Clinical Study Protocol

Drug Substance	D961H
Study Code	D961PC00001
Edition Number	1
Date	

A Phase III Multinational, Multicenter, Randomized, Double-blind, Parallel-group, Comparative Efficacy and Safety Study of D961H (20 mg once daily) Versus Placebo for Prevention of Gastric and/or Duodenal Ulcers Associated with Continuous Low-dose Aspirin (LDA) Use

Sponsor:

AstraZeneca K.K. 1-88, 1-chome, Ohyodo-naka, Kita-ku, Osaka 531-0076, Japan

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Phase III Multinational, Multicenter, Randomized, Double-blind, Parallel-group, Comparative Efficacy and Safety Study of D961H (20 mg once daily) Versus Placebo for Prevention of Gastric and/or Duodenal Ulcers Associated with Continuous Low-dose Aspirin

International Co-ordinating committee

-
-
-
-
-

Principal Investigator

As concerns the details of principal investigators in Japan, see Appendix A.

Study centre(s) and number of subjects planned

Study center(s): About 60 centers in Japan, Korea and Taiwan.

Number of subjects planned: 426

Study period		Phase of development
Estimated date of first subject enrolled	January 2010	Phase III
Estimated date of last subject completed	July 2011	

Objectives

Primary objective

To assess the efficacy of D961H 20 mg once daily (q.d.) (hereinafter referred to as D20) versus placebo in continuous treatment involving patients with a history of gastric and/or duodenal ulcers receiving daily LDA therapy by evaluating time from randomisation to occurrence of gastric and/or duodenal ulcers.

Secondary objectives

To assess the efficacy of D20 versus placebo in patients with a history of gastric and/or duodenal ulcer receiving daily LDA therapy by evaluating the following:

- Presence/absence of gastric and/or duodenal ulcers up to 12, 24, 36, 48, 60 and 72 weeks after randomisation
- Degree of gastric mucosal lesion evaluated by modified LANZA score (Lanza FL et al 1988) at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
- Presence/absence and severity of reflux esophagitis (RE) evaluated by the Los Angeles (LA) classification (Lundell LR et al 1999) at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
- Presence /absence and severity of gastrointestinal symptoms assessed by investigator(s) at each visit

Exploratory objective

To investigate the effect of CYP2C19 polymorphism on the efficacy of D20 in patients with a history of gastric and/or duodenal ulcer receiving daily LDA therapy by evaluating the primary and secondary efficacy outcome variables separately for CYP2C19 genotypes.

Safety

To assess safety and tolerability of D20 versus placebo in patients with a history of gastric and/or duodenal ulcers on continuous LDA therapy by evaluating adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate).

Long term safety

To assess long-term safety and tolerability of D20 during long-term treatment (52 weeks or longer) in patients (100 or more) with a history of gastric and/or duodenal ulcers on continuous LDA therapy by evaluating adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate).

Study design

The study is a multicenter, randomized, double-blind, parallel-group (2 groups), placebo controlled phase III study involving patients with a history of gastric and/or duodenal ulcers receiving daily LDA therapy.

Target subject population

Patients aged 20 years and above with a history of gastric and/or duodenal ulcers who are receiving daily LDA therapy for prevention of thrombosis/embolism

Investigational product, dosage and mode of administration

D961H 20 mg –capsules should be administered orally once a day.

Comparator, dosage and mode of administration

Placebo for D961H capsule (placebo comes in unidentifiable capsules with D961H 20 mg capsules) should be administered orally once a day.

Concomitant drug provided by the sponsor, dosage and mode of administration

Fifty (50) mg of gefarnate should be administered orally twice a day.

Duration of treatment

Up to 72 weeks

Outcome variable(s):

- Efficacy

Primary outcome variable

  - Time from randomization to occurrence of gastric and/or duodenal ulcers

Secondary outcome variables

  - Presence/absence of gastric and/or duodenal ulcers for up to 12, 24, 36, 48, 60 and 72 weeks after randomisation
  - Degree of gastric mucosal lesion by modified LANZA score at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
  - Presence/absence and severity of RE evaluated by the LA classification at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
  - Presence/absence and severity of gastrointestinal symptoms assessed by the investigator(s) at each visit

- Safety

Secondary outcome variables

  - Adverse events
  - Clinical laboratory values
  - Vital signs (blood pressure and pulse rate)

Statistical methods

The full analysis set (FAS) and the per-protocol set (PPS) will be used to analyse the time to occurrence of gastric and/or duodenal ulcer. Kaplan-Meier plots showing the occurrence-free rate of peptic ulcer against the time from randomisation will be prepared. The primary variable (time to occurrence of peptic ulcer) will be compared between D20 and placebo using a log-rank test. An interim analysis will be done at the time at least 18 patients had a occurrence of peptic ulcer. The multiplicity of the tests due to the interim analysis will be adjusted using the Lan-DeMets α-spending function in Pocock plan. Secondarily, the occurrence-free rates of peptic ulcer at the time points of EGDs will also be obtained based on the corresponding results of EGD. The FAS will only be used to analyse the LANZA scores and the LA classification of RE. Shift tables showing the changes in LANZA scores from pre-dose to post-dose will be made. The LANZA scores and the changes from pre-dose at each time-point will be summarised for each treatment group using descriptive statistics. The number and the proportion of subjects for each LA classification of RE at Weeks 12, 24, 36, 48, 60 and 72 will be summarised for each treatment group. The FAS will also be used to analyse the GI symptoms. Shift tables presenting the changes from pre-dose to post-dose will be prepared. To investigate an effect of CYP2C19 polymorphism on the efficacy of D20, subgroup analyses based on the CYP2C19 genotype will be performed for some efficacy outcome variables.

The safety analysis set will be used to analyse all safety variables. Safety variables will be presented using descriptive statistics.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline Phosphatase
ALT (GOT)	Alanine aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
ASA	Acetylsalicylic Acid
AST (GPT)	Aspartate aminotransferase (serum glutamic pyruvic transaminase [SGPT])
BUN	Blood urea nitrogen
CK	Creatine Kinase
C_{max}	Maximum plasma concentration
COX-2	Cyclooxygenase-2
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CYP	Cytochrome P450
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
DUS	Disease under Study
D20	D961H 20 mg once daily
D40	D961H 20 mg once daily
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	electronic Case Report Form
EGD	Esophagogastroduodenoscopy
EM	Extenxive Metaboliser
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
H. phylori	*Helicobacter pylori*
IBD	Inflammatory bowel disease

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LA	Los Angeles
LDA	Low Dose Aspirin
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OPZ	Omeprazole
PGx	Pharmacogenetic research
PI	Principal Investigator
PM	Poor Metaboliser
PPI	Proton pump inhibitor
PPS	Per-Protocol Set
RE	Reflux Esophagitis
SAE	Serious adverse event (see definition in Section 6.4.2).
$t_{1/2}$	Elimication half-life
WBDC	Web Based Data Capture
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
Investigator(s)	Principal investigator and investigators

1. INTRODUCTION

1.1 Background

1.1.1 D961H

D961H was developed as a proton pump inhibitor (PPI) and consists of the S-enantiomer of omeprazole (OPZ). In the metabolism of D961H, involvement of CYP2C19 is smaller than that in OPZ. Since the effects of genotype of CYP2C19 on pharmacokinetics and acid inhibition are smaller than in OPZ, it can be expected that individual differences in clinical effects may be smaller with D961H than with OPZ.

D961H has a low systemic toxicity after repeated oral administration to rats and dogs. All findings noted have also been seen after treatment with OPZ. 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 50% after a single dose of 20 mg and 68% after repeated dosing of 20 mg. The elimination half-life ($t_{1/2}$) in CYP2C19 extensive metabolizer (EM) was 0.9 hour 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 in those with mild or moderate liver dysfunction.

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

In overseas clinical studies to assess the efficacy and safety of D961H, results from Phase I studies, indicated a more pronounce and sustained acid inhibition than the corresponding dosed of OPZ. Short-term Phase III and long-term Phase III studies showed more effective healing of reflux esophagitis and maintenance of healed reflux esophagitis as compared to other PPIs. The frequency of adverse events (AEs) in comparative studies with OPZ and short-term placebo controlled studies was almost the same between D961H and OPZ group, and D961H and placebo group. In addition, the profile of reported AEs for the long-term treatment up to 1 year was similar to that seen in short-term treatment. The laboratory parameters, such as haemoglobin, serum iron, serum vitamin B12, did not indicate any significant changes over time. Also, The world wide post-marketing experience with D961H is similar to that of these clinical studies.

Approval status of D961H in overseas countries

Since approval in Sweden in 2000, D961H has been approved in more than 110 countries including Europe, U.S.A., Asian countries (as of August 2009) and has widely been used as a standard therapeutic drug for various acid-related diseases shown below.

- Healing of erosive reflux esophagitis and long-term management of patients with healed esophagitis to prevent relapse (adults and 1 to 18 year old children)
- Symptomatic treatment of gastroesophageal reflux disease (adults and 1 to 18 year old children)
- In combination with an appropriate antibacterial therapeutic regimen for the eradication of H. pylori, treatment of H. pylori-induced duodenal ulcer and prevention of relapse of H. pylori-induced peptic ulcer
- Treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug (NSAID) therapy
- Healing of gastric ulcers associated with non-steroidal anti-inflammatory drug therapy (including COX-2-selective non-steroidal anti-inflammatory drugs)
- Prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug therapy (including COX-2-selective non-steroidal anti-inflammatory drugs), in patients at risk
- Treatment of pathological gastric and hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion
- Posttreatment with esomeprazole intravenous injection for the purposes of maintenance of hemostasis and prevention of re-bleeding in gastric and/or duodenal ulcers

In Japan, a Phase I single dose study (Study SH-QBE-0094) and a Phase I multiple dose study (SH-QBE-0098) in healthy adult men have been conducted, and the safety and gastric acid suppression of D961H have been confirmed in these studies. Based on the results, the effects on prevention of reflux esophagitis and NSAID-associated ulcers are clinically being investigated.

1.1.2 Prevention of ulcers associated with low dose aspirin

Aspirin was widely used for anti-pyretic analgestic action conventionally. Aspirin at low doses (LDA) is also known for anti-platelet action. In the current medical practice in Japan, however, the drug is not often used for anti-pyretic analgestic action, antiplatelet therapy with LDA is common all over the world. The effect of anti-platelet therapy has been evidenced in many overseas studies (Juul-Moller S et al 1992; Antithrombotic Trialists' Collaboration 2002; Patrono C et al 2005). LDA (oral once daily administration at the dose range of 81 to 324 mg in Japan) has been widely used as anti-platelets therapy for prevention of thrombosis/embolism in patients with angina pectoris, myocardial infarction, ischemic cerebrovascular disorder since 2000. Patients with ischemic heart disease or ischemic cerebrovascular disorder are expected to further increase in Japan along with the aging population and accordingly LDA prescription is expected to increase.

Many NSAIDs including aspirin through its systemic effect inhibit prostaglandin production via cyclooxygenase inhibition and attenuate mucosal resistance due to reduced intrinsic prostaglandin in gastric mucosa and other sites. It also has local effect on mucosa under acidity and causes direct mucosal damage. It is considered that use of LDA for the purpose of prevention of thrombosis/embolism in patients with ischemic heart disease or ischemic cerebrovascular disorder damages the mucosal defence system and causes gastric ulcer or duodenal ulcer.

There are several reports describing frequency of ulcers induced by LDA in Japan. Shiotani et al. reports that ulcer lesion was observed in 38 out of 305 patients (12.4%) treated within LDA (Shiotani A et al 2009). Yamamoto et al. reported that of the 262 patients who took LDA, 19 patients caused bleeding and 101 patients experienced mucosal damage (Yamamoto T et al 2007). Data on the investigation into 238 patients with hemorrhagic peptic ulcer by Nakashima et al. shows that 67 patients developed the disease after taking NSAID, and of those 18 patients (26.9%) were taking LDA (Nakashima S et al 2005). Sakamoto et al. performed a case control study in patients with gastrointestinal bleeding and reported that odds ratio of the incidence of upper gastrointestinal bleeding was 7.7 in oral LDA users compared with non LDA users. (Sakamoto C et al 2006).

In Japan, there are mainly two aspirin formulations approved as LDA, i.e., enteric coated aspirin tablet (Bayaspirin® tablet 100 mg) and antacid buffered aspirin tablet (Bufferin 81 mg tablet). There are no big differences between the plain, and those formulations with regard to upper gastrointestinal complications (Kelly JP et al 1996). LDA is, in addition to be a risk factor for ulceration, presenting a tendency to exacerbate gastrointestinal symptoms (Brun J et al 2001). LDA-induced ulcers present few symptoms and, in not a few cases, are detected by bleeding observations such as occult blood in stool or hematemesis (Yeomans ND et al 2005), and it is reported that such severe upper gastrointestinal complication cases occur in LDA users at a frequency of 0.3 to 1.2% annually (The ACTIVE Investigators 2009; Hallas J et al 2006; Hansson L et al 1998; Serrano P et al 2002). It may not be easy to predict ulcer development from the subjective symptoms in patients taking LDA. Appropriate measures to prevent severe upper gastrointestinal complications are, therefore, necessary.

D961H has a potent effect on gastric acid suppression, and the efficacy of D961H on prevention of LDA-associated peptic ulcers has been shown in overseas studies (D9617C00011 and D961FC00003). Accordingly, it was decided that D961H is developed to get an approval for the indication for prevention of LDA-associated peptic ulcers in Japan.

1.2 Research hypothesis

To verify that, when D20 is administered once a day continuously to patients with a history of gastric and/or duodenal ulcers, who are treated continuously with LDA, throughout the period from randomization to the occurrence day of gastric and/or duodenal ulcers, D20 is effective for prevention of gastric and/or duodenal ulcers compared with placebo.

1.3 Rationale for conducting this study

1.3.1 Rationale for conducting this study

In overseas countries, multiple clinical studies, in which the effects on prevention of peptic ulcer in 6-month once-daily oral administration of 20mg or 40 mg (hereinafter abbreviated as D40) to patients continuously treated with LDA therapy were compared with placebo, have been conducted (see Table 1). In these studies, the estimated cumulative rate of patients showing gastric and/or duodenal ulcers until 6 months was significantly lower than in the placebo group.

Based on the results of these studies, D961H of 20 mg or 40 mg once a day for this indication was applied in U.S.A. on April 30, 2009, which is under examination now.

Table 1 Randomization studies of D961H 20 mg and 40 mg given once daily for 6 months

Study name	Target patients	Treatment period	Cumulative incidence (%) of peptic ulcer		
			Placebo	D20	D40
D9617C00011	Patients taking LDA	6 months	6.2(n=498)	1.8[*1] (n=494)	-
D961FC00003	Patients taking LDA	6 months	7.4(n=805)	1.1[*2] (n=804)	1.5[*2] (n=817)

*1: p<0.0007, *2: p<0.0001 (values estimated from life table, log-rank test)

There is no drug indicated for "Prevention of gastric or duldenal ulcer associated with low dose aspirin therapy" currently in Japan. However, the Guideline for Diagnosis and Treatment of Gastric Ulcer based on EBM states, while restricted by medical insurance system, "for prevention of occurrence with LDA, PPI should be used" (Guidelines for Diagnosis and Treatment of Gastric Ulcer Based on the EBM 2007). In the U.S.A., different academic societies (Bhatt DL et al 2008) and research groups in Asia-Pacific area (Sung J et al 2000) recommend preventive use of PPI during treatment with LDA.

1.3.2 Rationale for conducting this study as an Asian Multinational Study

The results of investigation of the influence of intrinsic and extrinsic factors have determined that D961H has pharmacokinetic and pharmacodynamic profiles sensitive to the intrinsic factors, particularly the difference in the frequencies of CYP2C19 polymorphism. However, the pharmacokinetic profiles of D961H stratified by CYP2C19 genotypes were similar between Japanese and Caucasian healthy adult subjects at the dose range of D961H 10 mg to 40 mg, and the pharmacodynamic parameter (percentage of time with gastric pH>4 hours) was sufficient for treatment at the doses of 20 to 40 mg independent of different genotypes in Japanese and Caucasian subjects in the Phase I single-and multiple-oral dosing studies of D961H that examined the safety, pharmacokinetics, and pharmacodynamics of D961H in Japanese and Caucasian healthy adult subjects grouped by CYP2C19 genotypes. No

difference in the safety profiles was noted among different CYP2C19 genotypes nor between Japanese and Caucasian subjects. These results suggest that the pharmacokinetic profiles of D961H stratified by CYP2C19 genotypes are similar between Japanese and Asians including Korean and Taiwanese.

Yamada et al have reported that there was no significant difference in the frequencies of CYP2C19 polymorphism among 4 Asian countries, ie, China, Thailand, Vietnam, and Japan. The frequencies of PM in Asian countries have been reported. According to the report by Chiba et al, PM accounted for 20%, 13%, and 18% in Japan, Korea, and China, respectively. Echizen et al has reported that the frequencies of PM were 18 to 23%, 13%, and 15% in Japan, Korea, and Taiwan, respectively. Although slight variability was observed in the frequency of PM among the countries, these reports support that the difference in pharmacokinetic profiles of D961H would not be large between Japanese patients and Korean or Taiwan patients.

Based on the above, it was considered that it was appropriate to assess the efficacy of D961H on prevention of development of gastric and/or duodenal ulcers in Korean, Taiwanese, Japanese patients receiving LDA continuously and who are at high risk to develop LDA-associated peptic ulcers, i.e. with a history of gastric and/or duodenal ulcers, compared with placebo.

1.4 Benefit/risk and ethical assessment

Status in overseas countries

D961H has been approved in more than 110 overseas countries (as of August 2009) such as Korea and Taiwan mainly for the treatment of gastroesophageal reflux disease. The evaluation of the postmarketing surveillance data, after more than 1030 million delivered treatment courses (as of August 2009), has not revealed any unexpected safety issues.

Moreover, the possibility of drug interaction after concomitant use of this product and LDA was examined in a single-centre (Sweden), open-label, randomized, 3-drug and 3-phase crossover study (Study D961FC00001). In each phase of study, male and female healthy adult subjects received once-daily repeated oral administration of D961H 40 mg alone, aspirin (ASA) 325 mg alone or concomitant use of D961H 40 mg and ASA 325 mg for 5 days. From the results of this study, no effect of concomitant use of this product and LDA was observed, and the possibility of clinically relevant drug interaction is considered low.

In 2 clinical studies, D961FC00003 and D9617C00011, in overseas countries, the safety of concomitant use of this product and LDA for 26 weeks was confirmed. The main adverse events were those belonging to the system organ classes of infection, parasitosis and gastrointestinal disorders. The incidence of these adverse events was almost similar to that in the placebo group. As concerns efficacy, occurrence of gastric and/or duodenal ulcers was significantly inhibited compared with the placebo group.

Status in Japan

D961H is PPI and was developed as the S- enantiomer of OPZ. OPZ was approved in Japan on January 18, 1991 for the indication for gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, and Zollinger-Ellison syndrome at a dose of 10 to 20 mg given once daily. Since its commercialization, OPZ 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, however clinical development, where the effects on prevention of reflux esophagitis and NSAID-associated peptic ulcers are being assessed in Japanese patients, is now ongoing, and the efficacy of D961H on prevention of peptic ulcers and the safety of D961H are confirmed.

Comparator, concomitant drug and study design in this study

The planned indication of D961H is “prevention of gastric or duodenal ulcer associated with low dose aspirin (LDA) therapy”. In this study, placebo is selected as a control since no drugs are approved in Japan, Korea and Taiwan for this indication. Daily use of LDA may induce development of peptic ulcers. Target population for this study is patients with a history of gastric or duodenal ulcer with a high risk of developing peptic ulcer (including the elderly) and with high possibility of recurrence of peptic ulcer. Continuous use of a gastroprotective agent, gefarnate, will be allowed in order to mimic the actual medical practice, where patients with high risk of developing ulcers are treated with mucoprotective agents with limited documented effect.

LDA-induced ulcers show few symptoms, and it may not be easy to predict the development of ulcer from subjective symptoms, etc. of patients. In order to secure the safety of patients, it was decided to confirm vital signs (blood pressure and pulse rate) and physical finding every 4 weeks and laboratory test values every 12 weeks during the study period for 72 weeks at the longest. Furthermore, haematology will be done every 4 weeks to check anemiat. If anemia is found, EGD will be performed to check peptic ulcer as needed. EGD will be performed every 12 weeks at planned clinical visits.

Thus, it is expected that patients with D20 will have a reduced risk of developing gastric or duodenal ulcers. For ethical reasons, a gastroprotective agent will be given concomitantly to all patients, including placebo treated patients. EGD, clinical laboratory tests etc. will be performed frequently during the study.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to assess the efficacy of D20 once daily (q.d.) versus placebo in continuous treatment involving patients with a history of gastric and/or duodenal ulcers receiving daily LDA therapy by evaluating time from randomisation to occurrence of gastric and/or duodenal ulcers.

2.2 Secondary objectives

The secondary objectives of this study are to assess the efficacy of D20 versus placebo in patients with a history of gastric and/or duodenal ulcer receiving daily LDA therapy by evaluating the following:

- Presence/absence of gastric and/or duodenal ulcers up to 12, 24, 36, 48, 60 and 72 weeks after randomisation
- Degree of gastric mucosal lesion evaluated by modified LANZA score (Lanza FL et al 1988) at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
- Presence/absence and severity of reflux esophagitis (RE) evaluated by the Los Angeles (LA) classification (Lundell LR et al 1999) at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
- Presence /absence and severity of gastrointestinal symptoms assessed by investigator(s) at each visit

2.3 Exploratory objective

The exploratory objective of this study is to investigate the effect of CYP2C19 polymorphism on the efficacy of D20 in patients with a history of gastric and/or duodenal ulcer receiving daily LDA therapy by evaluating the primary and secondary efficacy outcome variables separately for CYP2C19 genotypes.

2.4 Safety objective

- Safety
  - To assess safety and tolerability of D20 versus placebo in patients with a history of gastric and/or duodenal ulcers on continuous LDA therapy by evaluating adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate).
- Long term safety
  - To assess long-term safety and tolerability of D20 during long-term treatment (52 weeks or longer) in patients (100 or more) with a history of gastric and/or duodenal ulcers on continuous LDA therapy by evaluating adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate).

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This study is designed as a multinational, multicenter, randomized, double-blind, parallel-group (2 groups), placebo controlled, Phase III study involving patients with a history of gastric and/or duodenal ulcers receiving daily LDA therapy. A total of 426 patients with a history of gastric and/or duodenal ulcers with ulcer scar confirmed by the esophagogastroduodenoscopy (EGD) performed at screening will be randomized 1:1 to either D20 group or placebo group. The efficacy and safety of D20 or placebo will be assessed after up to 72-week oral administration based on the results of the EGD performed at Weeks 12, 24, 36, 48, 60 and 72 after randomisation to verify presence or absence of gastric and/or duodenal ulcers, modified LANZA score to evaluate the degree of gastric and/or duodenal mucosal lesion and presence/absence and severity of RE evaluated by LA classification, and investigator's assessment for presence/absence and severity of gastrointestinal symptoms performed every 4 weeks. In addition, the safety of the concomitant use of D961H and LDA for a long-term period will be confirmed. If development of gastric and/or duodenal ulcer was observed in 36 patients, data will be cut off and analysed. Therefore, it is speculated to administer the test product for up to 72 weeks, but the period of administration of test product may not reach 72 weeks. (See Figure 1)

When development of gastric and/or duodenal ulcer was observed in at least 18 patients and at least 250 patients were randomized, the interim analysis will be performed by an independent data monitoring committee (IDMC) following the data cut-off , data cleaning and data base lock for the analysis. IDMC will decide on a recommendation on continuing or discontinuing the comparative analysis based on the results of the interim analysis (See Section 12.2.3). If IDMC recommend to continue the study, a final comparative analysis will be performed when development of gastric and/or duodenal ulcer is observed in at least 36 patients following the data cut-off , data cleaning and the database lock.

The sponsor will count the number of subjects in the D20 groups who have completed the tests at Visit 15 (Week 52) quickly after the completion of the comparative analysis (including the completion by the interim analysis).

If the number is 100 or more, the sponsor will report the termination of the study to the investigator(s). The investigator(s) will perform the tests required for Visit 20 to all subjects at the next visit after receiving the report and will make the subjects complete the study.

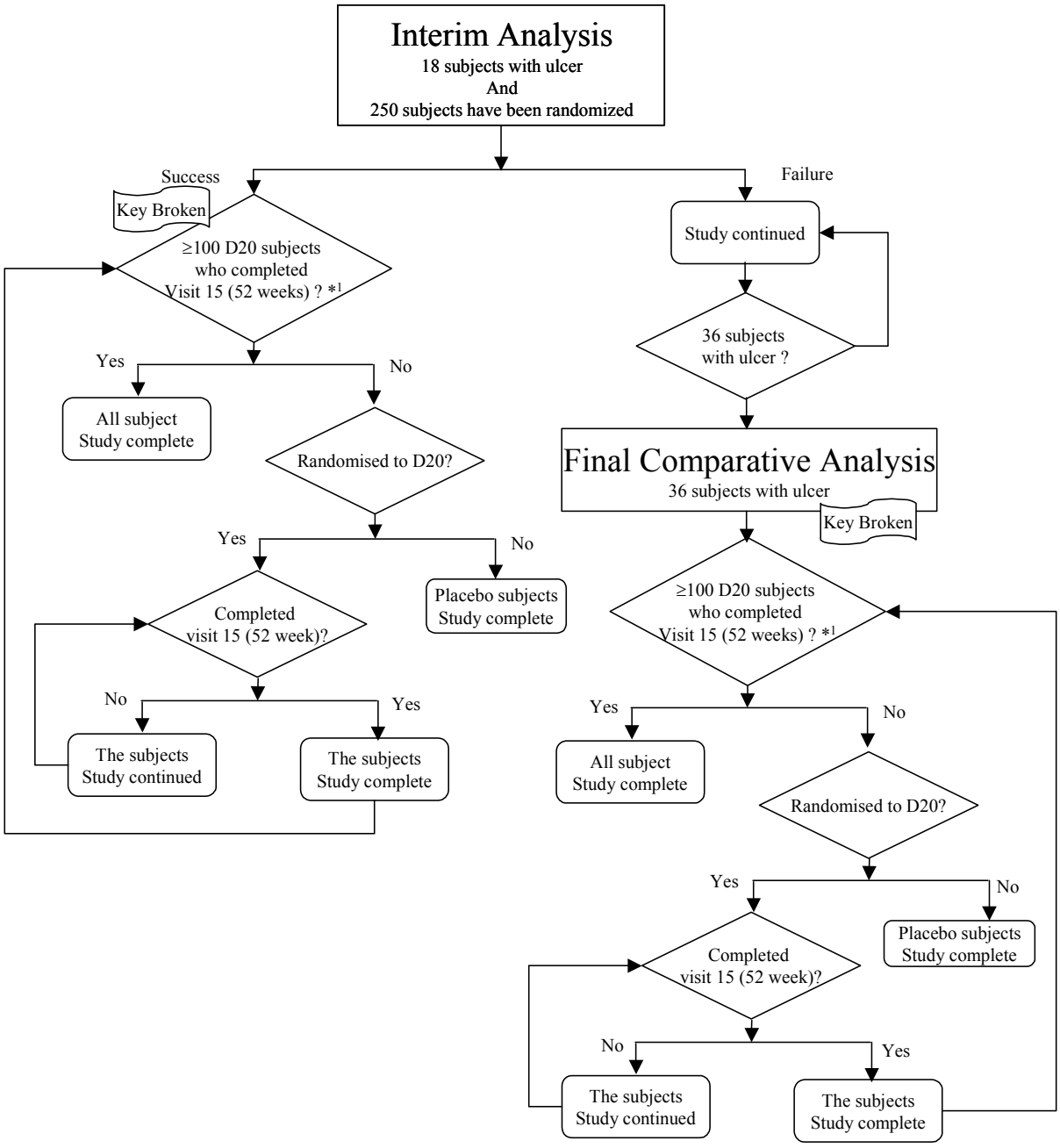
If the number is less than 100, the sponsor will report the continuation of the study and the key information of each subject at the site to the investigator(s). The investigator(s) will perform the tests required at Visit 20 to subjects who are randomised to placebo at the next visit after receiving the report and will make the subjects complete the study. For subjects who are randomised to D20, if the next visit after receiving the report is Visit 15 (Week 52) or later, the investigator(s) will perform the tests required for Visit 20 to the corresponding subjects at the visit and will make the subjects complete the study. If the next visit after receiving the report is before Visit 15 (Week 52), the investigator(s) will perform the tests required at the visit and make the subjects continue the study until Visit 15 (Week 52) after confirming that the subjects want to continue the investigational treatment. If subjects do not want to continue

the investigational treatment, then the investigator(s) will perform the tests required for Visit 20 and will make the subjects complete the study at the visit. The sponsor will report the termination of the study to the investigator(s) as soon as the number of subjects in the D20 group who have completed Visit 15 is reached 100 or more. The investigator(s) will perform the tests required for Visit 20 to all subjects at the next visit after receiving the report and will make the subjects complete the study.

EGD findings judged as an evidence of an ulcer scar at screening, those previously confirmed as ulcers and those judged as gastric and/or duodenal ulcers by the investigator(s) after randomisation as gastric and/or duodenal ulcers will be reviewed by the central evaluation committee (see Section 12.4) established by the sponsor under the blinded conditions any time.

Figure 2 shows the study design and Table 2 shows the study plan including frequency and time of visits.

Figure 1 Flow Chart in case of study completion before 72 weeks



*1 Investigators notice the study completion to the subjects, if applicable, at the next visit after the key broken. (See Section 5.8.2)

Figure 2 Study design

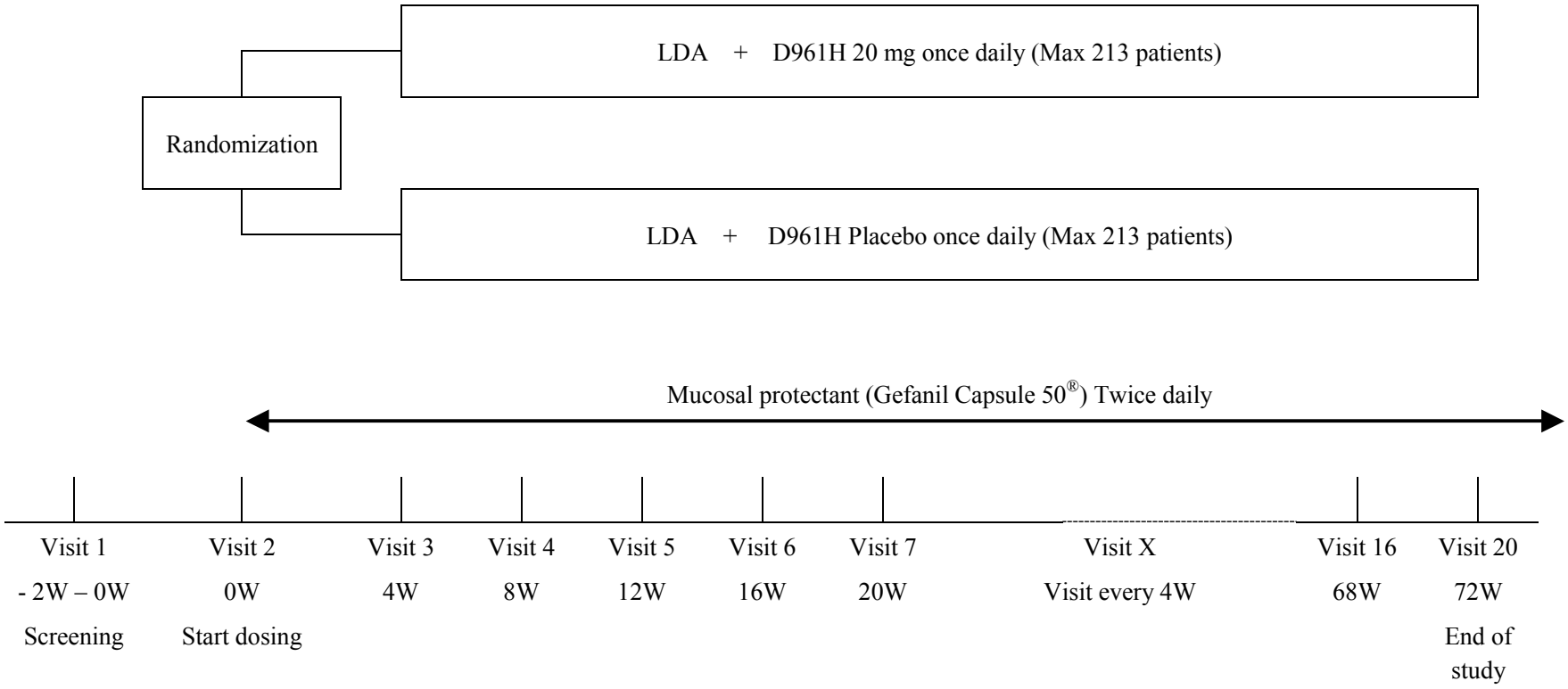


Table 2 Study plan

Period	**Screening**		**Study treatment**																	
		Randomization																		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20 (Completion/ Withdrawal) l**
No. of weeks from Visit 2	**- 2 W to 0 W**	**0 W**	**4 W**	**8 W**	**12 W**	**16 W**	**20 W**	**24 W**	**28 W**	**32 W**	**36 W**	**40 W**	**44 W**	**48 W**	**52 W**	**56 W**	**60 W**	**64 W**	**68 W**	**72 W**
Visit window (day)	**-**	**-**	**± 4**	**± 4**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Informed consent [a]	X																			
Inclusion/exclusion criteria	X	X																		
Demographic data [b]	X																			
Medical/surgical history [b]	X																			
Concomitant disease	X	X																		
Height, Weight	X																			
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure and pulse rate)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests [c]																				
- Haematology tests [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
- Biochemistry tests	X				X			X			X			X			X			X
- Urine tests	X				X			X			X			X			X			X
Pregnancy test (urine)[e]	X																			

Table 2 Study plan

Period	**Screening**		**Study treatment**																	
		Randomization																		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20 (Completion/ Withdrawal) l**
No. of weeks from Visit 2	**- 2 W to 0 W**	**0 W**	**4 W**	**8 W**	**12 W**	**16 W**	**20 W**	**24 W**	**28 W**	**32 W**	**36 W**	**40 W**	**44 W**	**48 W**	**52 W**	**56 W**	**60 W**	**64 W**	**68 W**	**72 W**
Visit window (day)	**-**	**-**	**± 4**	**± 4**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
*H. Pylo*ri test (IgG antibody)		X[m]																		
Genetic test for CYP2C19		X[m]																		
EGD [d,f]																				
- Confirmation of presence/absence of gastric and/or duodenal ulcer	X[n]				X			X			X			X			X			X[o]
- Assessment of degree of gastric mucosal lesions [g]	X[n]				X			X			X			X			X			X[o]
- Confirmation of presence/absence and severity of RE [h]	X[n]				X			X			X			X			X			X[o]
- Assessment of gastric mucosa	X[n]																			

Table 2 Study plan

Period	**Screening**		**Study treatment**																	
		Randomization																		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20 (Completion/ Withdrawal) l**
No. of weeks from Visit 2	**- 2 W to 0 W**	**0 W**	**4 W**	**8 W**	**12 W**	**16 W**	**20 W**	**24 W**	**28 W**	**32 W**	**36 W**	**40 W**	**44 W**	**48 W**	**52 W**	**56 W**	**60 W**	**64 W**	**68 W**	**72 W**
Visit window (day)	**-**	**-**	**± 4**	**± 4**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Evaluation of LDA-associated gastrointestinal symptoms by the investigator[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																		
Dispense the investigational products and mucosal protectant		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Confirm/collect the remaining investigational products and mucosal protectant			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance status of D961H, mucosal protectant and LDA[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE confirmation[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy/drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Should be obtained within 4 weeks prior to Visit 2 (randomization). Regarding EGD result for screening, see footnote m.
b. For the variables for demographic and disease history data, see Section 6.2.1.
c. Clinical laboratory tests will be conducted at the local laboratory.
d. The subject must be fasting.
e. Pregnancy test will be conducted for premenopausal women of childbearing potential.
f. Visit allowance for EGD is ±14 days.
g. According to the modified LANZA score.
h. According to the LA classification.
i. The subject will complete the medical interview form (see Appendix E) at each visit and the investigator(s) will confirm the contents of the form to assess severity of each symptom based on the severity classification.
j. The investigators will confirm the compliance of D961H, mucosal protectant and LDA. Regarding LDA, the subjects will be instructed to record compliance of taking LDA in the compliance record (see Appendix F) and bring it at each visit for confirmation of the compliance.
k. From obtained informed consent until randomisation, only SAEs will be collected and recorded in the eCRF. For AEs other than SAEs only those occurring from the randomization date (Visit 2) to the last scheduled visit or withdrawal will be recorded in the eCRF.
l. If the subject discontinues the study before completing the treatment period (72 weeks), the subject should undergo the tests planned for Visit 20 (Week 72) as much as possible.
m. The samples will be measured at the central laboratory. As a general rule, these tests were done at visit 2. However, if these tests were missed at visit 2, though they can be done at any visit until discontinuation/completion of the study, *H. pylori* test (IgG antibody) and CYP2C19 should be done at same visit as a general rule.
n. EGD obtained before informed consent date can be used with the consent of the subjects, if the EGD was conducted within 2 weeks prior to the randomization.
o. EGD for placebo arm study completion after the key broken is voluntary.

3.2 Rationale for study design, doses and control groups

Rationale for target subject population

In the Guidelines for Diagnosis and Treatment of Gastric Ulcer Based on the EBM (Guidelines for Diagnosis and Treatment of Gastric Ulcer Based on the EBM 2007), a history of gastric and/or duodenal ulcers is considered one of the certain risk factors in peptic ulcer induced with NSAIDs including LDA and taken similarly as a risk factor in various academic societies in U.S.A. (Bhatt DL et al 2008) and research groups in Asia Pacific area (Sung J et al 2000). Based on these, "patients with a history of gastric and/or duodenal ulcers" was established as a target population.

Rationale for D961H dose setting

In overseas, the clinical study of once daily administration of D20, D40 and placebo to investigate this indication has been completed and submitted for NDA in the U.S.. The planned doses for prevention of peptic ulcer in patients on LDA treatment are 20 and 40 mg once daily in the U.S.. In the Japanese Phase I study, acid inhibitory effect was evaluated by CYP2C19 genotype, using percentage of time with intragastric pH4>during the 24-hour intragastric pH monitoring in healthy male subjects who received orally the study medication once daily for 5 days. The doses studied were 10 mg, 20 mg and 40 mg. As a result, percentage of time with intragastric pH4> was lower in homo Extensive Metabolizer (EM) patients as compared with hetero EM and Poor Metabolizer (PM) patients at 10 mg. This suggests that 10 mg dose provides weak acid inhibitory effect to homo EM patients thereby provides only insufficient clinical efficacy in these patients. It is reported that the risk factors for LDA-induced peptic ulcer include history of peptic ulcer, concomitant use of anti-coagulant, concomitant use of anti-platelets, elderly patients, concomitant use of steroids, concomitant use of other NSAIDs (Bhatt DL et al 2008). Treatment with LDA needs to be continued for long (life-long) and over time, new risk factors for peptic ulcer will be added. Some patients receiving LDA treatment may abruptly present hematemesis or tarry stool without gastrointestinal symptoms such as abdominal pain and diagnosis peptic ulcer and/or gastrointestinal bleeding followed by serious conditions. Careful monitoring of the patients is, therefore, necessary. In addition to D961H acid inhibitory effect at different doses, characteristics of LDA-induced peptic ulcer and its prognosis need to be considered for D961H dose setting for combination use with LDA. This study, therefore, will not include 10 mg. Since the clinical dose of D961H for peptic ulcer treatment is planned to be 20 mg, doses above 20 mg was not considered necessary to investigate the possible clinical doses for prevention of peptic ulcer.

Rationale for setting the control group

The target indication of D961H is "Prevention of gastric or duodenal ulcer associated with low dose aspirin," since there is no drug approved for this indication in Japan, Korea and Taiwan, placebo was selected as the control to D961H.

Rationale for setting mucosal protectants

The patient population in this study is including elderly patients and those with high risk of peptic ulcer due to continuous use of LDA. The majority of these patients receive treatment with mucosal protectants in General Practice. Therefore, it was decided to treat all patients in the study with the mucosal protectant. And the most mucosal protectants are taken three times daily, but Gefarnate 50 mg is taken twice daily. So it was decided to take mucosal protectant, Gefarnate 50 mg, twice daily continuously in all the patients as considering drug compliance.

Rationale for length of study

LDA treatment is expected to be continuous to prevent thrombosis/embolism. It is considered that no fixed treatment length needs to be defined for each patient, to investigate LDA-induced peptic ulcer prevention, and thus, it was defined as a maximum of 72 weeks, since it seems possible to evaluate presence/absence of peptic ulcer development during this period.

Furthermore, at least 100 patients randomized to D20 group will continue the treatment for 52 weeks, because ICH E1 guideline requires safety data of 100 patients for 1 year is required.

Rationale for endpoint setting

The target population of this study is a set of subjects who have a history of gastric and/or duodenal ulcers. These subjects have high risk of recurrence of gastric and/or duodenal ulcers due to continuous use of LDA. In order to verify the efficacy of D20 for the prevention of the occurrence, it is important to show that D20 prolongs time to occurrence so that D20 decreases the number of subjects who have a occurrence of gastric and/or duodenal ulcer. Therefore, time from randomisation to a occurrence of gastric and/or duodenal ulcer confirmed by EGD was adopted as a primary outcome variable.

Rationale for a genetic test

D961H is mainly metabolized by CYP2C19 known as being polymorphic genotype, therefore, it is assumed that the clinical effect of D961H may be influenced by polymorphism of CYP2C19 gene. In this study the influence of genotype in the patients receiving long-term concomitant treatment with D961H and LDA will be examined and thus a genetic test of CYP2C19 gene is included.

Rationale for an *H. pylori* test setting

As concerns LDA-induced peptic ulcer, prevention of occurrence by removal of *H. pylori* was shown in the randomised controlled trial (Chan FK et al 2001). However, it is reported that the incidence of subsequent recurrence of gastric ulcer was high as 46.7% with removal of *H. Pylo*ri + placebo but significantly inhibited as 5.6% with removal of *H. Pylo*ri + PPI (Lai KC et al 2002). Moreover, the results of the investigation showed that recurrence rates of gastric ulcers in the three treatment groups of patients with history of *H. Pylo*ri negative gastric ulcer, *H. Pylo*ri positive gastric ulcer, and *H. Pylo*ri eradicated gastric ulcer showed no significant difference between the three groups (Bianchi Porro G et al 1996). Accordingly, since prevention of occurrence by the treatment by removal of *H. pylori* alone is controversial, it is considered necessary to conduct a versatile study to investigate the relationship between *H.*

pylori infection and peptic ulcers induced with NSAID including LDA. Based on the above, information on presence or absence of history of *H. pylori* infection will be collected in this study as a part of demographic data.

4. SUBJECT SELECTION CRITERIA

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

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study.

4.1 Inclusion criteria

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

1. Provision of written informed consent before starting the study-related procedures and examinations (including written informed consent to a genetic test)
2. Medical history of gastric and/or duodenal ulcer. This is defined as the presence of a gastric or duodenal ulcer scar confirmed by EGD findings obtained within two weeks prior to the randomization. The test data obtained before informed consent can be used with the consent of the subjects, if the test was conducted within two weeks prior to the randomization. In the case that the results of the test did not demonstrate the scar clearly but the subject had an evidence of ulcer confirmed by EGD performed in the past he/she will be eligible. If the finding shown below was obtained by EGD, it should be considered the ulcer scar to be present. "The condition in which ulcer-induced tissue defect is restored by exuberant granulation of regenerating epithelium, and the scar of healed ulcer and deformation. Including both red scar (redness is observed in the mucosa of scar) and white scar (the mucosa of scar showing the same color tone as the surrounding mucosa)."
3. A diagnosis of a chronic condition (angina pectoris, myocardial infarction and ischemic cerebrovascular disorder, etc., requiring prevention of thrombosis or embolism) that is taking the prescribed LDA of at least 5 out of 7 days each week during the study treatment period.
   - Dose of LDA is 81 mg to 324 mg per day.

4.2 Exclusion criteria

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

1. Less than 20 years of age at the time of informed consent.
2. Having gastric or duodenal ulcer (except for ulcer scar).
3. History of esophageal, gastric or duodenal surgery, except for simple closure of perforation.

4. Having severe liver disease or liver enzyme (AST [GOT], ALT [GPT], or ALP) or the total bilirubin level three times the upper limit of reference values at laboratory tests conducted within 2 weeks prior to randomization.
5. Having a chronic renal disease or impaired renal function or serum creatinine level two times the upper limit of reference values at laboratory test conducted within 2 weeks prior to randomization
6. Current or historical evidence of the following diseases/conditions:
   (i) Zollinger-Ellison syndrome

   (ii) Inflammatory bowel disease (IBD)

   (iii) EGD evidence or suspicion (not LDA-induced) of pathological or infiltrative process in gastric and/or duodenum (e.g., Crohn's disease, malignancy, sarcoidosis, amyloidosis, ischemic disease)

   (iv) Serious cardiac failure: New York Heart Association Functional Classification III – IV (NYHA III – IV), or left ventricular Ejection Fraction (EF) <40%

7. Any condition that requires surgery during the study period (from the day of informed consent to the day of the last scheduled visit or discontinuation)
8. History of malignant disease within 5 years before randomization. Mild superficial cutaneous disease is allowed.
9. Current or historical evidence (within 12 weeks prior to randomization) of the following disease/conditions:
   (i) Malabsorption syndrome

   (ii) Esophageal stricture

   (iii) RE (LA classification grade A to D)

   (iv) Dysplastic changes (based on the documented findings) of any grade in the gastrointestinal tract

   (v) Signs and symptoms of gastric outlet obstruction (e.g., abdominal distension or multiple episodes of vomiting)

   (vi) Pancreatitis

   (vii) Severe pulmonary disease

   (viii) Diabetes mellitus uncontrolled on dietary management, exercise therapy or medication

   (ix) Unstable hypertension

(x) Acute coronary syndrome

(xi) Cerebrovascular accident (if occur)

(xii) Pregnancy or lactation. Women of childbearing potential must have a positive urine pregnancy test at screening.

10. Use of any other investigational compounds or participation in another clinical study within 4 weeks prior to randomization

11. Prior randomized in the study. However, subjects who fulfil the followings and agree to provide informed consent for the second time can be re-enrolled:
- Subjects who are confirmed having gastric or duodenal ulcer by EGD at screening can be enrolled if the subjects are confirmed healing.
- Subjects who have not been confirmed having gastric or duodenal ulcer scar by EGD at screening can be enrolled if the subjects are confirmed having ulcer scar and provide informed consent again. The previous EGD must be performed equal to or more than 12 weeks before.

12. Need for continuous concomitant therapy with:

(i) PPI (except for the investigational product)

(ii) H2-receptor antagonists

(iii) M1-receptor antagonists

(iv) *H. pylori* eradication therapy

(v) Antacids

(vi) Prostaglandin analogue indicated for peptic ulcers e.g. Misoprostol)

(vii) Drugs with systemic anticholinergic effects

(viii) Gastrointestinal promotility drugs

(ix) Any drug known to have drug-drug interactions with D961H and/or OPZ, (e.g. atasanavir sulphate, diazepam, phenytoin, warfarin, tacrolimus hydrate, digoxin, methyldigoxin, itraconazole, gefitinib, voriconazole)

(x) Anticancer drugs

(xi) Continuous NSAID therapy (oral, intravenous, intramuscular or suppository)
Use of NSAIDs within 7 consecutive days will be allowed.

(xii) Anticoagulants (warfarin, vitamin K antagonists, heparin, lowmolecular weight heparin, anti-thrombin drug or anti Xa drug)

13. Any significant "alarm symptoms" within the past 24 weeks before randomization, such as, unintentional weight loss, gastrointestinal bleeding, jaundice, or any other sign indicating serious or malignant disease.
14. Subjects with disease/symptom allowing no administration of study drugs, such as known or suspected allergy or sensitivity to proton pump inhibitor.
15. Any history of a generalized bleeding disorder resulting from hemorrhagic diathesis (e.g., abnormalities in clotting factors or platelets)
16. History of drug addiction or alcoholism within the past 12 months prior to randomization.
17. Inability to understand or provide informed consent.
18. Inability or unwillingness to take study medication according to dosing instructions.
19. Inability to undergo EGD, or unwillingness to undergo multiple endoscopies.
20. Involvement in the planning and conduct of the study (applies to both sponsor staff or staff at the study site).
21. Subjects who, for whatever reason are unlikely to comply with study requirements as judged by the investigators.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The patients should observe the following items during the study.

1. The subject must fast before blood sampling for biochemistry test and undergoing EGD according to the procedures specified by the study centre.
2. 50 mg of gefarnate should be taken orally twice a day from randomized day to the last day of scheduled visit or day of discontinuation.
3. The subject must not stop the dosing temporarily and change the dose of LDA from informed consent day to the last day of scheduled visit or study discontinuation. As an exception, if the investigators judge that the temporarily stop dosing is necessary for treatments, e.g. biopsy, the subject can stop the LDA dosing temporality within consecutive 7 days.
4. The subject must maintain effective contraception from informed consent day to the last day of scheduled visit or day of discontinuation as judged by the investigator(s) during the study period.
5. The subject must not donate blood from informed consent day to the last day of scheduled visit or day of discontinuation.

5.2 Subject enrolment and randomisation method

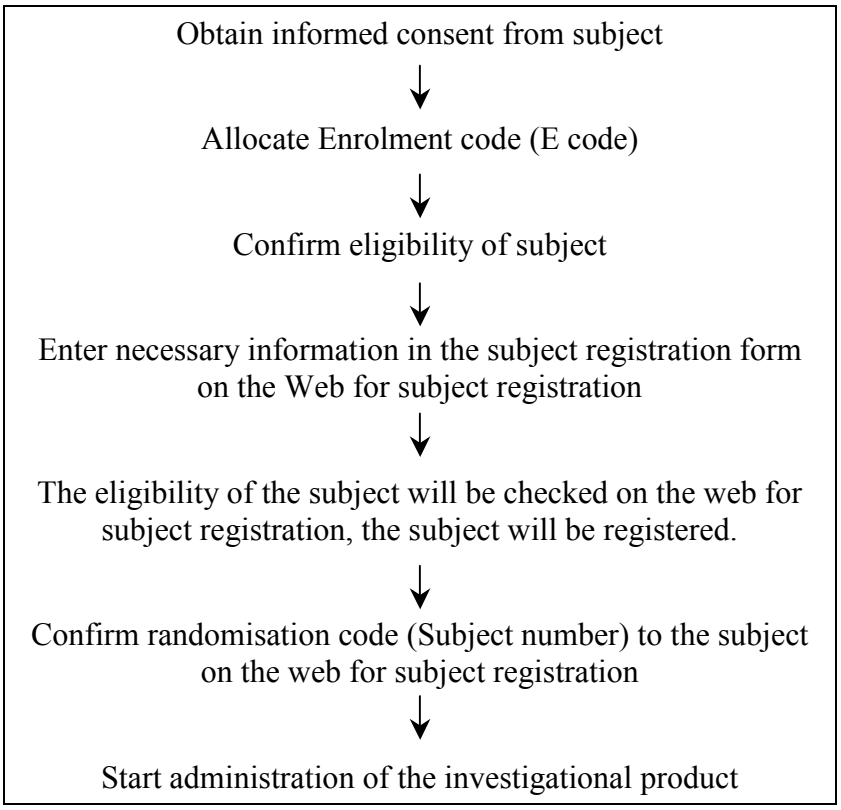
The Principal Investigator will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.
2. Assign potential subject a unique enrolment number, beginning with 'E'. The Enrolment code (EXXXXYYY) is composed of 4 digits (XXXX) of centre number and 3 digits (YYY) of consecutive number in order of registration to screening at each study site. For the subjects who are confirmed having gastric and/or duodenal ulcer by EGD at screening and re-enrolled after the subjects are confirmed healing and provide informed consent for the second time, the number added 500 to the previous consecutive number (YYY) will be allocated. The number added 600, 700, 800 and 900 will be allocated at the third, the fourth, the fifth and sixth time correspondingly. For centre number(s), see Appendix A "Investigators and Study Administrative Structure".
3. Determine subject eligibility. See Sections 4.1 and 4.2
4. If the subject is eligible , the investigator(s) will enter the necessary information in the subject registration form via the subject registration Web system.
5. The subject registration will be completed after the eligibility checks by the subject registration Web system. A randomization code (Subject number) will be allocated automatically and will be shown on the screen in the Web system.
6. After obtaining the randomisation code (Subject number), the investigator(s) will start administration of the investigational product to the registered subject. The investigator(s) will print out the registration confirmation form and keep in the investigator's study file (See Section 9.4.1)

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

The flowchart for subject registration, randomisation and prescription of the investigational product is shown in Figure 3.

Figure 3 Flow chart for subject registration and prescription of the investigational product



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 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".

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

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

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

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

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study will be performed under double-blind conditions. The closest attention should be paid to make the appearance, package and labelling of the investigational products indistinguishable. The investigational product will be allocated by the responsible person who is not related to this study.

5.4.2 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.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment taken actually. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca 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.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Formulation, content, and manufacturer of the investigational products are described in Table 3.

Table 3 Investigational product

Investigational product	Dosage form and strength	Formulation number	Manufacturer
D961H capsule 20 mg	Hard capsule containing 22.3 mg of D961H as enteric coated pellets.	H1189-04-01	AstraZeneca Sweden Operations Drug Product Supply
D961H placebo capsule	Hard capsule unidentifiable to D961H capsule 20 mg	H0459-06-03	AstraZeneca Sweden Operations Drug Product Supply

Packaging of the investigational product

Fourteen capsules of D20 or placebo will be packed in a blister pack and it will be packed in an aluminium pouch under the responsibility of investigational products, AstraZeneca R&D Mölndal, Sweden. Sixteen aluminium pouches (224 capsules in total) will be packed in a paper box.

5.5.2 Doses and treatment regimens

One capsule of the investigational product will be orally given once daily after breakfast for the period of 72 weeks. The investigator(s) must instruct the patients to take the investigational product regardless the time on the day of the first prescription and take the investigational product after examination on the days of EGD and biochemistry test conducted.

5.5.3 Additional study drug

Table 4 Mucosal protectant

Drug name	Dosage form and strength	Manufacturer
Gefanil Capsule 50®	1 capsule containing Gefarnate 50 mg	Dainippon Sumitomo Pharma Co. Ltd

Doses and treatment regimens

From randomized day to the last day of speculated visit or day of discontinuation, a capsule of gefarnate 50 mg should be taken orally twice a day (after breakfast and after dinner). On the day of the first prescription, dose should be adjusted considering randomization time. Gefarnate should be taken after examination on the days of EGD and biochemistry test conducted.

5.5.4 Labelling

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

The label will include the following information: the description of name of the investigational product, study code, batch number, quantity, expiry date, storage condition, randomisation code, instruction, name of sponsor and address and 'for clinical study use'. Details of labelling study drug will be described in a separate document, "Storage conditions of investigational products".

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

A description of the appropriate storage conditions is specified in the document 'Procedures for drug storage'.

5.6 Concomitant and post-study treatment(s)

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

5.6.1 Allowed concomitant treatments

Drugs used for pre-treatment of EGD (e.g. local anaesthetic, anticholinergic agents, anti-anxiety agents or sedative drug). Any drugs used for pre-treatment are not to be recorded in the eCRF.

5.6.2 Prohibited concomitant treatments

The following treatments cannot be used concomitantly after randomization:

(i) PPIs (except for investigational product)

(ii) H2-receptor antagonists

(iii) M1-receptor antagonists

(iv) *H. pylori* eradication therapy

(v) Antacids

(vi) Prostaglandin analogue indicated for peptic ulcers (e.g. Misoprostol)

(vii) Drugs with systemic anticholinergic effects (except for butylscopolamine bromide used for pre-treatment of EGD)

(viii) Gastrointestinal promotility drugs

(ix) Any drug known to have drug-drug interactions with D961H and/or OPZ (e.g atasanavir sulphate, diazepam, [use for pre-treatment before EGD is acceptable],

phenytoin, warfarin, tacrolimus hydrate, digoxin, methyldigoxin, itraconazole, gefitinib, voriconazole)

(x) Anticancer drugs

(xi) More than 8 days continuous NSAID therapy (oral, intravenous, intramuscular or suppository)

(xii) Anticoagulants (warfarin, vitamin K antagonists, heparin, lowmolecular weight heparin, anti-thrombin drug or anti Xa drug)

(xiii) Mucosal protectants (except for the ones provided by the sponsor)

5.7 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of the eCRF.

Compliance with the investigational product and mucosal protectant

The investigational product and mucosal protectant will be prescribed every visit. Treatment compliance will be verified by checking the number of remaining capsules returned. If the compliance rate is low because the subject missed taking capsules, and so on, the investigator(s) must instruct the subject to follow the instruction.

Compliance with LDA

The subjects will be asked to record the daily compliance status for LDA administration on the compliance record and bring it (See Appendix F) at each visit. If the compliance rate is low because the subject missed taking tablets, and so on, the investigator(s) must instruct the subject to follow the instructions.

5.7.1 Accountability

AstraZeneca 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. 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 D961H capsule and Gefanil Capcel 50®. The investigator(s) and/or the Investigational Product Storage Manager must also confirm the number of capsules 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.

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.

5.8 Discontinuation of investigational product

The study treatment and assessments can be discontinued 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 by the investigator(s) and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator(s) and/or AstraZeneca
- Incorrect enrolment i.e., the subject does not meet the required inclusion/exclusion criteria for the study except for the cases that the AstraZeneca Study Delivery Team Physician and the Investigator reach an agreement to continue the study as the result of the discussion. (See also Section 5.3)
- Subject lost to follow-up
- Occurrence of an event in conflict of exclusion criteria (e.g., pregnancy)
- Development of gastric and/or duodenal ulcer
- Difficulty to conduct the study as judged by the investigator(s) due to the presence of gastric and/or duodenal mucosal lesion such as bleeding.
- Stopping treatment with daily LDA
- Others as judged appropriate by the investigator(s) (reasons for discontinuation must be documented in the eCRF appropriately)

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up at the discretion of the investigator (See Sections 6.4.3 and 6.4.4). Compliance records, study drug and mucosal protectant should be returned by the subject.

If a subject is withdrawn from study, see Section 5.9.

For Japan, replace the above paragraph with the paragraph below

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/sub-investigator 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 at the discretion of the investigator. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4). Compliance records and study drug should be returned by the subject.

5.8.2 Procedures for subjects study completion before 72 weeks

When100 subjects or above who have taken the investigational products for 52 weeks or more are achieved and the comparative analysis (interim and/or final) has been completed, the study will be finished before 72 week. (See Figure 1) AstraZeneca will announce the study termination to the investigator(s) as soon as possible. The investigator(s) should inform the subjects of the termination and perform the withdrawal/study completion visit (Visit 20) assessments at the next visit after the key broken.

If the number of subjects who have taken the investigational products for 52 weeks or more is less than 100 after key break, the study will continue. AstraZeneca will report the continuation of the study and the randomised drug for each subject to the investigator(s). The investigator(s) should notice subjects who should complete the study (see Figure 1) and perform the withdrawal/study completion visit (Visit 20) assessments to them at the next visit after the key broken of efficacy analysis. Subjects who are fulfilled with the criteria of the study continuation (see Figure 1) will continue to take the investigational product after the investigator(s) should confirm the continuation of the investigational treatment with them. If subjects wish to terminate the study at the next visit after the key broken, the subjects will complete the study after the withdrawal/study completion assessments (Visit 20).

AstraZeneca will report the termination of the study to investigator(s) as soon as the number of subjects who have taken the investigational products for at least 52 weeks is 100 or more.

Subjects should take the investigational product and mucosal protectant until the last visit, the next visit after the key broken, as general rule.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up at the discretion of the investigator (See Sections 6.4.3 and 6.4.4). Compliance records, study drug and mucosal protectant should be returned by the subject.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

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

For Japan, add the below paragraph

The Principal Investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the electronic CRFs provided by AstraZeneca. The eCRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the eCRF including how to change data incorrectly recorded.

6.2 Data collection and enrolment

6.2.1 Recording of demographic characteristics and screening test

The data on the following demographic characteristics and the screening test are collected, and recorded in eCRF.

Visit 1 (within 2 weeks of randomization)

- Patient background (sex, date of birth, race, smoking habit or not, drinking habit or not, height, body weight)
- Primary disease (disease that requires continued LDA administration), history of ulcer (presence or absence of definite diagnosis in the past), history of *H. pylori* eradication, history of disease (critical symptom & finding in the past, though currently cured), incidental disease (disease currently under treatment [including the disease that is controlled by treatment]), history of operation, concomitant therapy & concomitant drug
- Physical findings, vital signs (blood pressure and pulse rate)

- EGD (see Section 6.2.2. The test results obtained by 2 weeks before randomization but before acquisition of informed consent may be used if the consent in this regard is obtained.)
- Blood test, blood biochemical test
- Urine tests
- Pregnancy test by urinalysis (hCG) (only the fertile females before menopause)

Visit 2 (randomization day)

- Physical findings
- Assessment of gastrointestinal symptoms attributable to LDA in the past 7 days (Section 6.3.4)
- *H. pylori* test (see Section 6.2.3)
- CYP2C19 gene test (see Section 6.8)
- Adverse events, incidental disease
- Concomitant therapy & concomitant drugs

6.2.2 EGD

EGD should be performed according to standard procedure in each study centre. Any drugs used for pre-treatment are not to be recorded in the eCRF.

6.2.2.1 Presence or absence of onset of gastric or duodenal ulcer

Refer to Section 6.3.1.

6.2.2.2 Degree of lesion in gastric mucosa

Refer to Section 6.3.2.

6.2.2.3 Presence/absence and severity of reflux esophagitis

Refer to Section 6.3.3.

6.2.3 *H. pylori* test (IgG antibody)

The blood (2 mL) is collected at visit 2 to determine IgG antibody and to diagnose the presence or absence of *H. Pylo*ri infection. If it is not possible to collect the blood at visit 2, the blood sample may be collected on patient's visit by the time of discontinuation or termination of study period. *H. pylori* test (IgG antibody) and CYP2C19 should be done at same visit as a general rule. The samples are collected and determined by

6.3 Efficacy

6.3.1 Presence or absence of onset of gastric or duodenal ulcer

EGD is performed under fasting condition on the visits 1, 5, 8, 11, 14, 17 and 20 (at the time of screening, 12 weeks after randomisation, every 12 weeks thereafter) to check the presence or absence of gastric or duodenal ulcer. EGD can be performed if the patient have symptoms or signs indicating an unscheduled EGD as well. If any ulcer is detected in the stomach or duodenum, the site and the longest diameter of ulcer are recorded in eCRF. If plural number of ulcers are detected, the largest site and the longest diameter of ulcer are recorded in the eCRF.

Presence or absence of gastric or duodenal ulcer:

It is judged that ulcer is present when the following findings are obtained in EGD.

[Mucosal defect of 3 mm or more. Accompanied by the ulcer bottom with annular or oval-shaped white fur. The borderline of ulcer bottom margin is clear and not irregular. There is no tumor lesion and no malignant finding.]

Site

Site I: Cardia, fundus, upper body, middle body, lower body, angular region, pyloric antrum, bulb, bulb posterior

Site II: Anterior wall, posterior wall, greater curvature, lesser curvature

Diameter of ulcer

The long diameter of ulcer is determined with reference to endoscopic forceps, etc.

Photography of EGD

For the central judgment to confirm the presence of ulcer in the stomach or duodenum, EGD photos of the site judged as the ulcer scar at the time of screening and those of the site judged as ulcer during the investigational product administration period (2 close-up shots and 1 long shot as a general rule. The same applies to the case when EGD photos taken in the past is used because the scar is ambiguous) are submitted to the sponsor. If plural number of ulcers are observed, EGD photos of the largest ulcer are submitted to the sponsor. In all cases, mask any private information (name, chart No., etc.) that can specify the subject before submission of photos to the sponsor.

6.3.2 Degree of lesion in gastric mucosa

EGD is performed under fasting condition on the visits 1, 5, 8, 11, 14, 17 and 20 (at the time of screening, 12 weeks after randomisatoin, every 12 weeks thereafter) to evaluate the degree of lesion in gastric mucosa (erosion, hemorrhage) in accordance with LANZA scores (modified edition).

LANZA scores (modified edition)

0: No hemorrhage, no erosion

+1: One hemorrhage or one erosion

+2: 2 ˜ 10 hemorrhages or erosions

+3: 11 ˜ 25 hemorrhages or erosions

+4: More than 25 hemorrhages or erosions, or ulcer

6.3.3 Presence or absence and the severity of reflux esophagitis

EGD is performed under fasting condition on the visits 1, 5, 8, 11, 14, 17 and 20 (at the time of screening, 12 weeks after randomisatoin, every 12 weeks thereafter) to check the presence or absence and the severity of RE in accordance with the LA classification (Lundell LR et al 1999).

LA classification (Lundell LR et al 1999)

Grade O: No mucosal break

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

6.3.4 Presence or absence of gastrointestinal symptoms and the severity (evaluation by investigators)

On each of the Visit 2 to 20 (at the time of randomization, after 4 weeks from randomisation, every 4 weeks thereafter), the subject is asked to state the overall severity of gastrointestinal symptoms (epigastric pain, stomach discomfort, abdomen enlarged feeling, nausea & vomiting, heartburn, anorexia) attributable to LDA administration in the past 7 days in the Medical Interview Form (See Appendix E). The investigator, etc. checks the Medical Interview Form, assesses each symptom according to the severity classification defined in the following, and record the result in eCRF.

Gastrointestinal symptoms

Epigastric pain:	Pain in the stomach and around the solar plexus
Stomach discomfort:	Discomfort such as heavy stomach feeling, etc.
Abdomen enlarged feeling:	Bloated stomach feeling
Nausea & vomiting:	Nausea and gagging, retching the stomach content (vomiting)
Heartburn:	Burning feeling in the stomach or in the region from chest to neck
Anorexia:	No appetite

Severity Grading

Each symptom is assessed by classifying into 4 grades of severity as follows:

Asymptomatic	No symptom
Mild	Symptomatic but tolerable
Moderate	So uncomfortable as disabling the activities of daily living
Severe	Precluding the activities of daily living

(The activities of daily living include taking a meal, working, and sleeping.)

6.4 Safety

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

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

For Japan, add the below paragraph

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.

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation

For Japan, replace the above paragraph with the paragraph below

Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), 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.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from the randomization date (Visit 2) to the last scheduled visit or withdrawal.

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE;

- AE (verbatim)

- Date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome
- Investigator causality rating against the mucosal protectant (yes or no)

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation (if applicable)
- Date of discharge (if applicable)
- Date of death (if applicable)
- Probable cause of death (if applicable)
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to mucosal protectant provided by AstraZeneca
- Description of AE.

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 6.4.2. 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 unless it is fulfilled with the

definitions in Section 6.4.2. 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.

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)

Causality collection

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

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

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

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: '*Have you/the child had any health problems since the previous visit/you were last asked?*', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

EGD findings of target disease (gastric or duodenal ulcer)

Ulcer, erosion, bleeding and RE in EGD findings of the target disease are efficacy assessment variables and are not recorded in eCRF, excepting when it meets definition of serious AE (see Section 6.4.2) or leads to study discontinuation for erosion, bleeding and RE (other than onset of ulcer). Investigator and/or sub-investigator should take an appropriate measure and follow up, if EGD detected onset of gastric or duodenal ulcer.

Symptoms of target disease

Symptoms of target disease and LDA-induced gastrointestinal symptoms as described in Section 6.3.4 are efficacy variables and are not recorded in eCRF as AEs unless any SAE criterion (see Section 6.4.2) is met or the symptoms leads to discontinuation of study drug (DAE).

Symptom of primary disease (necessary to be continuously treated with LDA)

Aggravation of primary disease (necessary to be continuously treated with LDA) is recorded in eCRF as AE.

Overdose

Overdose (accidental or intentional) is reported according to the procedure provided in Section 13.2, regardless of the presence or absence of overdose-associated symptom. Any of symptom associated with overdose is reported as AE.

Pregnancy

Pregnancy noticed after randomization is reported according to the procedure provided in Section 13.3. Pregnancy is not regarded as AE, except when the study drug was likely to impede the efficacy of contraceptive in use.

6.4.4 Reporting of serious adverse events

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

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

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

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

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

For Japan, Replace the above paragraphs with the paragraphs below.

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

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site 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 study treatment or to the study procedure(s). When a SAE is reported, "Reporting Procedure of Serious Adverse Events using Web-based Data Capture (WBDC) system" stated as below should be followed as much as possible. The Principal Investigator should provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator should notify the serious adverse events in writing to the head of the study site immediately.

Follow-up information on SAEs should 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 should 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, site number, Enrolment code, adverse event, seriousness, start date. The following detailed information should be sent to AstraZeneca as soon as 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 adverse event, 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.

In addition AstraZeneca will provide the information on the serious adverse drug reactions collected domestically and abroad regarding the investigational product to the Head of the study site, Principal Investigator and the regulatory agency as per local requirements. The Head of the study site must submit a written report to the IRB providing the information reported by AstraZeneca.

Reporting Procedure of Serious Adverse Events using Web-based Data Capture (WBDC) system.

The investigator(s) and other site personnel will access Web Based Data Capture (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.

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).

6.4.5 Laboratory safety assessment

Blood samples for hematological and biochemical tests and urine samples for urinalysis are collected at the time points predetermined in the study schedule and laboratory tests should be completed according to standard procedure in each study centre.(See Table 2.)

The screening (baseline) laboratory tests should be completed in all subjects who agreed participation in the study, at each study centre (or sub-contractor) after informed consent and 2 weeks before randomization.

Additional blood samples can be collected, if investigator/and or sub-investigator considered necessary (e.g., because of abnormal or severe AE).

Laboratory Test items: Hematological tests are only performed in some visit (refer to Table 2)

Biochemistry tests (on empty stomach)	AST(GOT), ALT(GPT), ALP, total bilirubin, creatinine, BUN, LDH, and CK (CPK)
Haematology tests	RBC count, Hb, WBC count, differential leukocytes (netrophils, eosinophils, basophils, lymphocytes, and monocytes), and PLT count
Urine tests	Blood, Protein, Glucose

For blood volume see Section 7.1.

6.4.6 Physical examination

A physical examination will be performed and include an assessment of the following: general appearance, lymph node, thyroid gland, cardiovascular system, lung, abdomen, musculoskeletal/extremities, and retortion.

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.

6.4.7 Vital signs

Blood pressure/pulse rate will be measured in a sitting position. For timing of assessments, see the study plan (Table 2).

6.5 Patient reported outcomes (PRO) – Not applicable

6.6 Pharmacokinetics – Not applicable

6.7 Pharmacodynamics – Not applicable

6.8 Pharmacogenetics

CYP2C19, D961H-metabolizing enzyme, is known to occur as EM (homologous and heterologous) and PM in genetic polymorphism, which makes different the time course of D961H blood concentration. The blood concentration is assayed as an background factor (see Appendix D for the judgment standards for phenotype).

6.8.1 Collection of pharmacogenetic samples

Two mL of blood for genetic assay of D961H-metabolizing enzyme, CYP2C19, that is subtype of cytochrome P450 is sampled at Visit 2.

measures the biosamples.

Enzyme genotype is a stable parameter, and therefore, blood can be collected at any visit until study discontinuation or completion, unless blood sample could be collected at Visit 2.
H. pylori test (IgG antibody) and CYP2C19 should be done at same visit as a general rule.

Collection of samples, labeling, storage, and delivery should follow Appendix D.

For blood volume see Section 7.1.

6.9 Health economics – Not Applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 5 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Characteristic of patient	*H. Pylo*ri test	2	1	2
Safety	Clinical chemistry	4	7	28
	Haematology	2	19	38
Genotyping CYP2C19		2	1	2
Total				70

7.2 Handling, storage and destruction of biological samples

The time frame specified by that can ensure the stability of samples will be applied all analyses required by the sponsor. will not perform any analyses on samples out of the time frame. If a sample is found to be out of the time frame to ensure its stability, will not report the result of analyses on the sample to the sponsor. Standard procedures to be applied to may be modified in accordance with Standard Operational Procedures of .

guarantees to the sponsor that the specified time frame should be applied to all analyses required by the sponsor even if the analyses are contracted to another laboratory organization. Such a contracted laboratory organization will not analyze any samples out of the time frame and not report the analytical results of such samples.

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Pharmacogenetic samples

Special cautions listed below are required for genetic analysis and should be included in explanation given to subjects at informed consent:

- Written informed consent to participate in genetic analysis should be obtained from every subject.
- Participation in genetic analysis is a mandatory part of this study due to its study design.
- The medical institution and study personnel of the sponsor will become to know the result of genetic analysis for each subject.
- Any information that allows third parties to identify the subject should not be included in the label attached to samples sent to the genetic analysis laboratory organization.
- If a subject withdrew consent to participate in genetic analysis, samples collected from the subjects will be promptly destroyed by the medical institution or If genetic analysis has already been completed, will promptly destroy all data and records of genetic analysis in the subject.
- The analytical results are disclosed to the sponsor and investigator and/or sub-investigator after the treatment code broken as a general.
- Subjects will not be notified of the result of genetic analysis in principle. However, if a subject demands notification of the genetic analysis result explicitly in the informed consent form, the subject will be informed of the test result via the

investigator or another appropriate person after database lock. However, the genetic analysis result may be notified to a subject even before database lock only if the subject demands disclosure of the genetic analysis result during the study period.

- All samples for genetic analysis collected from subjects will be used only for genetic analysis on CYP2C19. will destroy all remained samples for genetic analysis promptly after completion of genetic analysis on CYP2C19.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

Blood samples to be analyzed at the local clinical laboratory should be labeled, stored and shipped in accordance with local procedures.

Blood samples to be shipped to the central clinical laboratory should be labeled, stored and shipped in accordance with procedures specified in the study manual prepared by the central clinical laboratory.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of collection.

keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

7.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

For Japan, replace the above paragraph with the paragraph below

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements, the applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997), partially revised by MHLW Ordinance and their related notifications and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

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

For Japan, replace the above paragraph with the paragraph below

The Master Informed Consent Form will explain that:

- Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation.
- Subject data will be maintaining confidentiality in accordance with national data legislation.
- For data verification purposes, authorised representatives and auditors of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.
- All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).

All of the principles for data protection and maintenance of confidentiality specified in the protocol should be applied to genetic analysis. Every data generated in the conduct of genetic analysis of this study should be recorded in documents (and electronic data) essential for the study. The result of genetic analysis will be notified to the sponsor, investigators and other appropriate personnel after database lock. It will be also notified to subjects who demand its notification after database lock. However, the genetic analysis result may be notified to a subject even before database lock only if the subject demands disclosure of the genetic analysis result during the study period.

8.3 Ethics and regulatory review

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

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

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

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

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

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

For applicable countries, each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

For Japan, replace this section with below

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

The opinion of the Ethics Committee should be given in writing. The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject should into the study.

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

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

The contract between the study site and AstraZeneca should be concluded before the first subject enrolment. The protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

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

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

For Japan, add the below paragraph

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) should inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 8.5). The investigator(s) should re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

8.5 Changes to the protocol and informed consent form

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

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

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

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

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

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

For Japan, replace this section with below

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca 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 should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

For Japan, add the below paragraph

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

- Determine the adequacy of the facilities

- Determine availability of appropriate subjects for the study

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

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised. The responsible personnel will also highlight importance of ethical considerations and procedures for informed consent specific for genetic information.

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

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

9.3 Monitoring of the study

Monitors of the sponsor will visit each medical institution before enrolment of the first subject to:

- Determine the adequacy of the facilities

- Discuss with the investigator and study collaborators about their responsibilities as well as responsibilities of the sponsor and the monitor in complying with the protocol.

- Discuss with the investigator and study collaborators about requirements specific for genetic analysis in this study.

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

- Provide information and support to the investigator(s)

- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

- To confirm that informed consent to participate in genetic analysis has been obtained from each subject based on the source document and to give required support to the investigator and study collaborators to ensure that they can comply with requirements specific for genetic analysis.

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

9.3.1 Source data

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

For Japan, replace the above paragraph with the paragraph below

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 investigator.

For Japan, add the below section

9.3.2 Direct access to source data in Japan

The Head of the institution and the Principal Investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRFs against source data before collecting the eCRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/sub-investigator has submitted the eCRFs to AstraZeneca. If the investigator wishes to amend the collected eCRFs, the monitor will ensure that the Principal Investigator/sub-investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

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

For Japan, replace the above paragraph with the paragraph below

(i) **Study files**

AstraZeneca 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) 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's auditor, regulatory authorities, or IRB.

(ii) **Period of record retention**

The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those 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 documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca 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.

For Japan, add the below section

9.4.2 Deviation from the clinical study protocol in Japan

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical trial (e.g. changes to the organisation/structure of the sponsor, the name/department name of the medical institution, the address or phone number of the medical institution or the sponsor, the job title of the investigator, and monitors).

The investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the investigator should prepare and submit the records explaining the reasons thereof to the sponsor and the head of the study site, and retain a copy of the records.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval, only in the event of a medical emergency, e.g. it is only way to avoid an immediate hazard to the patients. 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 K.K. 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 K.K. should be obtained via the head of the study site.

9.5 Study timetable and end of study

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

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with D961H or OPZ.

Planned duration of the study:

Study period: January 2010 (First subject in) to July 2011 (Last subject last visit)

Registration period: January 2010 (First subject in) to January 2011 (Last subject in)

Registration period is changed depending on accumulation speed of gastric and/or duodenal ulcer events.

The principal investigator will be notified when the subject randomisation has completed and required number of gastric and/or duodenal ulcer events are confirmed.

Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator, sub-investigator, the head of the institution (for Japan), and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/sub-investigator 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.

Completion of the study (for Japan)

Upon terminating the study, the Principal Investigator/sub-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 institution's rules. The head of the study site, who is informed of the termination by the investigator, will provide a written notification of the results to the IRB and AstraZeneca.

10. DATA MANAGEMENT

Data will be entered in the Web Based Data Capture (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 guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. The principal investigator will then sign the eCRF electronically. Clean file occurs when all data have been declared clean and signed by the principal investigator. The data will be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Primary efficacy variable

The primary efficacy variable of this study is the time from randomization to occurrence of gastric or duodenal ulcers.

11.1.2 Secondary efficacy variables

The secondary efficacy variables of this study include:

- Presence/absence of gastric and/or duodenal ulcer until Weeks 12, 24, 36, 48, 60 and 72 after randomisation
- Degree of gastric mucosal lesion according to the modified LANZA score at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
- Presence/absence and severity of RE evaluated by LA classification at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
- Presence/absence and severity of gastrointestinal symptoms assessed by the investigator(s) at each visit

11.2 Calculation or derivation of safety variable(s)

Safety variables are as below.

- Adverse events
- Clinical laboratory values
- Vital signs (blood pressure and pulse rate)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations of investigational product due to AE (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs (blood pressure and pulse rate) data will be performed for identification of OAEs.

Examples of these are marked haematological, biochemical and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of pharmacogenetic variables

Pharmacogenetic variables are as below.

Genotypes of CYP2C19

- Homo EM
- Hetero EM
- PM

This variable will be used to investigate the effect of CYP2C19 polymorphism on the efficacy of D20.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

All analysis sets will be determined before unblinding the study.

12.1.1 Efficacy analysis set

For analysis of the efficacy data, two analysis populations will be set, namely; a full-analysis-set (FAS) and a per-protocol-set (PPS), and the primary statistical analysis of all efficacy data will be performed using the FAS.

The FAS will consist of all subjects randomized to the study who took at least one dose of study medication and who had no active/current gastric or duodenal ulcer at baseline. The PPS will be a subset of subjects from the FAS, and those who comply restrictions of the study treatment without any serious protocol deviations or violations.

12.1.2 Safety analysis set

All subjects who received at least one dose of randomised investigational product and for whom any post-dose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated subjects (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.2 Methods of statistical analyses

A comprehensive Statistical Analysis Plan (SAP) will be prepared before unblinding of the data. A significant level of $p<0.05$ (two-tailed) 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 K.K. using the SAS software.

12.2.1 Primary variable

The primary variable of this study is the time from randomisation to a occurrence of gastric and/or duodenal ulcer. Both FAS and PPS will be used for the analyses of the primary variable, but the primary analysis will be based on the FAS. In addition, a secondary analysis for the primary variable will be done using the FAS excluding the data of subjects who are judged not to have an ulcer scar by the central evaluation committee at baseline (see Section 12.4). In this analysis, the evaluation of the central committee for the presence/absence of gastric and/or duodenal ulcer after randomisation will be used.

If a occurrence of gastric and/or duodenal ulcer is confirmed by EGD, then the occurrence will be defined as an event. The time from the randomisation to the occurrence of the peptic ulcer will be analysed using the Kaplan-Meier method and shown as graphs. For subjects who have no occurrence of peptic ulcer throughout the study, they will be treated as censored at the timing of the last EGD. The time-to-event curves will be compared between D20 and placebo using a log-rank test.

As a secondary analysis, the primary variable will also be analysed based on a Cox proportional hazard model including effects of sex, age, *H. Pylo*ri status, dose of LDA and CYP2C19.

12.2.2 Secondary variables

12.2.2.1 Presence/absence of gastric and/or duodenal ulcers for up to 12, 24, 36, 48, 60 and 72 weeks after randomisation

Both FAS and PPS will be used for the analyses of these variables as well as the primary variable. In addition, a secondary analysis for these variables will be done using the FAS excluding the data of subjects who are judged not to have an ulcer scar by the central evaluation committee at baseline. In this analysis, the evaluation of the central committee for the presence/absence of gastric and/or duodenal ulcer after randomisation will be used.

Ulcer-free rates for each treatment group at Weeks 12, 24, 36, 48, 60 and 72 after randomisation will be calculated by the following two methods

Ulcer-free rate by the Kaplan-Meier method

The ulcer-free rates at Weeks 12, 24, 36, 48, 60 and 72 for each treatment group will be obtained from the Kaplan-Meier plot prepared in the analysis of the primary variable. These ulcer-free rates are defined as “estimated ulcer-free rates”. The two-sided 95% CIs of the estimated ulcer-free rates will be calculated using the Greenwood formula. Subgroup analyses for the estimated ulcer-free rates will be done for the following factors.

- Sex (Male, Female)
- Age (<65, 65-74, ≥75)
- *H. Pylo*ri status (Positive, Negative, Not evaluable/Sample lost)

- Dosage of LDA (≤ 100 mg, > 100 mg)
- Concomitant use of steroidal agent(s) (Yes, No)
- Concomitant use of antiplatelet drug(s) (Yes, No)
- Genotypes of CYP2C19 (Homo EM, Hetero EM, PM)
- Primary disease (Angina cordis, …)

Ulcer-free rate by EGD performed at each time point

For each time point of Weeks 12, 24, 36, 48, 60 and 72 after randomisation, the number of subjects who had a occurrence of gastric and/or duodenal ulcer confirmed by EGD at the corresponding time point or before will be calculated and the proportions of the subjects in the analysis sets will be obtained. These proportions will be defined as "observed ulcer-free rate". The 95% CIs of the observed ulcer-free rates will be calculated using the Newcombe-Wilson score method without continuity correction (Newcombe RG 1998). Subgroup analyses for the above factors will be done for the observed ulcer-free rates and thee 95% CIs.

12.2.2.2 Degree of gastric mucosal lesion by modified LANZA score at Weeks 12, 24, 36, 48, 60 and 72 after randomisation

These variables will be analysed using the FAS only. In addition, these variables will be analysed using the FAS excluding the subjects who were judged not to have an ulcer scar by the central evaluation committee at baseline.

Degree of gastric mucosal lesion will be evaluated using the modified LANZA score based on the results of EGD at pre-dose and at Weeks 12, 24, 36, 48, 60 and 72 after randomisation.

A cross table of the modified LANZA scores at pre-dose and each time point of post-dose will be prepared for each treatment group. In addition, scores at pre-dose, Week 12, 24, 36, 48, 60 and 72 and the changes from pre-dose to the time points at post-dose will be summarised for each treatment group using descriptive statistics.

12.2.2.3 Presence/absence and severity of reflux esophagitis at Weeks 12, 24, 36, 48, 60 and 72 after randomisation

These variables will be analysed using the FAS only. In addition, these variables will be analysed using the FAS excluding the subjects who were judged not to have an ulcer scar by the central evaluation committee at baseline.

Presence/Absence and the severity of RE will be evaluated using the LA classification based on the results of EGD at pre-dose and at Weeks 12, 24, 36, 48, 60 and 72 after randomisation.

The number and the proportion of subjects for each LA classification at Weeks 12, 24, 36, 48, 60 and 72 will be summarised for each treatment group.

12.2.2.4 GI symptoms assessed by the investigator(s) at each time point

These variables will be analysed using the FAS only. In addition, these variables will be analysed using the FAS excluding the subjects who were judged not to have an ulcer scar by the central evaluation committee at baseline.

GI symptoms will be assessed for each subject at pre-dose and each time point of post-dose on the 4-point scale 'None', 'Mild', 'Moderate' and 'Severe'. For each of the six GI symptoms, a cross table of the severities at pre-dose and each time point of post-dose will be prepared. For subjects who have 'None' for a symptom at pre-dose, the percentage of the subjects who have the symptom at the subsequent time points will be calculated at each time point of post-dose, and for subjects who have a symptom at pre-dose, the percentage of the subjects whose symptoms are resolved will be calculated at each time point of post-dose.

12.2.2.5 Safety variables

The safety evaluation of D20 will be performed based on AEs, clinical laboratory and vital signs (blood pressure and pulse rate) using the safety analysis set.

(a) AEs

AEs will be collected and recorded in the eCRF from the randomisation until the end of study. In addition, SAEs and DAEs will be collected and recorded from signing of informed consent. All AEs will be classified by system organ class and by preferred term using MedDRA. The number of subjects with AEs as well as total number of AEs will be summarised for each treatment group.

(b) Clinical laboratory test

Data of clinical laboratory values will be summarised for each treatment group using descriptive statistics.

(c) Vital sign

Data of vital signs (blood pressure and pulse rate) will be summarised for each treatment group using descriptive statistics.

12.2.3 Interim analyses

A single interim analysis to assess the superiority of D20 to placebo in the time to occurrence of peptic ulcer from randomisation will be performed when a minimum of 18 events have occurred in the overall population. However, if the number of randomised subjects is less than 250 at the time 18 events are confirmed, then the interim analysis will be postponed until 250 subjects are randomised.

After 18 events are observed, a date of the data cut off for the interim analysis will be decided as soon as possible. An event observed after the data cut off will not be used for the interim analysis.

The adjustment of the multiplicity for statistical tests will done using the Pocock-like alpha-spending function with Lan-DeMets approach, resulting that the nominal significance level will be two-sided 2.94% (Pocock SJ 1977) if exactly 18 events overall are reported at the time of the interim analysis. The exact nominal significance level will be determined based on the exact number of events at the time of the interim analysis.

The blind must be kept until the database lock for the interim analysis and after the database lock, the statistician of the IDMC will perform the interim analysis and will present the results to the other members of the IDMC. The IDMC will then make a recommendation that the study be stopped, amended or continue unchanged.

If 36 patients had an occurrence of gastric and/or duodenal ulcer prior to the randomisation of 250 patients, then the interim analysis will be cancelled.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The primary variable of this study is the time from randomisation to occurrence of peptic ulcer. The result of a phase III study (D961FC00003) was used to estimate the occurrence rates of peptic ulcer at 6 months for D20 and placebo. The event rates for peptic ulcer at 6 months were 1.5% for D20 and 7.4% for placebo, respectively.

In order to detect a difference in time to occurrence of peptic ulcer between D20 and placebo with two-sided 2.94% significance level and >90% power, assuming a recruitment period of 12 months and a minimum follow-up of 6 months; i.e. the total length of study is estimated to be 18 months, at least 36 events will be required. To get the number of events during the period in total 426 subjects (213 subjects per group) will be randomised in the study taking 15% of subjects who may discontinue the study without an event into consideration.

The final analysis of the primary variable will be performed when 36 events are observed. The nominal 2-sided significance level for all analyses will be 5%, except for the primary variable, where the nominal significance level will be adjusted using the Pocock-like alpha-spending function with Lan-DeMets approach to allow for a single interim analysis.

In this study, at least 100 subjects who are randomised to D20 will continue taking investigational product for one year to obtain long-term safety data because one-year safety data from at least 100 subjects are required according to the ICH E1 guideline "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions".

12.4 Central evaluation committee and independent data monitoring committee

12.4.1 Central evaluation committee

A central evaluation committee consisting of gastrointestinal specialists will be appointed for this study to validate the diagnosis by the investigator based on the EGD findings.

The central evaluation committee will review EGD findings regarded as ulcer scar, past EGD findings used for diagnosis in case of unclear scar, and EGD findings on the bases of which the investigator made a diagnosis of gastric or duodenal ulcer after starting the study treatment, as appropriate, for all subjects randomized to the investigational product. The central evaluation committee will report the review results to the sponsor.

The timing of meetings and responsibilities of the central evaluation committee will be specified separately.

12.4.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be appointed for this study. IDMC perform the interim analysis and decide on a recommendation on continuing or discontinuing the study. (See Section 12.2.3)

The timing of meetings and responsibilities of the IDMC will be specified separately.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

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

Name	Role in the study	Address & telephone number

13.2 Overdose

In this study, intake of 6 or more capsules of the investigational product per day by a subject will be considered an overdose.

No information is available on known antidotes for the investigational product. In case of an overdose or a suspected overdose, appropriate supportive measures should be given and the subject should be observed for vital condition.

In an overdose occurs, the following actions should b taken:

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

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

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

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

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study. The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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

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

The same timelines apply when outcome information is available.

14. LIST OF REFERENCES

The ACTIVE Investigators 2009
The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360.

Antithrombotic Trialists' Collaboration 2002
Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002, 324(7329): 71-86.

Bhatt DL et al 2008
Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2008, 52(18): 1502-17.

Bianchi Porro G et al 1996
Bianchi Porro G, Parente F, Imbesi V, Montrone F, Caruso I. Role of Helicobacter pylori in ulcer healing and recurrence of gastric and duodenal ulcers in longterm NSAID users. Response to omeprazole dual therapy. Gut. 1996 Jul;39(1):22-6.

Brun J et al 2001
Brun J, Jones R. Nonsteroidal anti-inflammatory drug-associated dyspepsia: the scale of the problem. Am J Med 2001, 110(1A):12S-13S.

Chan FK et al 2001
Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, Wu JC, Lau JY, Hui Y, Lai MS, Chan HL, Sung JJ. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med. 2001 Mar 29;344(13):967-73.

Hallas J et al 2006
Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ 2006, 333(7571): 726-8.

Hansson L et al 1998
Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998, 351: 1755-62.

Juul-Moller S et al 1992
Juul-Moller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Lancet 1992, 340(8833): 1421-5.

Kelly JP et al 1996
Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996, 348(9039): 1413-6.

Lai KC et al 2002
Lai KC, Lam SK, Chu KM, Wong BC, Hui WM, Hu WH, Lau GK, Wong WM, Yuen MF, Chan AO, Lai CL, Wong J. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med. 2002 Jun 27;346(26):2033-8.

Lanza FL et al 1988
Lanza FL, Aspinall RL, Swabb EA, Davis RE, Rack MF, Rubin A. Double-blind, placebo-controlled endoscopic comparison of the mucosal protective effects of misoprostol versus cimetidine on tolmetin-induced mucosal injury to the stomach and duodenum. Gastroenterology 1988;95:289-94

Lundell LR et al 1999
Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, J P Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of Los Angeles classification. Gut 1999;45:172-80

Nakashima S et al 2005
Nakashima S., et al.:A clinical study of Japanese patients with ulcer induced by low-dose aspirin and other non-steroidal anti-inflammatory drugs. Aliment Pharmacol. Ther 2005, 21 (Suppl. 2): 60-6

Newcombe RG 1998
Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Statist. Med. 1998; 17:857-72

Patrono C et al 2005
Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005, 353(22): 2373-83.

Pocock SJ 1977
Pocock SJ. Group sequential methods in the design and analysis of clinical trials. Biometrika 1977, 64,2: 191-9.

Sakamoto C et al 2006
Sakamoto C., et al.:Case-control study on the association of upper gastrointestinal bleeding and nonsteroidal anti-inflammatory drugs in Japan. Eur. J. Clin. Pharmacol, 2006, 62: 765-72

Serrano P et al 2002
Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment Pharmacol Ther 2002, 16(11): 1945-53.

Shiotani A et al 2009
Shiotani A, Sakakibara T, Yamanaka Y, Imamura H, Tarumi K, Manabe N, Kamada T, Kusunoki H, Hata J, Haruma K. Upper gastrointestinal ulcer in Japanese patients taking low-dose aspirin. J Gastroenterol. 2009, 44(2): 126-31. Epub 2009 Feb 13.

Sung J et al 2000
Sung J, Russell RI, Nyeomans, Chan FK, Chen S, Fock K, Goh KL, Kullavanijaya P, Kimura K, Lau C, Louw J, Sollano J, Triadiafalopulos G, Xiao S, Brooks P. Non-steroidal anti-inflammatory drug toxicity in the upper gastrointestinal tract. J Gastroenterol Hepatol. 2000 Oct;15 Suppl:G58-68

Yamamoto T et al 2007
Yamamoto T, Sanaka M, Nagasawa K, Abe K, Fukami M, Nakayama S et al. Gastroduodenal mucosal injury in patients on antiplatelet therapy. Thrombosis Research 2007, 120(4): 465-69

Yeomans ND et al 2005
Yeomans ND, Lanas AI, Talley NJ, Thomson AB, Daneshjoo R, Eriksson B, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. Aliment Pharmacol Ther 2005, 22(9):795-801.

Guidelines for Diagnosis and Treatment of Gastric Ulcer Based on the EBM 2007
Research Group for Applying and Evaluating a Guideline for Gastric Ulcer. A Guideline for the Diagnosis and Treatment of Gastric Ulcer based on EBM. Jiho, 2007