), (diffuse esophageal spasm, achalasia)
- Systemic sclerosis (scleroderma)
- Irritable Bowel Syndrome
- Inflammatory bowel disease
- Zollinger-Ellison syndrome
- Malabsorption syndrome

3. Gastric or duodenal ulcer verified by EGD within 12 weeks before randomisation

4. Previous esophageal, gastric or duodenal surgery except simple closure of perforated ulcer

5. Patients with current or a history of significant or unstable:

   - Cardiovascular diseases or cardiac chest pain
   - Cerebrovascular diseases, such as cerebral ischemia, infarction, or haemorrhage
   - Diabetes mellitus uncontrolled on dietary management, exercise therapy or medication
   - Pulmonary, renal, pancreatic or liver diseases or any other serious diseases as judged by the investigator(s) to interfere with the evaluation of the study
   - Hepatic enzymes (AST [GOT], ALT [GPT] or ALP) or total bilirubin is more than or equal to three times of the upper limit of normal within 2 weeks before randomisation.
   - Serum creatinine is greater than 2.0 mg/dL within 2 weeks before randomisation.
   - Malignant disease (except for minor superficial skin disease)
   - Generalised bleeding disorders
   - Any conditions that will require surgery during the study period (from the day of informed consent to the last scheduled visit or withdrawal)

6. Use of any PPI from 14 days before EGD performed at the screening visit to the day of randomisation.

7. Need for continuous concomitant therapy with:

   - PPI (except for the investigational product)
   - H_2 receptor antagonist
   - M_1 receptor antagonist
   - Hp eradication therapy
   - Antacids
   - Anticholinergics used for GI indications
   - Gastrointestinal promotility drugs (eg, metoclopramide)
   - Prostaglandin analogs having the indication of peptic ulcer (eg, misoprostol)
   - Antineoplastic drugs
   - Gastroprotective agents
   - Bisphosphonates (eg, etidronate disodium, alendronate sodium)
   - Steroids (oral, intravenous, suppository)
   - Drugs that are known to induce drug interaction with D961H and/or omeprazole (eg, human immunodeficiency virus [HIV] proteinase inhibitors including atasanavir sulphate, diazepam, phenitoin, warfarin, tacrolimus hydrate, digoxin, methyldigoxin, itraconazole, gefitinib, voriconazole)

8. Endoscopic Barrett's esophagus (3 cm or longer Barrett’s epithelium) or significant dysplastic changes in the esophagus

9. Pregnancy or lactation. Women of childbearing potential must have a negative urine pregnancy test at screening, and maintain effective contraception during the study period as judged by the investigator.

10. Use of any other investigational compounds or participation in another clinical study within 4 weeks before randomisation.

11. Prior randomisation in this study

12. Any significant "alarm symptoms" within the past 24 weeks before randomisation, such as, unintentional weight loss, gastrointestinal bleeding, jaundice, or any other signs indicating serious or malignant disease.

13. Patients with diseases/symptoms such as allergy or sensitivity to PPIs in whom the investigational products are contraindicated

14. Any history of a generalised bleeding disorder resulting from haemorrhagic diathesis (eg, abnormalities in clotting factors or platelets)

15. History of drug addiction or alcoholism within the past 12 months before randomisation

16. Inability to understand or provide informed consent

17. Inability or unwillingness to take the investigational products as instructed

18. Inability to undergo EGD or unwillingness to undergo multiple EGDs.

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

Rationale for exclusion criteria

Since the above underlying diseases, concurrent medications, and conditions may affect evaluation of effects of the investigational products in healing of RE and these exclusion criteria are considered to be necessary for the safety of subjects, these exclusion criteria were established.

3.3.4 Restrictions

Subjects must follow the following restrictions during the study period:

- The subject must fast according to the procedures specified by the study centre before EGD.

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for discontinuation

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

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment

- Safety reasons as judged as the patient to be discontinued by the investigator(s) and/or AstraZeneca KK

- Severe non-compliance to protocol as judged by the investigator(s) and/or AstraZeneca KK
- Incorrect enrolment, ie, the subject does not meet the required inclusion/exclusion criteria for the study
- Subject lost to follow-up
- Occurrence of an event in conflict of exclusion criteria (eg, development of gastric or duodenal ulcer, pregnancy)
- Others as judged appropriate by the investigator(s) (reasons for discontinuation must be recorded in eCRF)

3.3.5.2 Procedures for discontinuation

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

Should protocol led dosing be stopped during the study, the investigator(s) will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. In addition, they will record on the eCRF the date of withdrawal, the reasons, and so on. They will also immediately inform AstraZeneca KK of the withdrawal. Any SAE should be communicated to AstraZeneca KK according to the procedures defined in Section 4.7.1.3.

3.4 Treatments

3.4.1 Identity of investigational products

Formulation, content, and manufacturer of the investigational products are described in Table 2.

Table 2 Investigational products

Investigational products	Formulation and content	Formulation number	Batch number	Manufacturer
D961H capsule 20 mg	Enteric coated capsule containing D961H 22.3 mg with D961H pellets filled into a hard capsule	H 1189-04-01	H 1189-04-01-14	AstraZeneca Sweden Operations Drug Product Supply

Table 2 Investigational products

Investigational products	Formulation and content	Formulation number	Batch number	Manufacturer
D961H capsule 40 mg	Enteric coated capsule containing D961H 44.5 mg with D961H pellets filled into a hard capsule	H 1222-04-01	H 1222-04-01-17	AstraZeneca Sweden Operations Drug Product Supply
D961H capsule placebo	Hard capsules matching with D961H capsule 20 mg and 40 mg	H 0459-06-03	H 0459-06-03-15	AstraZeneca Sweden Operations Drug Product Supply
Omeprazole tablet 10 mg	Enteric tablet containing 10 mg of omeprazole	-	020400	AstraZeneca KK
Omeprazole tablet placebo	Enteric tablet matching with omeprazole 10 mg tablet	-	020010	

Packaging of the investigational product:

Fourteen capsules of D961H (20 mg, 40 mg or placebo) will be packed in a blister pack. Fourteen tablets of omeprazole (10 mg or placebo) will be packed in a blister pack, and 6 blister packs will be packed in an aluminum pillow with desiccant. Six blister packs of D961H capsules and 2 aluminum pillows of omeprazole tablets will be packed in a box for one patient.

3.4.2 Doses and treatment regimens

One D961H capsule and 2 omeprazole tablets will be orally administered once daily after breakfast for 4 weeks or 8 weeks. However, on the days of dispensing the investigational products, patients must be instructed to take the investigational products at any time on the same day. On the days when EGD are conducted (Visits 3 and 4), patients must be instructed to take the investigational products after the completion of the tests.

Table 3 shows combination of the investigational products for each group.

Table 3 Combination of investigational products

	D40	D20	O20
D961H capsule 40 mg	1 capsule	-	-
D961H capsule 20 mg	-	1 capsule	-
D961H capsule placebo	-	-	1 capsule

Table 3 Combination of investigational products

	D40	D20	O20
Omeprazole tablet 10 mg	-	-	2 tablets
Omeprazole tablet placebo	2 tablets	2 tablets	-

3.4.3 Labeling

Each box will be labelled with name of investigational products, study code, batch number, quantity, expiry, storage conditions, randomisation code, attention, name and address of sponsor, 'for clinical study use only'.

3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. Each box will be labelled with appropriate storage conditions. A description of the appropriate storage is also specified in 'Procedures for drug storage'.

3.4.5 Accountability

AstraZeneca KK will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage', which describe the specific requirements.

Investigational product will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca KK. The investigational product provided to the study site must only be used for the purpose and the dosage as directed by the clinical study protocol.

The investigator(s) and/or the Investigational Product Storage Manager must instruct the subject to return unused investigational products and used blister packs. The investigator(s) and/or the Investigational Product Storage Manager must also confirm the number of capsules/tablets returned and recorded in the 'Investigational Product Log'. If there is any discrepancy in the number of capsules prescribed, administered, and returned, the investigator(s) or the study coordinator must confirm the reason with the patient and record it in the eCRF. The Investigational Product Storage Manager and the monitor must confirm that all unused and remaining investigational products are returned to AstraZeneca K.K..

The Investigational Product Storage Manager is responsible for managing the unused investigational products and remaining investigational products returned from the patients from distribution to the study site until the return to AstraZeneca KK.

3.5 Method of assigning subjects to treatment groups

Subjects will be classified based on the LA classification in grade A/B and C/D, and randomised to one of the D20, D40 or O20 groups in the proportion of 1:1:1 in each group. A randomisation list will be prepared by the Subject Registration Centre.

The investigator(s) will explain about the study to potential candidates and obtain written informed consent. At the time of informed consent obtained, an Enrolment code will be allocated to each subject at each study site to identify the subject. The Enrolment code (E00XXYYY) is composed of 4 digits (00XX) of centre number and 3 digits (YYY) of consecutive number in order of registration to screening at each study site. For centre number(s), see [redacted]

Prior to randomisation, the investigator(s) will judged eligibility of the subjects who provided informed consent. After confirming the eligibility of the subject who has given his/her consent, the investigator(s) will enter necessary information in the subject registration form and send it to the Subject Registration Centre by facsimile.

The Subject Registration Centre will check the eligibility of the subject and register the subject. The Subject Registration Centre will allocate a Randomisation code to the subject and send the registration confirmation form containing Randomisation code to the investigator(s) and AstraZeneca KK by facsimile.

After obtaining the registration confirmation form from the Subject Registration Centre, the investigator(s) will start administration of the investigational product to the registered subject following the randomisation code written in the registration confirmation form.

The investigator(s) will keep the registration confirmation form sent from the Subject Registration Centre in the investigator's study file (see Section 7.6.5.1).

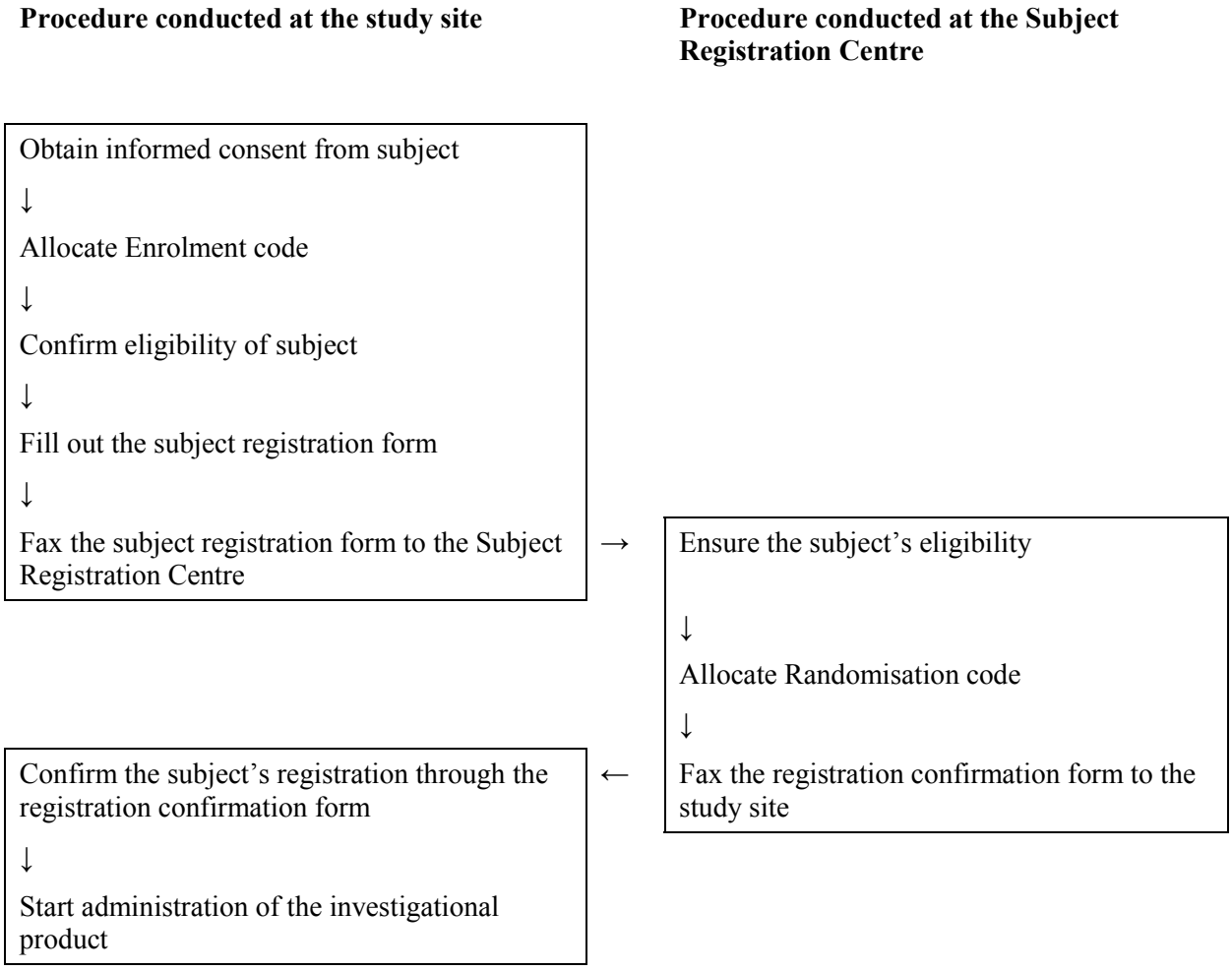
Information on the Subject Registration Centre is given below.

[Subject Registration Centre]

[redacted]

The flowchart for subject registration and prescription of the investigational product is shown in Figure 2.

Figure 2 Flow chart for subject registration and prescription of the investigational product



If a subject discontinues from the study, the enrolment code of the subject will not be reused, and the subject will not be allowed to re-enter the study.

If a Randomisation code is assigned incorrectly, no attempt should be made to remedy the error once investigational products were dispensed. The subject will continue with the allocated randomised code and investigational products. AstraZeneca KK should be notified as soon as the error is discovered. Randomisation of subsequent subjects will continue using the first unallocated Randomisation code in the original sequence.

The investigational product given to individual subjects will be determined by a randomisation schedule. The details of the treatment allocations are described in "Procedures for drug accountability".

At least 100 patients with grade C or D RE according to LA classification will be enrolled. If 455 subjects with grade A/B according to LA classification are allocated, no more subject

with grade A/B according to LA classification will be allocated except for the subject who have already start the screening test.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

The investigational product is a hard capsule filled with enteric coated D961H pellets. The active ingredient content of D961H capsule 20 mg is different from that of D961H capsule 40 but they are indiscriminable in appearance. On the other hand, the comparator is an enteric tablet that contains omeprazole 10 mg as the active ingredient. To maintain the blind feature of these investigational products, the double dummy method is employed in this study. The appearance of D961H capsule placebo and that of omeprazole tablet placebo are indiscriminable from respective active drugs in appearance. Their packages and labels are also indiscriminable from respective active drugs.

It is not planned in this study to conduct interim analysis and data evaluation by the Data monitoring board under blind condition.

3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the investigator(s) and the personnel who are independent to the study evaluation at the Drug Safety Department, AstraZeneca KK.

The treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomisation. The investigator(s) will break the code according to the manual of procedure of emergency key code break provided by AstraZeneca in emergency. AstraZeneca KK retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

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

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

The use of all medications including investigational products and over-the-counter drugs during the study period (from the day of informed consent to the last scheduled visit or withdrawal) must be recorded in the appropriate sections of the eCRF. However, drugs used for pre-treatment of EGD (eg, xylocaine, anticholinergic agents, anti-anxiety agents) will not be recorded in the eCRF.

3.7.1 Allowable concomitant treatments

The following treatments can be used concomitantly during the study period.

- Treatments, which are considered necessary for the subject's safety and well-being

- Drugs used for pre-treatment of EGD (eg, xylocaine, anticholinergic agents, anti-anxiety agents)

3.7.2 Prohibited concomitant treatments

The following drugs and treatments will be prohibited since these may affect interpretation of results of the investigational products or cause general complications (eg, gastrointestinal bleeding).

[Prohibited concomitant treatments within 14 days prior to EGD performed at the screening visit]

- PPI

[Prohibited concomitant treatments after EGD performed at the screening visit]

- PPI (except for the investigational product)
- H_2 receptor antagonist
- M_1 receptor antagonist
- Hp eradication therapy
- Antacids (treatment with antacids for relief of symptoms is allowed until randomisation)
- Anticholinergics used for GI indications (except for agents used for pre-treatment of EGD such as scopolamine butylbromide)
- Gastrointestinal promotility drugs (eg, metoclopramide)
- Prostaglandin analogs having the indication of peptic ulcer (eg, misoprostol)
- Antineoplastic drugs
- Gastroprotective agents
- Bisphosphonates (eg, etidronate disodium, alendronate sodium)
- Steroids (oral, intravenous, suppository)

[Prohibited concomitant treatments during the treatment period]

During the treatment period, the following drugs as well as those in the above “prohibited concomitant treatments after EGD performed at the screening visit” will be prohibited.

- Drugs that are known to induce drug interaction with D961H and/or omeprazol (eg, HIV proteinase inhibitors including atasanavir sulphate, diazepam [except for pre-

treatment of EGD], phenitoin, warfarin, tacrolimus hydrate, digoxin, methyldigoxin, itraconazole, gefitinib, voriconazole)

3.8 Treatment compliance

The investigational product is prescribed every 4 weeks in principle, that is, on Visits 2 and 3. The subjects are instructed to return all unused investigational products and used blister packs on Visits 3 and 4. The quantity of returned investigational product is confirmed to check the compliance status.

If the subject's compliance rate is low due to missing doses, etc, the investigator(s) will instruct the subject to comply with the treatment. Missing doses over 25% will be defined as incompliance.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary variable of this study is presence/absence of RE at Week 8 according to LA classification.

4.2 Screening and demographic measurements

Before performing the screening test, the investigator(s) must obtain written informed consent from the subject, and then will assess whether the subject meets the eligibility criteria (see Sections 3.3.2 and 3.3.3).

The following will be assessed, measured or performed.

Visit 1 (within 1 week prior to randomisation)

- Demographic data (sex, birth date, race, smoking status, alcohol consumption, height, weight)
- Past medical history (eg, a condition which a patient has had in the past and which has been declared cured), surgical history
- Underlying diseases (diseases or symptoms under treatment [including being controlled by treatment]
- Concomitant therapy/drug
- Physical examinations (see Section 4.7.3)
- Vital signs (blood pressure and pulse rate measured in a sitting position)

- Clinical laboratory tests (haematology, biochemistry, urinalysis)
- Urine pregnancy test (only for premenopausal women of childbearing potential)
- Hp test (IgG antibody)
- Genetic test for CYP2C19 (see Section 4.9)
- EGD (see Section 4.6.1.1)

Visit 2 (day of randomisation)

- AEs (all the SAEs and AEs resulting in discontinuation that occur after informed consent are recorded)
- Underlying diseases (those that are currently under treatment and those that do not correspond to the above mentioned SAEs and AEs resulting in discontinuation)
- Concomitant therapy/drug
- Physical examinations
- QOLRAD (see Section 4.3)
- Patient diary (Assessment of baseline GERD symptoms: see Section 4.6.2)

4.2.1 Hp test (IgG antibody)

At screening, blood sample (2 mL) will be collected to measure IgG antibody to determine presence/absence of Hp infection. If not performed at screening, the Hp test may be performed at any visit during the period before the subject withdraw or complete the study. Collection of the samples and the measurement will be performed by [redacted]

4.3 Patient-Reported Outcomes (PRO)

As the patient-reported outcome (PRO), the effect of D20, D40 and O20 on HRQOL is evaluated. QOLRAD is used to investigate HRQOL.

Table 4 shows PRO objectives and outcome variables in this study.

Table 4 PRO objective and outcome variable

Objective	Outcome variable
Secondary objective	
To evaluate the effect of D20, D40 and O20 on HRQOL by assessment of the following.	QOLRAD

4.3.1 QOLRAD

QOLRAD is the self-administered questionnaire specific to the disease and consists of 25 questions about the patients' condition during the latest 7 days that cover 5 dimensions (Emotion, Sleep, Food/drink, Physical/social functioning and Vitality). Each question will be answered in 7 grade scale (1-7) and HRQOL will be assessed by the scores of 25 questions summed up for each 5 dimensions. The bigger the score is, the better HRQOL is. In this study, QOLRAD-J Version 1.40, which is the official Japanese QOLRAD, will be used.

The subjects fill in the QOLRAD on Visits 2 (baseline), 3 and 4. They are asked to complete the QOLRAD after the EGD on Visits 3 and 4.

[redacted] is a sample of QOLRAD.

4.3.2 Administration of PRO

Standardization of procedure for collection of PRO is important. To minimise the bias and enhance the procedure compliance rate, it is preferable to appoint a study coordinator at each site to be responsible for HRQOL evaluation. The study coordinator instructs the subjects the standardized procedure for completing the QOLRAD. The completion method is described in the QOLRAD.

Major cautions for completing the QOLRAD are as follows.

- The questionnaire is completed by the subject himself/herself.
- Only one reply is selected for each question.
- The responses should reflect the patient's perceptions and views rather than those of family, friends, study coordinator, etc.

The study coordinator checks the questionnaire for completeness in order to reduce the amount of missing values. The checked QOLRAD is submitted to the sponsor.

4.4 Health Economic measurements and variables (Not applicable)

4.5 Pharmacokinetic measurements and variables (Not applicable)

4.6 Efficacy and pharmacodynamic measurement and variables

Table 5 shows efficacy objectives and outcome variables.

Table 5 Efficacy objective and outcome variable

Objective	Outcome variable
Primary objective	
To evaluate the efficacy of D20 and D40 for 8 weeks on healing of RE in patients with RE in comparison with O20 by assessment of the following.	Presence/absence of RE at Week 8 according to LA classification
Secondary objective	
To evaluate the efficacy of D20 and D40 on healing of RE in comparison with O20 by assessment of the following.	Presence/absence of RE at Week 4 according to LA classification.
To evaluate the efficacy of D20 and D40 on GERD symptoms in comparison with O20 by assessment of presence/absence and severity of the patient-reported symptoms.	Time to sustained resolution of each GERD symptom (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of that symptom).
	Time to sustained resolution of all GERD symptoms (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of all symptoms).
	The proportion of subjects without each GERD symptom during the 7 days preceding visits at Week 1, 2, 4 and 8.
	The proportion of subjects without each GERD symptom or with 'Mild' GERD symptom up to 1 day during the 7 days preceding visit at Week 1, 2, 4 and 8.

4.6.1 Healing effect of RE according to LA classification

4.6.1.1 EGD

The EGD of esophagus, stomach and duodenum is performed on Visits 1, 3 and 4 in fasting condition.

As to the EGD on Visit 1, if the EGD data within 1 week before randomisation are available, they may be used with the consent of subject even though these are the results of test conducted before informed consent.

The EGD is performed by the method usually employed at each medical institution. The drug used for the pre-treatment of EGD is not recorded in eCRF. However, if other drug is used, the name of drug is recorded in eCRF.

The endoscopic findings in esophagus are scored according to the following LA classification. If the patient is diagnosed as RE, it is to be recorded in the eCRF whether the RE is first-time diagnosis or recurrent. If the RE is recurrent, the date of onset of initial RE is recorded. The presence or absence of esophageal hiatus hernia, Barrett's esophagus (3 cm or longer Barrett's epithelium), esophageal stricture, and gastric and duodenal ulcer is also checked, and the presence or absence of esophageal hiatus hernia is recorded in eCRF.

The subjects who are definitely diagnosed to have RE classified into LA classification Grade A, B, C or D based on the EGD on Visit 1 are registered (randomised). Those detected to have esophageal stricture, Barrett's esophagus (3 cm or longer Barrett's epithelium), and gastric or duodenal ulcer should not be registered (see Section 3.3.3).

LA classification

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

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

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

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

Photo documentation, preferably as colour printouts, is essential as the record of endoscopic images.

For the central review of the grade of LA classification, all EGD images of all patients allocated the investigational products during the study period will be submitted to AstraZeneca K.K.. The personal information (such as the name and the medical record number) which can specify the patient should be masked before submission to AstraZeneca K.K..

4.6.1.2 Method of assessment

When no breaks in the esophageal mucosa are found by EGD, the RE will be judged as "healed". When healing of RE is verified on Visit 3, the subject will complete the study at the time point.

4.6.2 Patient-reported symptoms

4.6.2.1 Patient diary

The patient diary ([redacted] is used to record the presence or absence of GERD symptoms and, if any, the intensity (severity) and frequency of symptoms during the treatment period. The investigator(s) or study coordinator instructs the subject how to complete the patient diary and asks the subject to start the diary from the day of diary distribution (at Visit 2).

The patient diary is distributed to the subjects on the scheduled visit of Visits 2 and 3 and the patient is asked to bring it on the next scheduled visit (Visits 3 and 4). The investigator(s) or study coordinator collects the diary after verifying the completion of diary by the subject as instructed. The collected patient diaries are submitted to the sponsor.

Once a day (preferably at the time of getting up) every day, the subject completes (selects) the replies to the questions about the presence or absence of GERD symptoms and the intensity the day before. However, on the starting day of diary, the subject completes (selects) the replies to the questions about the presence or absence of GERD symptoms during the 7 days before Visit 2, the intensity and frequency for the purpose of baseline symptom assessment.

Questions and replies

Questions:
Presence/absence of GERD symptoms
(Replies on the starting day of diary are for the past 7 days and those on Day 2 onward are for the day before.)

I A burning feeling, rising from the stomach or lower part of the chest towards the neck?

II Flow of sour or bitter fluid into mouth?

III Central upper abdominal pain?

IV Difficulties in swallowing?

Reply choices (the patient selects one of the following 4 grades):

Intensity of GERD symptom

0 No symptom.

1 Awareness of symptoms but easily tolerated.

2 Discomfort sufficient to cause interference with daily activities (meals, work, sleep, etc.).

3 Incapacitating, with inability to perform daily activities (meals, work, sleep, etc.).

Frequency (only on the starting day of diary):

How often did these symptoms occur in the past week?

a) 0 day

b) 1 day

c) 2-3 days

d) 4-6 days

e) 7 days

4.6.2.2 Method of assessment

Only the symptom assessment by the subject himself/herself is used as an efficacy assessment item and the symptom assessment by physician is not done in this study.

4.6.3 PRO

See Section 4.3.

4.7 Safety measurements and variables

Table 6 shows safety objectives and outcome variables.

Table 6 Safety objective and outcome variable

Objective	Outcome variable
Secondary objective	
To evaluate the safety and tolerability of D20, D40 and O20 by assessment of the following.	AEs, clinical laboratory test values, vital signs (blood pressure and pulse rate)

The methods of collection of safety data are shown below.

4.7.1 AEs

4.7.1.1 Definitions

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

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (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.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

SAE

A SAE is an AE occurring during any study phase, and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to AEs), except hospitalisation that has been planned before enrolment.
- 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.

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

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

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked haematological, biochemistry and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of AEs

For AEs spontaneously reported by the subject and/or in response to an open question "Have you had any health problems since the previous visit/during the study period?" asked by the investigator(s) or revealed by observation, only those occurring from initial administration to the last scheduled visit or withdrawal will be recorded at each visit.

Of SAEs and AEs leading to discontinuation of the subject from the study, those occurring during the time from informed consent to the last scheduled visit or withdrawal will be recorded at each visit.

In case any AE occurs, details (such as a description of the event, seriousness, maximum intensity, date of onset, date of resolution, outcome, action taken [investigational products], and causality with the investigational products) should be recorded in the eCRF.

(a) Abnormal findings

The investigator(s) will confirm whether clinically important values and changes from baseline on clinical laboratory or vital signs are observed or not. If any, such findings will be recorded in the specified module of eCRFs. However, if the abnormality meets any of the following criteria, the abnormality should be recorded in eCRF as AE:

- The abnormality results in discontinuation of the study.
- The abnormality meets any criterion for SAE.
- Investigator(s) insists it should be reported as an AE.

If the abnormality is associated with clinical signs and symptoms, the sign/symptom should be recorded in eCRF as AE.

If any abnormal laboratory values and vital signs considered as clinically important values or changes were observed at the time of completion or discontinuation of the study treatment, the investigator(s) will perform additional tests and follow-up until they are recovered or until the investigator(s) consider it is not necessary to be followed. However, there is no need to record the test results in the eCRF. The monitor will record the follow-up results on the monitoring visit report.

(b) EGD findings of disease under the study (RE)

The EGD findings of RE are not reported as the AEs except for those that correspond to the SAE definition (see Section 4.7.1.1), or those whose aggravation resulted in discontinuation of study.

(c) Assessment of causality

The causality of all AEs (i.e., the relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant eCRF must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?” A guide to the interpretation of the causality question is found in the [redacted]

Occurrence or aggravation of symptoms due to RE will be recorded on eCRF as AE whose causality with the investigational product is ‘None’.

As for SAEs, the causality with the study procedures and concomitant mediations will be judged.

(d) Maximum intensity

Maximum intensity of the reported AEs will be assessed according to the following scale:

- Mild (Awareness of sign or symptom, but easily tolerated)
- Moderate (Discomfort sufficient to cause interference with normal activities)
- Severe (Incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

(e) Follow-up of AEs (ongoing AEs at the end of/withdrawal from treatment)

The AE information will be recorded in the eCRF until the last scheduled visit or withdrawal.

All AEs unresolved when the study is completed or at the time of withdrawal will be followed until the AE in concern is resolved or the investigator(s) decides that no further follow-up is necessary. More information about such AEs may be requested be AstraZeneca KK.

(f) Overdose

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

(g) Pregnancy

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

4.7.1.3 Reporting of SAEs

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs at his or her centre in the course of the study within 1 day (in this section, within 1 day is defined as “immediately but no later than the end of the next business day”) of

when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the investigational product or to the study procedure(s). Wherever possible, this report should be made following the "Reporting Procedure of SAEs using Web-based Data Capture (WBDC) system" described below. The principal investigator must provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The principal investigator must notify the SAEs in writing to the head of the study site immediately.

Follow-up information on SAEs must also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s); study code, centre number, subject number, AE, seriousness, start date. The following detailed information must be sent to AstraZeneca within 1 day after it becomes available; severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of AE, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into eCRF via WBDC system by the investigator(s).

For all SAEs, the AstraZeneca representative will inform the AstraZeneca Drug Safety Department of it by Day 1 and will work with the investigator(s) to compile all the necessary information and ensure that the Drug Safety Department receives a report within 4 calendar days.

In addition AstraZeneca will provide details of any unexpected serious adverse drug reactions or expected fatal or life-threatening serious adverse drug reactions reported with regard to the test product and the control drug if not unblinded in this study or other compound available overseas in which the active ingredient is known to be equivalent to the test product, to the head of the study site, principal investigator and the regulatory agency. The head of the study site must submit a written report to the IRB providing the details of all AE case(s) reported by AstraZeneca.

(a) Reporting Procedure of SAEs using WBDC system

The investigator(s) and other site personnel will access WBDC system and report SAE information by entering it into the relevant eCRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative.

If the system is unavailable, the investigator(s) should take other appropriate measures to provide SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator(s) is responsible for completing the eCRF as soon as the system becomes available again.

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Test items

Laboratory tests are performed on Visits 1 (baseline), 3 and 4.

The test items are shown below. See Table 8 for the collected amount of blood.

Table 7 The items of laboratory safety

	Items
Biochemistry test:	AST (GOT), ALT (GPT), γ-GTP, ALP, LDH, total bilirubin, total protein, albumin, BUN, creatinine, uric acid, sodium, potassium, total cholesterol, neutral fat, CK (CPK)
Haematology test:	Red blood cell count, hemoglobin, hematocrit, white blood cell count, leukocyte differential count (neutrophil, eosinophil, basophil, lymphocyte, monocyte), platelet count
Urinalysis (qualitative)*:	Occult blood, protein, glucose

* About 10 mL of urine is collected and tested by the test paper method.

4.7.2.2 Methods of assessment

During the study period, [redacted] will be designated as a central laboratory for this study in order to assure that the standardisation of the assessment and clinically significant comparison between the 3 treatment groups will be accomplished.

Clinical laboratory tests at Visit 1 must be conducted at the central laboratory for all subjects who provided informed consent within 1 week prior to randomisation. The investigator(s) may confirm the eligibility of the subjects based on the results of tests performed the study centre within 2 week prior to randomisation, even if the test values were collected before provision of informed consent. However, baseline clinical laboratory tests must be conducted at the central laboratory within 1 week prior to randomisation.

If the investigator(s) considers it clinically necessary (eg, in the case of abnormal or severe adverse event), additional blood samples may be taken.

For the blood samples measured by [redacted], the central laboratory will supply the materials (eg, test tubes, labels) necessary for collection of the blood samples, storage, and transfer. Methods of collection of the blood sample, processing, and transfer are described in the manual that will be provided to each study centre.

See Section 4.7.1.2 for details of methods for recording and reporting AEs based on the findings of clinical laboratory values.

4.7.3 Vital signs and physical examination

(a) Vital signs

At all visits except for Visit 2, blood pressure/pulse rate will be measured in a sitting position.

(b) Physical examinations

At all visits, general appearance, lymph node, thyroid gland, cardiovascular system, lung, abdomen, musculoskeletal/extremities, and reflex will be examined. Presence/absence of deterioration or new findings from the baseline (Visit 2) will be checked, and if relevant findings are found, they will be recorded as AEs in the eCRF.

4.8 Volume of blood sampling and handling of biological samples

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

Table 8 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Characteristic of patient	Hp test	2	1	2
Safety	Biochemistry	4	3	12
	Haematology	2	3	6
Genotyping	CYP2C19	2	1	2
Total				22

4.8.1 Analysis of biological samples

4.8.1.1 Biochemistry samples

The analyte stability limits defined by [redacted] will be applied to all analyses performed on behalf of AstraZeneca KK. [redacted] will not analyse samples that fall outside these stability limits. The results will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by [redacted] may be amended in accordance with its Standard Operating Procedures.

If [redacted] chooses to sub-contract the analytical work to another laboratory, [redacted] must assure itself and provide assurance to AstraZeneca KK that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca KK. Samples falling outside these limits must not be analysed or data reported.

4.9 Genetic test

4.9.1 Purpose of genetic test

The purpose of the genetic research is to investigate the genotype of CYP2C19, a metabolising enzyme of D961H known to have two genotypes, namely 'EM' (homo- and hetero-types) and 'poor metaboliser (PM)'. Since the changes in the blood D961H concentrations showed different tendency between the two metabolisers and the difference is considered to affect the efficacy of D961H, they will be examined (see [redacted] for criteria for evaluation of phenotypes).

4.9.2 Collection of samples for genetic research

Subjects will provide a blood sample of 2 mL at screening to be used for genetic test of cytochrome P450 subtype CYP2C19, a metabolising enzyme of D961H.

[redacted] will carry out collection of the samples and measurement.

Genotype is a stable parameter, therefore if for any reason the blood sample is not drawn at screening, it may be taken at any visit until the discontinuation or completion of the study. It is preferable that the blood sample for genotype will be collected at the same time when blood samples for other assessment are collected.

Procedures for sample collection and shipment must be followed as described in [redacted]

4.9.3 Storage and coding of samples for genetic test

Special attention is required for conducting a genetic test. The following items should be obeyed to conduct a genetic test and explained to the subjects at the time informed consent is provided:

- Written informed consent to a genetic test must be provided by each subject.
- From the aspect of this study design, implementation of a genetic test is a requirement for the subject to participate in the study.
- From the aspect of this study design, personnel involved in the study at the study centres and AstraZeneca KK will have knowledge of genetic information on the subjects based on the genetic test results.
- Samples for the genetic test to be sent to the laboratory will not be labelled with subject identifiers so that the information on the subject will not be revealed to any other parties.
- Samples of the subject who is not enrolled in the study will be destroyed immediately by the study site or [redacted].

- If the genetic test for the sample of the subject who is not enrolled in the study was completed, the results of the test and the records will be destroyed immediately by [redacted].

- In the case the subject in concern wishes a release of the genetic test results in the informed consent form, the result will be disclosed to the subject via investigator(s) after the database of the following study (D961HC00006) is locked. However, the result will be disclosed to the subject immediately even before the database is locked only when the subject requests to do so during the study period.

- All samples collected for a genetic test will be used only for CYP2C19 genotyping and will be destroyed immediately by [redacted] after completion of the genetic test on CYP2C19.

5. DATA MANAGEMENT

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. AstraZeneca KK will make an inquiry to the investigator(s) for missing, unreal, or conflict data that have been entered using the WBDC system. When data have been entered, reviewed and edited, and Source Data Verification performed, the principal investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the eCRF will be archived at the study site. Quality control procedures will be applied to each stage of the data handling to ensure that all data are reliable and have been processed correctly.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan will be prepared before unblinding of the data. A significant level of $p<0.05$ (two-sided) will be used, in principle, for statistical tests and interval estimation.

All statistical analyses in this study will be performed by Statistics and Programming Department of AstraZeneca KK using the SAS software.

6.2 Description of outcome variables in relation to objectives and hypotheses

6.2.1 Primary outcome variables

The primary variable of this study is the presence/absence of RE at Week 8 according to LA classification.

6.2.2 Secondary outcome variables

The secondary outcome variables of this study are as follows.

Efficacy

- Presence/absence of RE at Week 4 according to LA classification.
- Time to sustained resolution of each GERD symptom (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of that symptom.
- Time to sustained resolution of all GERD symptoms (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of all symptoms).
- The proportion of subjects without each GERD symptom during the 7 days preceding visits at Week 1, 2, 4 and 8.
- The proportion of subjects without each GERD symptom or with 'Mild' GERD symptoms up to 1 day during the 7 days preceding visit at Week 1, 2, 4 and 8.
- QOLRAD

Safety

- AEs
- Laboratory test values
- Vital signs (blood pressure and pulse rate)

6.3 Description of analysis sets

For the efficacy data analysis, two analysis sets, that is, the full analysis set (FAS) and per protocol set (PPS) will be used. The FAS will be used as the primary efficacy analysis set. Both FAS and PPS will be used for the analysis of the primary variable but only FAS will be used in the analysis of secondary efficacy variables.

All the randomised subjects who are definitely diagnosed to have RE by the EGD before the start of administration and who have taken at least one dose of investigational product will be included in the FAS. Of the subjects included in the FAS, those who have no major protocol violations or deviations that may affect the efficacy assessment and those who have a good compliance with the study will be included in the PPS. The population excluding subjects who are declared not to have RE by the central evaluation committee (see Section 6.7) before dosing will be also evaluated. In this analysis, the evaluation of the central evaluation committee for the healing of RE after dosing will be used.

All the analysis sets will be determined before unblinding of the data.

All the subjects who have taken at least one dose of investigational product and whose data after the treatment start are available will be included in the safety analysis set. All the safety analyses will be conducted using the safety analysis set.

6.4 Method of statistical analysis

6.4.1 Primary outcome variables

The proportion of subjects with healed RE verified at Visits 3 or 4 in the analysis set is defined as the healing rate at Week 8.

The healing rate of RE at Week 8 and its two-sided 95% confidence interval will be calculated for each group. The difference in healing rates between the D40 group and O20 group (D40 group – O20 group) and between the D20 group and O20 group (D20 group – O20 group) along with the two-sided 95% confidence intervals will be obtained. It is concluded that the non-inferiority of D40 to O20 is verified if the lower limit of the two-sided 95% confidence interval of the difference between D40 group and O20 group exceeds -10%. If the non-inferiority of D40 to O20 is verified, the verification of the non-inferiority of D20 to O20 will be investigated similarly.

The healing rate at Week 8 will be compared between D40 group and O20 group and between D20 group and O20 group using Cochran-Mantel-Haenszel test stratified by baseline LA classification or CYP2C19 genotype. In these comparisons, the significant level will not be adjusted.

The healing rate at Week 8 in each subgroup and its two-sided 95% confidence interval will be calculated by dose group regarding the following factors.

- Sex
- Age (<65 years old, ≥65 years old)
- Presence or absence of Hp infection
- CYP2C19 genotype (homo EM, hetero EM, PM)

- Baseline LA classification (grade A/B, grade C/D)

6.4.2 Secondary outcome variables

In the analyses for the secondary outcome variables, only FAS will be used for the efficacy variables and the safety analysis set will be used for all safety variables.

6.4.2.1 Efficacy

Presence/absence of RE at Week 4 according to the LA classification

The proportion of subjects with healed RE verified at Visit 3 in the analysis set is defined as the healing rate at Week 4.

The healing rate of RE at Week 4 and its two-sided 95% confidence interval will be calculated for each dose group. The two-sided 95% confidence intervals of the differences between the D40 group and O20 group and between the D20 group and O20 group are calculated, and the data will be analysed as in the case of primary variable.

Presence/absence and severity of patient-reported GERD symptom

Since the presence or absence of GERD symptom is not included in the eligibility judgment criteria, not all of the subjects have symptoms at the baseline. Therefore, the subject will be classified and assessed by the presence or absence of symptom at the baseline.

Sustained absence of each symptom or all symptoms are handled as an event. The time to event (up to the first day of 7 consecutive days free of each GERD symptom or of all GERD symptoms) from the starting day of investigational product administration will be analysed by Kaplan-Meier method and Kaplan-Meier plot of sustained absence (the proportion of subjects without each GERD symptom during the 7 days preceding visits at Week 1, 2, 4 and 8) will be for each dose group. The sustained absence-time curves between the D40 group and O20 group, and between the D20 group and O20 group will be compared by Log-rank test. If possible, the median value of the time to event will be obtained in each dose group by Kaplan-Meier method.

The proportion of subjects without each GERD symptom or with ‘Mild’ GERD symptoms up to 1 day during the 7 days preceding visits at Week 1, 2, 4 and 8 and their 95% confidence interval will be calculated for each dose group.

PRO

The descriptive statistics of 5 domain scores of QOLRAD at each assessment point will be obtained for each group.

6.4.2.2 Safety variables

AEs

All AEs will be classified by system organ class and by preferred term using MedDRA and those occurred at baseline and after administration of the investigational products will be

summarised in separate lists. AEs occurred after administration of the investigational products will be classified by system organ class and by preferred term using MedDRA independently for each treatment group. Data on drug-related AEs will be collected in the same manner, as required. The number of subjects who developed AEs, drug-related AEs, SAEs, and AEs led to withdrawal from the study will be summarised for each treatment group, together with the total number of AEs, drug-related AEs, SAEs and AEs leading to withdrawal from the study.

Clinical laboratory values

Quantitative data of clinical laboratory values will be summarised using descriptive statistics and qualitative data will be summarised using frequency table for each treatment group at each timepoint.

Vital signs

Quantitative data of vital signs will be summarised for each treatment group at each timepoint using descriptive statistics.

6.5 Determination of sample size

There are two criteria that are used to determine the sample size for this study.

One is the statistical power to show the non-inferiority of D20 to O20 in healing of RE at Week 8. The other is the probability of obtaining that the observed healing rate of D20 is lower than that of O20 under an assumption that the true healing rate of D20 is higher than that of O20.

The non-inferiority will be concluded when the lower limit of two-sided 95% confidence interval of the difference of healing rates at Week 8 between D20 and O20 is higher than or equal to –10%. Based on the results of the overseas studies (SH-QBE-0013/172, SH-QBE-0016/173, SH-QBE-0017/174, SH-QBE-0052/222), 172 patients per treatment group are required to keep a 90% power or more with the lower limit of two-sided 95% confidence interval of the difference to be greater than or equal to –10% under the assumption that the healing rates of RE at Week 8 are 85% for D20 and 82% for O20, respectively.

In order to ensure sufficient “power” for the observed responses to show that the healing rate of D20 is numerically higher than that of O20, it is calculated that 182 patients will be needed for each of these treatment groups to ensure a less than 20% probability that the healing rate of D20 would result in an observed response rate greater than that for O20.

Accordingly, we decided to randomize 185 patients per group in the planned study to fulfil the above two criteria (a total of 555 patients in 3 groups).

6.6 Interim analyses (Not applicable)

6.7 Central evaluation committee

For this study, a central evaluation committee that consists of experts in the gastrointestinal area will be established to confirm the rationale for judgement by the investigator(s) based on the EGD images.

The board will review all EGD images of all patients allocated the investigational products during the study period as needed and report the results of the review to AstraZeneca K.K..

Time to hold the meeting and the responsibilities of the board members will be determined separately.

7. STUDY MANAGEMENT

7.1 Monitoring

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

- Determine the adequacy of the facilities
- Discuss with the investigator(s) (and study coordinators) 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 principal investigator
- Discuss the specific requirements of the genetic test with the investigator(s) (and study coordinators)

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigator(s) and study coordinators are adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (eg, clinic charts).

- Perform source verification of the genetic consent of participating subjects and ensure that the investigational team is adhering to the specific requirements of this genetic test

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or study coordinators at the centre need information and advice.

Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records. Original data recorded on the eCRFs and regarded as source data are specified in the Clinical Study Agreement between AstraZeneca and the principal investigator

7.1.1 Direct access to source data in Japan

The head of the study site and the investigator(s) should cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data should be open for direct access to source data at the request of the monitor and the auditor representing AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRFs against source data to ensure accuracy and completeness of documentation. When the data in the eCRF are changed or modified, the monitor will confirm the amended part (and the reason for amendment) with the investigator(s).

7.2 Audits and inspections

Auditor representing AstraZeneca, a regulatory authority, an IRB may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, regulatory requirements described in Section 8.2 and ethical principles.

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

7.3 Training of staff

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

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

Before the first subject is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic tests with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be clarified. The requirements for the collections of the subjects' samples will also be clarified.

7.4 Changes to the protocol

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

If it is necessary for the study protocol to be amended, the amendment must be submitted to the head of the study site and be approved by its IRB. If applicable, AstraZeneca KK should submit a notification to the regulatory authority before it is implemented.

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

AstraZeneca will distribute amendments and if applicable the amended protocol to each principal investigator and the head of study site, who in turn is responsible for the distribution of these documents to IRB, and the principal investigator will distribute them to the sub-investigator and study coordinator. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

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

7.6 Study timetable and end of study

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

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the principal investigator/study site.
- Approval of the study in written form by the IRB
- Head of Study Site Approval Letter
- Approval of the study, if applicable, by the regulatory authority.

7.6.1 Planned duration of the study

Study period: December 2007 – March 2009

Registration period: December 2007 – January 2009

7.6.2 Discontinuation or suspension of the whole study programme

If AstraZeneca KK decides to prematurely terminated or suspended the study, the principal investigator, the head of the study site, and regulatory authorities must receive written notification of the reasons for the premature termination.

The investigator(s) will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

7.6.3 Completion of the study

Upon completion of the study, the principal investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the study site's rules. The head of the study site who is informed of the termination by the principal investigator will provide a written notification of the results to the IRB and AstraZeneca.

7.6.4 Deviations from the protocol and the recording

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca KK or the IRB approval based on its deliberations.

The investigator(s) will record all deviations from the protocol. The principal investigator will report details of the deviation and its reason to AstraZeneca KK, and retain a copy of the report.

The principal investigator should submit a report to AstraZeneca KK and the head of the study site (and the IRB via the head of the study site), to notify any change that may give a significant impact on the conduct of the study or increase a risk to the patient.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca KK or the IRB approval, only in the event of a medical emergency, e.g. it is only way to avoid an emergency risk to the patient. In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca KK and the head of the study site (and IRB via the head of the study site) as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca KK should be obtained via the head of the study site.

7.6.5 Archiving of records at the study centre

7.6.5.1 Filing of study related materials

AstraZeneca KK will provide the principal investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca KK) should be retained in this file by the principal investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca KK's auditor, regulatory authorities, or IRB.

7.6.5.2 Archiving period

The study site (and the principal investigator) will retain the essential documents specified in the GCP (e.g., source document such as medical records, contract, signed consent form) until the day shown below, whichever is the latest.

- The day when a manufacturing/marketing approval for the investigational product is obtained
- At least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product if the development is discontinued
- At least 3 years have elapsed since the early termination or discontinuation of the study

However this is not always applied to items that are not preservable such as blood samples.

In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These essential documents should be retained for a longer period however if needed by AstraZeneca KK, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca KK. AstraZeneca KK should notify the head of the study site in writing when the study related records are no longer needed.

The records should be managed by a responsible person appointed by the head of the study site.

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, and eCRF must be approved or given a favourable opinion in writing by an IRB as appropriate. The IRB must approve all advertising used to recruit patients for the study, if planned. The head of the medical institute must submit a copy of the written approval and documents describing decision of the head of the study centre along with the institutions related to the approval to

AstraZeneca KK. A valid contract between the medical institution and AstraZeneca KK must be signed before the investigator(s) can enrol any patient into the study.

The head of the study centre is responsible for informing the IRB of any amendments to the protocol in accordance with Japanese GCP. The protocol must be re-approved by the IRB annually. The principal investigator must submit progress reports to the IRB via the head of the study centre at the time of the protocol re-approval.

Where there is a genetic test, approval must be obtained for this genetic test and the associated genetic informed consent from the IRB. The head of the study centres must submit a copy of the approval by the IRB and documents describing the instructions based on the contents approved and decisions by the head to AstraZeneca KK before conducting a genetic test.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997), its partially revised and their related notifications and the AstraZeneca policy on Bioethics.

Since this study includes genetic tests, special precautions are taken as described in Section 4.9.

8.3 Informed consent

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

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

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

The genetic test is mandatory and the subject cannot participate in the main study without participating in the genetic component. To participate in the study the subject must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue the genetic aspect of the study at any time (if the subject withdraw his/her consent to the genetic test, the entire study will be terminated for the subject).

If modifications are made to the informed consent form, the new version has to be approved by AstraZeneca KK and an IRB.

8.4 Subject data protection

The Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with Japanese data legislation. All data computer processed by AstraZeneca KK will be identified by enrolment code.

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

All data protection and confidentiality principles, described in the main study protocol, are also applicable to this genetic test.

In implementation of this genetic test, all relevant information should be recorded in the clinical study records (and electronic data).

The results of the genetic test will be informed to AstraZeneca KK and the investigator(s) after the database of the follow-on clinical study (D961HC00006) is locked. In this regard, however, they will be informed to AstraZeneca KK team members who engage in the preparation of the clinical study report of this study after the database lock of this study. In the case the subjects wished to be informed of the test results, the relevant information will be disclosed to the subject via investigator(s) after the database of the follow-on clinical study (D961HC00006) is locked. However, the result will be disclosed to the subject immediately even before the database of the follow-on clinical study (D961HC00006) is locked only when the subject requests to do so during the study period.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Monitor. If the Monitor is not available, contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician shown below.

Role in the study	Name	Address & telephone number
Monitors	See [redacted]	

Role in the study	Name	Address & telephone number
Study Delivery Team Leader	[redacted]	[redacted]
Study Delivery Team Physician	[redacted]	[redacted]

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

9.3 Procedures in case of overdose

In this study, overdose is defined as 3 capsules or more of D961H per day or 6 tablets or more of omeprazole per day.

No antidote is known for D961H and omeprazole. Omeprazole has a low acute toxicity. Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported.

In case of a known or suspected overdose, symptomatic treatment should be given and general statement including vital signs should be monitored.

Procedures followed in case of overdose will be as follows:

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRFs (See Section 4.7.1.3). In addition, the overdose should be recorded on the relevant overdose module in the eCRF.
- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. In addition, the overdose should be recorded on the relevant overdose module in the eCRF.
- An overdose without associated symptoms should not be recorded as an AE in the eCRFs. The overdose should be recorded on the relevant overdose module in the eCRF.

9.4 Procedures in case of pregnancy

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

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be recorded on the relevant pregnancy module in the eCRF.

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