Clinical Study Protocol

Drug Substance	D961H
Study Code	D961HC00005
Date	
Edition Number	1

A Long Term Study to Investigate the Efficacy and Safety of D961H (20 mg once daily) for the Prevention of Gastric and/or Duodenal Ulcers Associated with Daily Nonsteroidal Anti-inflammatory Drug (NSAID) Use

Sponsor:

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

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

PROTOCOL SYNOPSIS

A Long Term Study to Investigate the Efficacy and Safety of D961H (20 mg once daily) for the Prevention of Gastric and/or Duodenal Ulcers Associated with Daily Nonsteroidal Anti-inflammatory Drug (NSAID) Use

Investigator

Study centre(s) and number of subjects planned

Study centre(s): Approximately 20 centres are planned for participation.

Number of subjects planned: 130 subjects

Study period		**Phase of development**
Estimated date of first subject enrolled:	October 2007	Phase III (A confirmatory study)
Estimated date of last subject completed:	June 2009	

Objectives

Primary objective:

To assess the safety and tolerability of D961H 20 mg once daily (D20) for up to 52 weeks of treatment involving patients with a history of gastric and/or duodenal ulcers receiving daily nonsteroidal anti-inflammatory drug (NSAID) therapy by evaluating AEs, clinical laboratory values and vital signs.

Secondary objectives

The secondary objectives are as follows:

- To assess the efficacy of D20 for prevention of development of gastric and/or duodenal ulcers in patients with a history of gastric and/or duodenal ulcer receiving daily NSAID therapy by evaluating the following:
  - Presence/absence of gastric and/or duodenal ulcers at Weeks 4, 12, 24 and 52 after initial administration

- Severity of gastric mucosal lesion evaluated by modified LANZA score (Lanza FL, et al., 1988) at Weeks 4, 12, 24 and 52 after initial administration

- Presence/absence and severity of NSAID-induced gastrointestinal (GI) symptoms assessed by investigator(s) every 4 weeks from Week 4 to Week 52 after initial administration

Study design

The study is a multicentre, open-label, single arm, long term study involving patients with a history of gastric and/or duodenal ulcers receiving daily NSAID therapy.

Target subject population

Patients aged 20 years and above with a history of gastric and/or duodenal ulcers (diagnosed having osteoarthritis, rheumatoid arthritis, lumbago, etc.) who are receiving daily NSAID therapy.

Test product, dosage and mode of administration

In this study the following test products will be used:

- D961H 20 mg-capsules

  Patients will receive one D961H 20 mg capsule once daily orally after breakfast for 52 weeks.

Comparator, dosage and mode of administration

In this study any comparator will not be used.

Duration of treatment

52 weeks

Outcome variables

- **Safety**
  - **Primary outcome variables:**
    - AEs
    - Clinical laboratory values
    - Vital signs
- **Efficacy**
  - **Secondary outcome variables:**

- Presence or absence of gastric and/or duodenal ulcers at Weeks 4, 12, 24 and 52 after initial administration

- Severity of gastric mucosal lesion by modified LANZA score at Weeks 4, 12, 24 and 52 after initial administration

- Presence/absence and severity of NSAID-associated gastrointestinal (GI) symptoms assessed by investigator(s) every 4 weeks from Week 4 to Week 52 after initial administration

Statistical methods

In this study, no hypothesis will be tested.

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

For gastric and/or duodenal ulcer free status, ulcer-free rates of gastric and/or duodenal ulcer at Week 4, 12, 24 and 52 and their 95% confidence intervals will be calculated by Kaplan-Meier Method. Also, ulcer-free rates based on EGD results of each measurement and its 95% confidence intervals will be calculated. Modified LANZA scores will be summarised for each measurement using descriptive statistics, and descriptive statistics of the changes from baseline will also be summarised. Presence/absence and severity of NSAID-associated GI symptoms will be summarised using a frequency table.

Since results from this study will be submitted for application for drug approval, interim analysis will be performed when 24-week data are locked.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.7.1.1)
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamic pyruvic transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
CK (CPK)	Creatine kinase (Creatine phosphokinase)
COX-2	Cyclooxygenase-2
CYP	Cytochrome P450
DMARD	Disease Modifying Anti-Rheumatic Drug
D20	D961H 20 mg once daily
D40	D961H 40 mg once daily
EBM	Evidence Based Medicine
eCRF	Electronic Case Report Form
EGD	Esophagogastroduodenoscopy
EM	Extensive Metaboliser
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
γ-GTP	γ-glutamyltranspeptidase
HIV	Human Immunodeficiency Virus
Hp	*Helicobacter pylori*
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MISO	Misoprostol

Abbreviation or special term	Explanation
NSAID	Nonsteroidal anti-inflammatory drug
OAE	Other Significant Adverse Event (i.e., adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.7.1.1).
PM	Poor Metaboliser
PPS	Per Protocol Set
SAE	Serious adverse event (see definition in Section 4.7.1.1).
WBDC	Web Based Data Capture
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective.
Principal investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator.
Investigator(s)	The investigator(s) in the study protocol means the principal investigator and co-investigators.

1. INTRODUCTION

1.1 Background

1.1.1 D961H features and background

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

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

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

In overseas clinical studies to assess pharmacokinetics, D961H was rapidly absorbed with maximal plasma concentration (C_{max}) reached within 1 to 2 hours after oral administration to humans. Bioavailability was 50% after a single dose of 20 mg and 68% after repeated dosing of 20 mg. The elimination half-life ($t_{½}$) in CYP2C19 extensive metaboliser was 0.9 hours after a single dose and 1.3 hours after repeated dosing. The metabolic rate of D961H was decreased in patients with severe liver dysfunction, but not decreased in those with mild or moderate liver dysfunction.

Drug interaction studies conducted overseas indicate that D961H interacts with the metabolism via CYP2C19 but not via CYP3A4.

Overseas clinical studies to assess the efficacy and safety of D961H, results from Phase I studies (approximately 860 subjects), indicated a more pronounced and sustained acid inhibition than corresponding doses of omeprazole. Short term (approximately 6800 subjects) showed more effective healing of reflux esophagitis as compared to other PPIs. On the other hand, the frequency of adverse events (AEs) in comparative studies with omeprazole and short-term placebo controlled studies was almost the same between D961H and omeprazole 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 B_{12}, did not indicate any significant changes over time. Also, from overseas experience, the general safety profile of esomeprazole derived from post-marketing surveillance is similar to that seen in the clinical studies.

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

Based on the above results, D961H is expected to be effective and safe for acid-related gastrointestinal diseases as omeprazole.

Approval status of D961H abroad

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

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

1.1.2 NSAID-associated peptic ulcer

NSAID is widely used agent with anti-inflammatoric and analgetic properties, being indicated for a variety of diseases such as rheumatic disease, painful disease and pyretic disease with the established efficacy. Of those with such diseases, patients with rheumatoid arthritis, osteoarthritis, lumbago or sciatic neuralgia require relatively long-term treatment with NSAID. The number of patients in Japan with these diseases is reported to be approximately

320,000, 860,000 and 290,000, respectively, which makes a total of 1.48 million (based on the result of the national survey of patients, 2002). Out of these patients, given the fact that the number of Japanese patients with osteoarthritis has been markedly increasing since 1993 (the national survey of patients, 2002), and osteoarthritis is caused by cartilage degeneration that is associated with aging, it is likely that the number of patients with osteoarthritis will increase reflecting the aging society, suggesting that more and more patients will have long-term use of NSAID.

While it is generally acknowledged that NSAID is effective and safe drug, it may cause clinically significant adverse drug reactions including gastrointestinal disorder, renal disorder and hepatic disorder. One of the most frequently reported adverse drug reactions caused by NSAID is gastrointestinal mucosal disorder. The survey conducted by the Japan Rheumatism Foundation showed that 15.5% and 1.9% of Japanese patients with rheumatoid arthritis who were treated with NSAID for 3 months or longer developed gastric ulcer and duodenal ulcer, respectively, thus, the prevalence of peptic ulcer was 3.8-4.7 times higher than that in the general population (Shiokawa Y, et al., 1991). The prevalence of peptic ulcer in patients with rheumatoid arthritis who used NSAID was 22% (Nakashima S, et al., 2005). The result from the questionnaire survey in members of the Japan Rheumatism Patient Group (dated December 5, 2000) showed that 1146 (65%) out of 1,764 patients with rheumatoid arthritis, who responded to the questions, had experienced any gastrointestinal disorders and 28% of these 1146 patients were diagnosed as having peptic ulcer (Rheumatic Disease Information Center).

The biggest caution should be given to upper gastrointestinal haemorrhage and perforation associated with peptic ulcer of all the gastrointestinal mucosal disorders caused by NSAID. The US national survey showed that 13 of 1,000 patients with rheumatoid arthritis who had taken NSAID for one year and 7.3 of 1,000 patients with osteoarthritis developed severe gastrointestinal complications, which suggests that at least 16,500 patients with rheumatoid arthritis or osteoarthritis per year would die in such complications (Singh G, et al., 1999). According to the recent Japanese epidemiological survey on upper gastrointestinal haemorrhage, the result from a case control study in the general population reported 5.8-fold higher risk of upper gastrointestinal haemorrhage in patients treated with NSAID including low-dosed aspirin (Sakamoto C, et al., 2005), compared to those not treated with NSAID. There is another report that approximately 30% of patients who were hospitalised due to haemorrhage associated with peptic ulcer have NSAID-associated peptic ulcer (Nakashima S, et al., 2005). Given the fact that NSAID-associated peptic ulcer is often asymptomatic (Shiokawa Y, et al., 1991), however, it is not easy to predict occurrence of peptic ulcer, judging from subjective symptoms. These reports suggest that appropriate preventive measures should be taken for patients on NSAID.

The use of NSAID is recommended as the first line therapy for the treatment of rheumatoid arthritis (The Manual for Diagnosis and Treatment of Rheumatoid Arthritis). Meanwhile, the following measures may reduce the risk of occurrence of peptic ulcer in patients on NSAID: (1) medication is switched to another drug with lower risks, (2) anti-peptic ulcer agent is given to prevent occurrence of gastrointestinal mucosal disorders. Selective COX-2 inhibitors are

currently developed to reduce the risk of adverse drug reactions caused by NSAID, which are one of the options for (1). Cardiovascular adverse drug reactions, etc. have been reported from selective COX-2 inhibitors, however, Food and Drug Administration (FDA) has instructed the pharmaceutical companies since April 2005 to include additional precaution in the Box Warning Section that NSAID including selective COX-2 inhibitors may cause cardiovascular and gastrointestinal events. Considering the above, selective COX-2 inhibitors have not been positioned as an alternative with lower risks. A prostaglandin derivative such as misoprostol [MISO], high-dosed H_2-receptor antagonists such as famotidine and proton pump inhibitors (PPIs) such as omeprazole are available as anti-peptic ulcer drugs described in (2). Although the efficacy of MISO for prevention of peptic ulcer has already been confirmed in many randomised comparative study and MISO is also approved as a drug for the treatment of gastric and duodenal ulcer in patients on NSAID in overseas, it has been reported that many patients treated with MISO developed diarrhoea and/or abdominal pain (package insert of Cytotec®). Meanwhile, omeprazole is effective to peptic ulcer without such adverse drug reactions as reported from MISO in overseas.

D961H has a potent action to inhibit gastric acid secretion and the efficacy to prevent development of NSAID-associated peptic ulcers has been confirmed in the results of the overseas clinical studies (SH-NEN-0013 and SH-NEN-0014). Based on these results, development of D961H, aiming at the approval for indication for prevention of NSAID-associated peptic ulcers in Japan, was planned.

1.2 Rationale

Gastrointestinal mucosal disorders associated with continuous treatment with NSAID are one of the major issues in clinical practice, and may lead to death caused by upper gastrointestinal bleeding due to peptic ulcer especially in the elderly, requiring appropriate measures. In Japan, as there is no drug available that has an effective action to prevent peptic ulcer, there is no report of clinical performance of the such drugs.

On the other hand, in the overseas placebo controlled clinical studies, the inhibitory effect on peptic ulcer was investigated several times in the patients who have been receiving NSAID for a long period and given D961H 20 mg once daily (D20) and D961H 40 mg once daily (D40) for 6 months orally (see Table 1). In these studies, the cumulative incidence of peptic ulcer was reduced by approximately 75% in the both groups of D20 and D40 comparing with the placebo group and there was no significant difference between two groups.

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

Study name	Target patients	Treatment period	Cumulative incidence of peptic ulcers (%)		
			Placebo	D20	D40
SH-NEN-0013	Having a history of peptic ulcers or over 60 years old	6 months	12.3 (n=185)	5.2* (n=192)	4.4* (n=196)

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

Study name	Target patients	Treatment period	Cumulative incidence of peptic ulcers (%)		
			Placebo	D20	D40
SH-NEN-0014	Having a history of peptic ulcer or over 60 years old	6 months	20.4 (n=267)	5.3* (n=267)	4.7* (n=271)

*p<0.05 (Log-rank test, vs placebo)

Based on the above clinical study results, D961H 20 mg once daily was approved in Europe and 20 mg to 40 mg once daily in the US for indications for prevention of NSAID-associated peptic ulcers.

In Japan, there is no drug approved for the indication for prevention of development of NSAID-associated peptic ulcer as mentioned above, 'A Guideline for the Diagnosis and Treatment of Gastric Ulcer based on EBM' (issued in 2007 by a research group for applying and evaluating a guideline for gastric ulcer) suggests that a preventive measure should be taken when NSAID is prescribed for the patients at high risk and recommends the use of prostaglandin preparation, PPIs, and high-dose H_2 receptor antagonist.

Based on the above, it was considered that it was appropriate to assess the efficacy and safety of D961H on prevention of development of gastric and/or duodenal ulcers in Japanese patients receiving NSAID for a long period and who are at high risk to develop NSAID-associated peptic ulcers, i.e. patients with a history of gastric and/or duodenal ulcers.

Another study is now ongoing to assess the efficacy of D20 24-week treatment for prevention of development of gastric and/or duodenal ulcers versus placebo in above-mentioned patients. In the present study, the primary objective is to assess the safety of concomitant use of D961H and NSAID for 52 weeks on the basis of 'The Size of Population and Treatment Period to Assess Safety at Clinical Study Phase for Drugs Intended for Long-Term Treatment of Non-life-threatening Conditions' (PMSB Notification No.592 dated 24 May 1995), which reflects ICH E1 guideline. As a secondary objective, the study will also assess the efficacy of concomitant use of D961H and NSAID for 52 weeks for prevention of development of gastric and/or duodenal ulcers.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to assess the safety and tolerability of D20 for up to 52 weeks of treatment involving patients with a history of gastric and/or duodenal ulcers receiving daily NSAID therapy by evaluating AEs, clinical laboratory values and vital signs.

2.2 The secondary objectives

The secondary objectives of this study are as follows:

- To assess the efficacy of D20 for prevention of development of gastric and/or duodenal ulcer in patients with a history of gastric and/or duodenal ulcer receiving daily NSAID therapy by evaluating the following:
  - Presence/absence of gastric and/or duodenal ulcers at Weeks 4,12, 24 and 52 after initial administration
  - Severity of gastric mucosal lesion evaluated by modified LANZA score (Lanza FL, et al., 1988) at Weeks 4, 12, 24 and 52 after initial administration
  - Presence/absence and severity of NSAID-associated gastrointestinal (GI) symptoms assessed by investigator(s) every 4 weeks from Week 4 to Week 52 after initial administration

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

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

This study is designed as a multicentre, open-label, single arm, long-term study involving patients with a history of gastric and/or duodenal ulcers receiving daily NSAID therapy.

A total of 130 patients with a history of gastric and/or duodenal ulcers with ulcer scar confirmed by the esophagogastroduodenoscopy (EGD) performed at screening will receive D20.

The safety of the concomitant use of D961H and NSAID for a long-term period will be assessed. The efficacy of D20 will be also assessed after 52-week oral administration based on the results of the EGD performed at Weeks 4, 12, 24 and 52 after initial administration to verify presence or absence of gastric and/or duodenal ulcers, and to evaluate the severity of gastric and/or duodenal mucosal lesion at Weeks 4, 12, 24 and 52 after initial administration according to modified LANZA score, and investigator's assessment for presence/absence and severity of GI symptoms performed every 4 weeks. If development of gastric and/or duodenal ulcer is observed, the patient will be discontinued from the study.

Findings of EGD including those judged from screening results with an evidence of an ulcer scar and those judged by the investigator(s) after initial administration as gastric and/or duodenal ulcers will be reviewed as needed by the central evaluation committee (see Section 6.7) established by AstraZeneca K.K..

An interim analysis will be performed when 24-week data is locked. The results from this analysis will be submitted to the authority for application for drug approval.

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

Table 2 Study Plan

Period	**Screening**		**Study Treatment**								
		Regis-tration									
Visit	**1**	**2**	**3**	**4**	**5**	**6 7**	**8**	**9 10**	**11**	**12 13 14**	**15 or at discontinuation[k]**
Number of weeks before and after Visit 2	**2W – 0**	**0**	**4W**	**8W**	**12W**	**16W 20W**	**24W**	**28W 32W**	**36W**	**40W 44W 48W**	**52W -**
Time window	**-**	**-**	**±4d**	**±4d**	**±4d**	**±4d**	**±4d**	**±7d**	**±7d**	**±7d**	**±7d**
Informed consent[a]	X										
Inclusion/exclusion criteria	X	X									
Demographic data	X										
Medical/surgical history	X										
Complications	X	X									
Physical examination	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	X	X
Clinical laboratory tests[b, c]	X		X	X[l]	X	X[l]	X	X[l]	X	X[l]	X
Pregnancy test (urine) [d]	X										
Hp test (IgG antibody)	X[m]										
Pepsinogen I/II	X										
Genetic test for CYP2C19	X[m]										
EGD[e]											
- Confirmation of presence/absence of gastric and/or duodenal ulcer[e]	X[n]		X		X		X				X
- Assessment of severity of gastric mucosal lesions[f]	X[n]		X		X		X				X
- Assessment of gastric mucosal atrophy expansion[g]	X[n]										
Evaluation of NSAID-associated GI symptoms by the investigator[h]		X	X	X	X	X	X	X	X	X	X
Registration		X									

Table 2 Study Plan

Period	**Screening**		**Study Treatment**								
		Regis-tration									
Visit	**1**	**2**	**3**	**4**	**5**	**6 7**	**8**	**9 10**	**11**	**12 13 14**	**15 or at discontinuation[k]**
Number of weeks before and after Visit 2	**2W – 0**	**0**	**4W**	**8W**	**12W**	**16W 20W**	**24W**	**28W 32W**	**36W**	**40W 44W 48W**	**52W -**
Time window	**-**	**-**	**±4d**	**±4d**	**±4d**	**±4d**	**±4d**	**±7d**	**±7d**	**±7d**	**±7d**
Dispense the investigational products		X	X	X	X	X	X	X	X	X	
Confirm/collect the remaining investigational products			X	X	X	X	X	X	X	X	X
Compliance status of D961H and NSAID[i]			X	X	X	X	X	X	X	X	X
AE confirmation[j]	◄	———	———	———	———	———	———	———	———	———	——►
Concomitant therapy/drug	◄	———	———	———	———	———	———	———	———	———	——►

a Should be obtained within 4 weeks prior to Visit 2 (registration)
b Clinical laboratory tests will be conducted at the central laboratory. The investigator(s) may confirm the eligibility of the subjects based on the results of measurements taken at the local laboratory within two weeks prior to registration, even if the measurement values were obtained before informed consent was given. However, baseline clinical laboratory values should be measured at the central laboratory within two weeks prior to registration.
c The subject must fast (for clinical laboratory tests, the subject must fast only for biochemistry tests).
d Pregnancy test will be conducted for premenopausal women of childbearing potential.
e According to the Sakita/Miwa classification.
f According to the modified LANZA score.
g According to the Kimura/Takemoto classification.
h The subject will complete the medical interview form (see Appendix D) at visit and the investigator(s) will confirm the contents of the form to assess severity of each symptom based on the severity classification.
i The subject will be instructed to record compliance of taking NSAID daily in Patient's Diary (see Appendix E) and bring the Diary at each visit for confirmation of the compliance.
j All SAEs and AEs resulted in the subject's withdrawal that occurred from the time when informed consent was obtained will be recorded in the eCRF. For AEs other than SAEs and AEs resulted in the subject's withdrawal, only those occurring from initial administration to the last scheduled visit or withdrawal will be recorded in the eCRF.

k If the subject discontinues the study before completing the treatment period (52 weeks), the subject should undergo the tests planned for Visit 15 (Week 52) as much as possible.
l Only a haematology test should be conducted (See Section 4.7.2 for details.)
m If these tests were missed at screening, they can be done at any visit until discontinuation/completion of the study.
n Test data obtained before informed consent can be used with the consent of the subjects, if the test was conducted within 2 weeks prior to the registration.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

A risk factor for development of NSAID-associated peptic ulcers

The results of the survey conducted by the Japan Rheumatism Foundation show that the prevalence rate of gastric ulcer accounted for 32.7% in patients with a history of gastric ulcer significantly higher than those without a history of gastric ulcer (11.8%) among the patients receiving daily NSAID. The prevalence rate of duodenal ulcer accounted for 10% in patients with a history of duodenal ulcer significantly higher than those without a history of duodenal ulcer (1.6%) (Shiokawa Y, et al., 1991). Moreover, the history of peptic ulcer is considered as one of primary risk factors of peptic ulcer occurrence in 'A Guideline for the Treatment and Prevention of NSAID-associated Ulcers' (Lanza FL, et al., 1998). The Guideline for the Diagnosis and Treatment of Gastric Ulcer based on EBM (issued in 2007 by a research group for applying and evaluating a guideline for gastric ulcer) also states that the history of ulcer is a risk factor to develop ulcer.

For above reasons a history of gastric and/or duodenal ulcers is included in the criteria as a risk factor to select target subjects for this study.

Rationale for setting the length of treatment period

The treatment period of 52 weeks was also set on the basis of 'The Size of Population and Treatment Period to Assess Safety at Clinical Study Phase for Drugs Intended for Long-Term Treatment of Non-life-threatening Conditions' (PMSB Notification No.592 dated 24 May 1995), which reflects ICH E1 guideline.

Rationale for setting the dosage

Based on the results of the overseas clinical studies giving D961H 20 mg and 40 mg once daily (see Table 1, Section 1.2), the dosage approved for prevention of peptic ulcers in the patients receiving NSAID for a long period in the overseas is 20 mg in Europe and 20 to 40 mg once daily in the US.

In Japanese Phase I study, the antisecretory effect was examined in each genotype of CYP2C19 based on the percentage of time with >pH 4 during 24-hour intragastric pH monitoring in the healthy adult males given D961H once daily orally for 5 days. The examined dosage was D961H 10 mg, 20 mg and 40 mg. From the results in 10 mg administration, compared with hetero Extensive Metabolizer (EM) and Poor Metabolizer (PM), the percentage of time with intragastric >pH 4 in homo EM was lower, and its level was similar to the one in placebo. For above reason, it was considered that more definitive antisecretory effect would be needed for prevention of peptic ulcers, and that sufficient antisecretory effect and clinical effect could not be obtained in homo EM with 10 mg. Therefore, 10 mg is not included in this study. In addition, since it is predicted that clinical dose of D961H for treatment of peptic ulcers is 20mg, more than 20 mg as clinical dose for prevention of development of peptic ulcers is not included in this study.

For the above reasons, it is considered appropriate to select D20 as an optimal dose to prevent peptic ulcers in the Japanese patients receiving NSAID for a long period. Therefore, the efficacy and safety of D20 will be investigated in this study.

Rationale for not setting comparator

The safety profile has been well established with results from clinical studies and post-marketing surveillance data in overseas. Results from Phase I study in Japan indicate that the safety profile of Japanese is similar to that of Caucasian. Therefore, it was considered that the safety of D20 in long-term treatment could be sufficiently evaluated as the primary objective in an open-label, single arm study in patients continuously receiving NSAID for a long period.

Rationale for a genetic test

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

Rationale for a Hp test

In the meta-analysis for the overseas clinical studies to investigate the relationship of Hp infection and NSAID-associated peptic ulcers, it was concluded that there is a synergistic effect between Hp infection and use of NSAID to increase the ulcers (Huang JQ, et al., 2002). In Japan Hp infection and use of NSAID increase development of upper GI haemorrhage synergistically (Sakamoto C, et al., 2005). Furthermore, 'A Guideline for the Diagnosis and Treatment of Gastric Ulcer based on EBM' suggests the relevance of Hp as it describes that Hp eradication decreases the development of ulcers especially for the patient who are going to use NSAID and the effect for the prevention of NSAID-associated peptic ulcers of Hp eradication is inferior to that of PPI. However, the results of the investigation showed that recurrence rates of gastric ulcers in the three treatment groups of patients with history of Hp negative gastric ulcer, Hp positive gastric ulcer, and Hp eradicated gastric ulcer showed no significant difference between the three groups (Bianchi-Porro G, et al., 1996). It has been reported that the percentage of Hp positive patients with NSAID-associated peptic ulcer is usually lower than those with common peptic ulcer (Mizogami Y, et al., 2005, Chiba T, et al., 2005, Maeda A, et al., 2002). For this, it is considered necessary to conduct a versatile study to investigate the relationship between Hp infection and NSAID-associated peptic ulcers. Based on the above, information on presence or absence of history of Hp infection will be collected in this study as part of demographic data.

Rationale for pepsinogen I/II measurements

It is assumed that numbers of elderly patients are on the long-term treatment with NSAID. Based on the report on the investigation of gastric acid secretory capacity in the adult Japanese population using the index of pH5, gastric pH tends to be increased with age (Morihara M, et al., 2001). For this, patients with hypochlorhydria may be included in the target population aiming at prevention of NSAID-associated peptic ulcers.

On the other hand, considering from the results of the report showing that the incidence of NSAID-associated peptic ulcers increased with age (Shiokawa Y, et al., 1991) and that the gastric acid secretion inhibitor is also significantly effective for the peptic ulcers induced by the use of NSAID and other various stresses although the acid secretion is not increased in these peptic ulcers (A Guideline for the Diagnosis and Treatment of Gastric Ulcer based on EBM), it is also considered that NSAID-associated peptic ulcers can be prevented by inhibition of gastric acid secretion.

In this study, the subjects with hypochlorhydria will be specified and the efficacy of D961H in those subjects will be confirmed. In general, progression of gastric mucosa atrophy may cause decreases in gastric acid secretion, therefore, pepsinogen I/II will be measured in order to identify the level of the atrophy in this study.

3.2.2 Risk/benefit and ethical assessment

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

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

The planned indication of D961H is prevention of NSAID-associated peptic ulcers, and long term combination therapy with D961H and NSAID will be assumed; therefore, it is necessary to review the safety of long-term combination therapy with D961H and NSAID. In the overseas clinical studies (I-1001, I-1002, I-1003, and I-1004), the preventive effects of omeprazole against NSAID-associated peptic ulcers were examined. The incidence of AEs in the omeprazole group (60.1-67.6%) was similar to that for the ranitidine group (58.3%) and MISO group (71.4%) and it seemed slightly higher than that for the placebo group (53.2%). The reason why the incidence of AEs in the omeprazole group was slightly higher comparing with the placebo group was considered that there were a number of subjects who discontinued the study treatment due to development of gastric and/or duodenal ulcers and this may have been the influence to shorten the treatment period for the group. Most common AEs observed in each study in which the treatment with omeprazole and its preventive effects were examined as mentioned above were gastrointestinal related events (diarrhoea, abdominal pain, meteorism, etc.) in all treatment groups including the placebo group. As for the incidence of SAEs, there was no remarkable difference between the omeprazole group and control groups (including the placebo group) in all clinical studies mentioned above. Based on these results, it was considered that a trend of the incidence of AEs in the combination therapy with omeprazole and NSAID would not markedly differ from that was seen in the monotherapy group given NSAID alone (i.e., placebo group) or in the combination therapy group given NSAID and ranitidine or MISO. For this, there is little possibility that unexpected or new safety problem is caused by the concomitant therapy with omeprazole and NSAID.

As for the possibility of the drug interactions when omeprazole is used concomitantly with NSAID, clinically significant drug interactions occur at the low possibility (Andersson T, et al., 1998) based on the results of the overseas clinical studies of NSAID (naproxen, diclofenac, and piroxicam) and omeprazole in combination therapy to investigate pharmacokinetic drug interactions (SH-OMN-0002, SH-OMN-0003, and SH-OMN-0004).

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

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

In the overseas studies (SH-NEN-0002, SH-NEN-0004, SH-NEN-0013, SH-NEN-0014), the long-term safety of D961H used concomitantly with NSAID was examined. The frequency of patients reporting AEs was about 64% in all treatment groups (D961H 20 mg, D961H 40 mg, placebo). The most common AEs during treatment with D961H for 6 months were gastritis and flatulence. Symptoms from the gastrointestinal disorders were the most commonly reported system organ class of AEs. For this, there would be little possibility that unexpected or new safety issues are caused by the concomitant therapy with D961H and NSAID, as in the case of omeprazole.

The general rule used to predict the possibility of metabolic drug-drug interactions between compounds is that interactions are most likely to be limited to drugs metabolized by the same enzyme. Since D961H is mainly metabolised by cytochrome P450 (CYP) isoform, CYP2C19 and CYP3A4 (Andersson T, et al., 1990, Andersson T, et al., 1993, Chiba K, et al., 1993, Andersson T, et al., 1994), and the NSAID has been shown to be mainly metabolized by another CYP isoform, CYP2C9 (Leemann T, et al., 1993, Newlands AJ, et al., 1992, Leemann TD, et al., 1993). A drug-drug interaction at the metabolism level would not be expected to appear during coadministration of D961H and NSAID. The clinically significant drug interactions may occur at low possibilities when D961H is used concomitantly with NSAID based on the results from the overseas clinical studies of NSAID (naproxen and rofecoxib) and D961H in combination therapy to investigate pharmacokinetic drug interactions (SH-NEN-0016 and SH-NEN-0017).

3.3 Selection of study population

3.3.1 Study selection record

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

3.3.2 Inclusion criteria

For inclusion in the study subjects must fulfil all of the following criteria:

1. Provision of written informed consent (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 registration. 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 registration. In the case that the results of the test did not demonstrate the scar clearly but the subject had an evidence of ulcer conformed by EGD performed in the past he/she will be eligible.
3. A diagnosis of a chronic condition (rheumatoid arthritis, osteoarthritis, lumbago, etc.) that is expected to require daily NSAID treatment during the study treatment period. Daily NSAID treatment is defined as taking the prescribed dose at least 5 out of 7 days each week following the physician's instruction.
4. Dose* and type of the NSAID must be:
   - expected to be used at a constant dose during the period from the registration to the day of the last scheduled visit.
   - administered orally. Additional oral NSAID and external application with NSAID are acceptable in addition to daily oral NSAID.

* Handling of aspirin when used as a analgesic agent:
1) When aspirin alone is used, the dose should be more than or equal to 1000 mg/day.
2) When aspirin is used as an additional NSAID, the dose should be more than 324 mg/day.

5. Following criteria must be satisfied when Disease-Modifying Antirheumatic Drug (DMARD [such as methotrexate]) is taken:
   - If the subject has been taking DMARD before registration, it must have been taken for four weeks or longer before registration at the constant dose.
   - DMARD is expected to be taken at the constant dose during the period from the registration to the day of the last scheduled visit.

Rationale for inclusion criteria

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

2. In order to enrol patients at a high risk to develop NSAID-associated peptic ulcer, a history of gastric and/or duodenal ulcers is included in the criteria as a risk factor.

3. In order to enrol patients at high risk to develop NSAID-associated peptic ulcer, this criterion is established to assure that patients who require the long-term treatment with NSAID are enrolled.

4. This criterion is established since there is a relationship between the doses of NSAID and development of peptic ulcer (Rodriguez G, et al., 1994, Singh G, et al., 1998, Carson JL, et al., 1987, and Griffin MR, et al., 1991). Thus, influences of NSAID on the evaluation of the efficacy of D961H will be minimised by providing the conditions for use of NSAID.

5. This criterion is established to minimise the influence of DMARD on the evaluation of the efficacy of D961H by defining the requirement when DMARD are taken.

3.3.3 Exclusion criteria

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

1. Less than 20 years of age at the time of informed consent obtained.
2. Having gastric or duodenal ulcer in active or healing stage according to the Sakita/Miwa classification.
3. History of esophageal, gastric or duodenal surgery, except for simple closure of a perforation.
4. Having severe liver disease, including cirrhosis and acute or chronic hepatitis.
5. Liver enzyme (AST, ALT, or ALP) or the total bilirubin level three times the upper limit of reference values at laboratory tests conducted within 2 weeks prior to registration.
6. Having a chronic renal disease or impaired renal function or serum creatinine >2.0 mg/dL as a result of laboratory test conducted within 2 weeks prior to registration.
7. Current or historical evidence of the following diseases/conditions:
   - Zollinger-Ellison syndrome
   - Inflammatory bowel disease (IBD)
   - EGD evidence or suspicion of a (non NSAID-related) pathologic or infiltrative process in gastric and/or duodenum (e.g., Crohn's disease, malignancy, sarcoidosis, amyloidosis, ischemic disease)
   - Any condition that requires surgery during the study period (from the day of informed consent to the day of the last scheduled visit or withdrawal).
8. History of malignant disease except for mild superficial cutaneous disease (within 5 years before registration)
9. Current or historical evidence (within 12 weeks prior to registration) of the following diseases/conditions:
   - Malabsorption
   - Esophageal stricture
   - Esophagitis, other than simple erythema

- Endoscopic Barrett's esophagus (columnar-lined epithelium more than or equal to 3 cm) or dysplastic changes (based on the documented findings) of any grade in the esophagus
- Signs and symptoms of gastric outlet obstruction (e.g., abdominal distension or multiple episodes of vomiting)
- Pancreatitis
- Severe cardiovascular or pulmonary disease
- Diabetes mellitus uncontrolled on dietary management, exercise therapy or medication
- Cerebral vascular disease, such as cerebral ischemia, infarction or haemorrhage.

10. Pregnancy or lactation. Women of childbearing potential must have a negative urine pregnancy test at screening, and have to maintain effective contraception during the study period as judged by the investigator(s).
11. Use of any other investigational product or participation in any other clinical study within 4 weeks prior to registration.
12. Prior enrolment in the study. (Only of subjects who are confirmed having gastric or duodenal ulcer in active or healing stage according to the Sakita/Miwa classification by EGD at screening can be re-enrolled if the subjects are confirmed healing and provide informed consent for the second time.)
13. Need for continuous concomitant therapy with:
    - anticoagulants/antiplatelets (including aspirin <325 mg daily)
    - PPI (except for the investigational product)
    - H_2-receptor antagonists
    - M_1-receptor antagonists
    - Hp eradication therapy
    - Antacid
    - Prostaglandin analogue indicated for peptic ulcers (e.g. MISO)
    - Anticholinergics used for GI indications
    - Gastrointestinal promotility drugs
    - any drug known to have drug interactions with D961H and/or omeprazole, (e.g. human immunodeficiency virus (HIV) proteinase inhibitor such as atasanavir

sulphate and so on, diazepam, phenitoin, warfarin, tacrolimus hydrate, digoxin, methyldigoxin, itraconazole, gefitinib, voriconazole)

– Anticancer drugs

– mucosal-protectants

14. Any significant "alarm symptoms" within 24 weeks prior to registration, such as, unintentional weight loss, gastrointestinal bleeding, jaundice, or other sign indicating severe or malignant disease.
15. Subjects with disease/symptom allowing no administration of investigational product, such as known or suspected allergy or sensitivity to PPI.
16. Any history of a generalised bleeding disorder resulting from haemorrhagic diathesis (e.g., abnormalities in clotting factors or platelets).
17. Use of a PPI, or H_2-receptor antagonist within one week prior to registration.
18. History of drug addiction or alcoholism within the past 12 months before registration.
19. Inability to understand or provide informed consent.
20. Inability or unwillingness to take investigational product according to dosing instructions.
21. Inability to undergo EGD, or unwillingness to undergo multiple EGD.
22. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

Rationale for exclusion criteria

Above criteria for excluding concomitant diseases, concomitant drugs, and specific patients' conditions are established since these factors may influence on the evaluation of the inhibitory effects of the investigational products and the safety of the patients.

3.3.4 Restrictions

Subjects must follow the following restrictions during the study period:

1. The subject must fast before blood sampling for biochemistry test and undergoing EGD according to the procedures specified by the study centre.

2. If the subject has been taking DMARD before registration, it must have been taken for four weeks or longer before registration at the constant dose. The dose is expected to be taken at the constant dose during the period from the registration to the day of the last scheduled visit or withdrawal.

3.3.5 Discontinuation of subjects from study treatment or assessment

3.3.5.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time.

Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged as the patient to be discontinued by the investigator(s) and/or AstraZeneca K.K.
- Severe non-compliance to protocol as judged by the investigator(s) and/or AstraZeneca K.K.
- Incorrect enrolment i.e., the subject does not meet the required inclusion/exclusion criteria for the study
- Subject lost to follow-up
- Occurrence of an event in conflict of exclusion criteria (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.
- Permanently stopping treatment with daily NSAID
- Others as judged appropriate by the investigator(s) (reasons for discontinuation must be recorded in eCRF)

3.3.5.2 Procedures for discontinuation

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

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

3.4 Treatments

3.4.1 Identity of test product and comparator

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

Table 3 Investigational products

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

Packaging of the investigational product:

Fourteen capsules of D961H 20 mg will be packed in a blister pack under the responsibility of Investigational Products, AstraZeneca R&D Mölndal, Sweden. 30 blister packs (420 capsules in total) will be packed in a paper box.

3.4.2 Doses and treatment regimens

One capsule of the investigational product will be orally given once daily after breakfast for the period of 52 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.

3.4.3 Labelling

Labels are affixed to the paper box. Each label will contain the description of name of the investigational product, study code, batch number, quantity, expiry date, storage condition, instruction, name of sponsor and address, 'for clinical study use'.

3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. Appropriate storage conditions are described on the investigational product label. They are also described in the document 'Procedures for drug storage'.

3.4.5 Accountability

AstraZeneca K.K. 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 K.K.. The investigational product provided to the study site must only be used for the purpose and the dosage as directed by the clinical study protocol.

The investigator(s) and/or the Investigational Product Storage Manager must instruct the subject to return unused investigational products and used blister packs. The investigator(s) and/or the Investigational Product Storage Manager must also confirm the number of capsules 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 unprescribed and remaining investigational products are returned to AstraZeneca K.K..

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

3.5 Method of assigning subjects to treatment groups

The investigator(s) will explain about the study to potential candidates, and obtain written informed consent. Prior to registration, the investigator(s) will judge eligibility of the subjects who provided informed consent. Only of the subjects who are confirmed having gastric and/or duodenal ulcer in active or healing stage according to the Sakita/Miwa classification by EGD at screening can be re-enrolled once the subjects are confirmed healing and provide informed consent for the second time. Registration should be done only once for the same subject. Enrolment code and registration code once given to the patient who withdrawn from the study should not be reused.

At the time of informed consent obtained, an enrolment code will be allocated to each subject at each study site to identify the subject. The enrolment code (E01XXYYY) is composed of 4 digits (01XX) 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. For centre number(s), see Supplement A "Investigators and Study Administrative Structure".

After confirming the eligibility of the subject who has given his/her consent, the investigator(s) will register the subject in accordance with the manual of procedure of subject registration provided by AstraZeneca K.K.

3.6 Blinding and procedures for unblinding the study (Not applicable)

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

The use of all medications including investigational products and over-the-counter drugs during the study period must be recorded in the appropriate sections of the eCRF. However, drugs used for pre-treatment of EGD (e.g. xylocaine, anticholinergic agents, anti-anxiety agents) will not be recorded in the eCRF.

3.7.1 Allowed concomitant treatments

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

- The treatment, which is considered necessary for the subject's safety and well-being (also when deterioration of underlying disease such as osteoarthrosis, rheumatoid arthritis, or lumbago is observed).

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

3.7.2 Allowed concomitant treatments with some limitations

The following treatments can be used concomitantly with some limitations.

- DMARD (However, if the subject has been taking DMARD before registration, it must have been taken for four weeks or longer before registration at the constant dose. The dose must be kept constant as much as possible during the period from the registration to the day of the last scheduled visit or withdrawal.)

3.7.3 Prohibited concomitant treatments

[Prohibited treatments prior to registration]

The following treatments cannot be used concomitantly for one week prior to registration.

- PPI
- H_2-receptor antagonists

[Prohibited concomitant treatments after registration]

The following treatments cannot be used concomitantly after registration:

- anticoagulants/antiplatelet drugs (doses of aspirin >324 mg daily are acceptable)
- PPI (except for investigational product)
- H_2-receptor antagonists
- M_1-receptor antagonists
- Hp eradication therapy
- antacid
- drugs classified as anticholinergics used for GI indications (scopolamine butylbromide used for pre-treatment before EGD is acceptable)
- gastrointestinal promotility drugs
- prostaglandin analogue indicated for peptic ulcer (e.g. MISO)
- any drug known to have drug interactions with D961H and/or omeprazole (e.g. HIV proteinase inhibitor such as atasanavir sulphate and so on, diazepam [use for pre-treatment before EGD is acceptable], phenitoin, warfarin, tacrolimus hydrate, digoxin, methyldigoxin, itoconazole, gefitinib, voriconazole)

- anticancer drugs
- mucosal-protectants

3.8 Treatment compliance

3.8.1 Compliance with the investigational product

The investigational product will be prescribed every 4 weeks, in principle. 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 instructions.

3.8.2 Compliance with NSAID

The subjects will be asked to record the daily compliance status for NSAID administration on the patient's diary and bring the diary (See at each visit. The investigator(s) will confirm the compliance status at each visit. 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 instructions.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary variables for this study will be AEs, clinical laboratory values and vital signs.

4.2 Screening and demographic measurements

The investigator(s) will obtain written informed consent from the subject prior to screening tests and assess if the subject meets the criteria for eligibility (see Sections 3.3.2 and 3.3.3).

Assessment and measurements will be performed for the following items:

Visit 1 (within 2 weeks prior to registration)

- Demographic data (sex, date of birth, race, smoking status, drinking habit, height, weight)
- Underlying diseases (requiring daily NSAID therapy), history of ulcers (existence/non-existence of previous definite diagnosis), history of Hp eradication, medical history (clinically significant symptoms/findings observed in the past but have been cured now), complications (diseases or symptoms under treatment [including being controlled by treatment]), surgical history, concomitant therapy/drug

- Physical examinations, vital signs (blood pressure and pulse rate measured in the sitting position)
- EGD (If EGD was performed within 2 weeks prior to registration, the data on the test before informed consent can be used with the consent of the subjects)
- Haematology, biochemistry, and urinary tests
- Hp test
- Pepsinogen I/II
- Genetic test for CYP2C19 (see Section 4.9 for details)
- Urine pregnancy test (for premenopausal women of childbearing potential only)

Visit 2 (the registration day)

- Physical examinations
- Assessment of NSAID-associated GI symptoms for the last 7 days (see Section 4.6.3 for details)
- AEs and complications
- Concomitant therapy/drug

4.2.1 EGD

4.2.1.1 Presence/Absence of gastric and/or duodenal ulcer

See Section 4.6.1.

4.2.1.2 Severity of gastric mucosal lesions

See Section 4.6.2.

4.2.1.3 Degree of expansion of gastric mucosal atrophy

At screening, types of the atrophy will be classified as follows according to the Kimura/Takemoto classification based on the site and shape of the atrophic border.

1. Closed type (atrophy is limited to the areas of the gastric antrum and lower part of the body of the stomach)

   C-1: Mild, C-2: Moderate, C-3: Severe

2. Open type (atrophy is widely expanded to the areas from the gastric antrum to upper part of the body of the stomach)

O-1: Mild, O-2: Moderate, O-3: Severe

3. No atrophy observed

4.2.2 Hp test (IgG antibody)

At screening, 2 mL of blood sample will be collected to measure IgG antibody and diagnose presence/absence of Hp infection (3 mL in total if samples for pepsinogen I/II measurement are collected at the same time). If this test was not done at screening, it can be performed at any visit until the study for the subject is discontinued or completed.
will collect and measure the sample.

4.2.3 Pepsinogen I/II

At screening, 2 mL of blood sample will be collected to measure pepsinogen I and II (3 mL in total if samples for IgG antibody measurement are collected at the same time).
will collect and measure the sample.

4.3 Patient-Reported Outcomes (PROs) (Not applicable)

4.4 Health Economic measurements and variables (Not applicable)

4.5 Pharmacokinetic measurements and variables (Not applicable)

4.6 Efficacy and pharmacodynamic measurement and variables

Objectives and variables for the efficacy measurement for this study are described in Table 4.

Table 4 Objectives and variables for the efficacy measurement

Objectives for the efficacy measurement	Variables
Secondary objective: To assess the efficacy of D20 for prevention of development of gastric and/or duodenal ulcer in patients with a history of gastric and/or duodenal ulcer receiving daily NSAID therapy by evaluating the following.	Presence/absence of gastric and/or duodenal ulcers at Weeks 4, 12, 24 and 52 after initial administration Severity of gastric mucosal lesion by modified LANZA score at Weeks 4, 12, 24 and 52 after initial administration Presence/absence and severity of NSAID-associated GI symptoms assessed by the investigator(s) every 4 weeks from Week 4 to Week 52 after initial administration

4.6.1 Presence/Absence of gastric and/or duodenal ulcer

4.6.1.1 Methods of assessment

At Visits 1, 3, 5, 8 and 15 (at screening, Weeks 4, 12, 24 and 52 after initial administration), EGD will be performed in the fasting state to confirm presence/absence of gastric and/or

duodenal ulcer based on the following criteria. If gastric and/or duodenal ulcer is present, the site, stage (the Sakita/Miwa classification) and longitudinal diameter of ulcer will be recorded in the eCRF.

Presence/Absence of gastric and/or duodenal ulcer

If gastric and/or duodenal ulcer is verified by EGD and is in the active stage (A1 or A2) or in the healing stage (H1 or H2) according to the Sakita/Miwa classification, "presence of ulcer" should be defined.

Site of ulcers:

Site I: cardia part, fornix, upper gastric corpus, middle gastric corpus, lower gastric corpus, gastric angle, pyloric vestibular part, bulb, retrobulbar region

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

Stage (Sakita/Miwa classification)

Active stage:

A1: Slough in the ulcer is thick with inflammatory swelling in the marginal area.

A2: Circumferential white ring and hyperemia are seen in the marginal area of the ulcer.

Healing stage:

H1: The ulcer is shrunk with redness in the marginal area, and mucosal plicae are gathering.

H2: The ulcer is further healed and upheaved, being covered with thin slough

Scar stage:

S1: so-called 'Red Scar': Hyperemia still remains in the centre of the scar.

S2: so-called 'White Scar': Hyperemia in the scar disappears, turning into the same colour as adjacent mucosa.

The longitudinal diameter

The longitudinal diameter will be measured referring such as endoscopy forceps. If several ulcers are found, record the longitudinal diameter of the largest ulcer.

EGD images

For the central review of confirmation about presence/absence of gastric and/or duodenal ulcer, EGD images showing the sites judged to be the scar of ulcers at screening and the sites

judged to be the ulcers during the treatment period with the investigational product (one each of close and distant views. The same is required for EGD images in the past used for a lesion with unclear scar) will be submitted to AstraZeneca K.K.. The personal information (such as the name and the medical record number) which can specify the patient should be masked before submission to AstraZeneca K.K..

4.6.2 Severity of gastric mucosal lesions

4.6.2.1 Methods of assessment

At Visits 1, 3, 5, 8 and 15 (at screening, Weeks 4, 12, 24 and 52 after initial administration), EGD will be performed to evaluate the severity of gastric mucosal lesions (erosion, haemorrhage) by modified LANZA score.

Modified LANZA Score:

0: Absence of haemorrhage and erosion

+1: One haemorrhage or erosion

+2: 2-10 haemorrhage or erosion

+3: 11-25 haemorrhages or erosion

+4: > 25 haemorrhage or erosion or an ulcer

4.6.3 Presence/absence and severity of NSAID-associated GI symptoms (assessment by investigator(s))

4.6.3.1 Methods of assessment

At each visit between Visits 2 and 15 (at registration, every 4 weeks from Week 4 to Week 52 after initial administration), the subject will complete the medical interview form (See about overall severity of each GI symptom associated by NSAID administration (epigastric pain, discomfort in the stomach, abdomen enlarged feeling, nausea/vomiting, heartburn, and anorexia) during the last 7 days. The investigator(s) will confirm the contents of the medical interview form to assess severity of each symptom based on the following severity classification and record in the eCRF.

GI symptoms

Epigastric pain: Pain in the stomach and epigastric fossa

Discomfort in the stomach: Discomfort with heaviness in the abdominal area

Abdomen enlarged feeling: Feeling enlargement in the abdomen

Nausea/vomiting: Feeling of throwing up and nauseous/throwing up stomach contents

Heartburn: Feeling burning in the areas from the stomach or lower part of the chest to the neck

Anorexia: Having no appetite

Severity classification

Each symptom will be assessed and classified into either severity given below:

None: Symptom free

Mild: Awareness of symptom, but easily tolerated

Moderate: Discomfort sufficient to cause interference with normal activities

Severe: Incapacitating, with inability to perform normal activities

(Normal activities include eating meals, working, and sleeping.)

4.7 Safety measurements and variables

The objective and variables of the safety measurements for this study are described in Table 5.

Table 5 Objective and variables for the safety measurements

Objective of the safety measurements	Variables
Primary objective: To assess the safety and tolerability of D20 after the 52 weeks treatment in patient with a history of gastric and/or duodenal ulcers receiving daily NSAID therapy by evaluating the following.	AEs, clinical laboratory values, vital signs

4.7.1 AEs

4.7.1.1 Definitions

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

AE

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an

AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

SAE

A SAE is an AE occurring during any study phase, and regardless of administration of the test product and comparator, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to 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.

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

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

Other Significant AEs (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of study treatment to the subject from study, will be classified as 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. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of AEs

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

For SAEs and AEs resulted in the subject's withdrawal, those occurred from the time when informed consent was obtained throughout the last scheduled visit or until withdrawal will be recorded at each visit.

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

(a) Abnormal findings

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

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

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

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

(b) Symptoms (gastric and/or duodenal ulcers) under study

Occurrence or deterioration of EGD findings (ulcer, erosion, bleeding) will not be recorded in the eCRF as AEs since they will be included in the efficacy evaluation, unless the symptom or finding is serious according to the definitions (See Section 4.7.1.1) or leading to withdrawal from the study due to reasons other than ulcer.

The investigator(s) will give an appropriate treatment and observe the course when the presence of gastric and/or duodenal ulcer is verified by EGD.

(c) Symptoms related underlying disease (requiring daily NSAID therapy)

Deterioration of underlying disease (requiring daily NSAID therapy) will be recorded on the eCRF as AE.

(d) Assessment of causality

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

Occurrence of symptoms (gastric and/or duodenal ulcers) under study will be recorded as the causality with the investigational product is 'None'.

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

(e) Maximum intensity

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

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

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

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

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

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

(g) Overdose

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

(h) Pregnancy

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

4.7.1.3 Reporting of SAEs

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs at his or her centre in the course of the study within 1 day (in this section, within 1 day is defined as "immediately but no later than the end of the next business day") of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the investigational product or to the study procedure(s). Wherever possible, this report should be made following the "Reporting Procedure of SAEs using Web-based Data Capture (WBDC) system" described below. The Principal Investigator must provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator must notify the SAEs in writing to the head of the medical institution immediately.

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

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

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

For all SAEs, the AstraZeneca representative will inform the AstraZeneca Drug Safety Department of it by day 1 and will work with the investigator(s) to compile all the necessary

information and ensure that the Drug Safety Department receives a report within 4 calendar days.

In addition AstraZeneca will provide details of any unexpected serious adverse drug reactions or expected fatal or life-threatening serious adverse drug reactions reported with regard to the test product or other compound available overseas in which the active ingredient is known to be equivalent to the test product, to the head of the medical institution, Principal Investigator and the regulatory agency. The head of the medical institution must submit a written report to the IRB providing the details of all AE case(s) reported by AstraZeneca.

(a) Reporting Procedure of SAEs using 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.

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Methods of assessment

During the study period, will be designated as a central laboratory for this study in order to assure that the standardisation of the assessment.

Baseline clinical laboratory test at screening must be conducted at the central laboratory for all subjects who provided informed consent within 14 days prior to registration. In the case that the results of the measurement cannot be confirmed before registration, the investigator(s) may confirm the eligibility of the subjects based on the results of tests performed the study centre within two weeks prior to registration, even if the test values were collected before provision of informed consent.

If the investigator(s) deemed it necessary from the clinical aspects (e.g., in the case of abnormal or severe AEs), additional blood samples may be collected.

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

Measurements of the following items should be performed in accordance with Table 2 'Study Plan'. See Section 4.7.1.2 for details of methods for recording and reporting AEs based on the findings of clinical laboratory values.

(a) Measurement items at Visits 1, 3, 5, 8, 11 and 15 (at Screening, Weeks 4, 12, 24, 36 and 52 after initial administration)

Biochemistry (in the fasting state)

For measurements of the following biochemistry test items (all with serum), a blood sample of approximately 4 mL at a time will be collected.

- AST(GOT), ALT(GPT), ALP, total bilirubin, albumin, creatinine, sodium, potassium, γ-GTP, total protein, BUN, total cholesterol, uric acid, triglyceride, LDH, CK(CPK)

Haematology

For measurements of the following haematology test items, a blood sample of approximately 2 mL at a time will be collected.

- Erythrocyte count, haemoglobin, haematocrit, leukocyte count, differential count of leukocytes (neutrophil, eosinophil, basophil, lymphocyte, monocyte), platelet count

Urinalysis (Dipstick)

A urine sample of 10 mL will be collected to examine occult blood, protein, and glucose.

(b) Measurement items at Visits 4, 6, 7, 9, 10, 12, 13 and 14 (Weeks 8, 16, 20, 28, 32, 40, 44 and 48 after initial administration)

Haematology

For measurements of the following haematology test items, a blood sample of approximately 2 mL at a time will be collected.

- Erythrocyte count, haemoglobin, haematocrit, leukocyte count, differential count of leukocytes (neutrophil, eosinophil, basophil, lymphocyte, monocyte), platelet count

4.7.3 Vital signs and physical examination

(a) Vital signs

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

(b) Physical examinations

At all visits, general appearance, lymph node, thyroid gland, cardiovascular system, lung, abdomen, musculoskeletal/extremities, and retortion will be examined. Presence/absence of

deterioration or new findings from the baseline (Visit 2) will be checked, and if relevant findings are found, they will be recorded as AEs in the eCRF.

4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each subject in this study is shown in Table 6.

Table 6 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Hp test		2	1	2
Pepsinogen I/II		2	1	2
Safety	Biochemistry	4	6	24
	Haematology	2	14	28
CYP2C19 genotype		2	1	2
Total				58

If blood samples for Hp test (IgG antibody measurements) and pepsinogen I/II are collected at the same time, a total of 3 mL will be appropriate.

4.8.1 Analysis of biological samples

4.8.1.1 Biochemistry samples

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

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

4.9 Genetic tests

4.9.1 Purpose of genetic tests

The purpose of the genetic research is to investigate the genotype of CYP2C19, a metabolising enzyme of D961H known to have two polymorphic genotypes, namely ‘extensive metabolisers’ (homo- and hetero-types) and ‘poor metaboliser’. Since the changes in the blood D961H concentrations show different tendency between the two metabolisers,

they will be examined as a background factor (for criteria for evaluation of phenotypes).

4.9.2 Collection of samples for genetic tests

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

will carry out collection of the samples and measurement. The results will be disclosed to AstraZeneca K.K. and the investigator(s).

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

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

4.9.3 Storage and coding of DNA samples

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

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

  In the case the subject in concern wishes a release of the genetic test results in the informed consent form, the result will be disclosed to the subject via investigator(s) after the database is locked. However, the result will be disclosed to the subject

immediately even before the database is locked only when the subject requests to do so during the study period.

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

5. DATA MANAGEMENT

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before the database lock.

Only descriptive analysis will be used in this study.

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

6.2 Description of outcome variables in relation to objectives and hypotheses

6.2.1 Primary variable

The primary variables of this study are as follows:

Safety variables

- AEs
- Clinical laboratory values

- Vital signs

6.2.2 Secondary variables

The secondary variables of this study are as follows:

Efficacy variables

- Presence or absence of gastric and/or duodenal ulcers at Weeks 4, 12, 24 and 52 after initial administration
- Severity of gastric mucosal lesion by modified LANZA score at Weeks 4, 12, 24 and 52 after initial administration
- Presence/absence and severity of NSAID-associated GI symptoms assessed by the investigator(s) every 4 weeks from Week 4 to Week 52 after initial administration

6.3 Description of analysis sets

The safety analysis set for the safety evaluation as the primary objective will include all subjects who take at least one dose of study medication, and who have data after initial administration.

The analysis of the efficacy variables that is the secondary objective will be preformed using a full-analysis-set (FAS). For gastric and/or duodenal ulcer free status, the analysis based on a per-protocol-set (PPS) will be also performed.

The FAS will consist of all subjects registered 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.

All analysis sets will be determined before database lock.

6.4 Method of statistical analysis

6.4.1 Primary variable

The safety evaluation of D20 as the primary objective of this study will be performed based on AEs, clinical laboratory values and vital signs using the safety analysis set.

(a) AEs

All AEs will be classified by system organ class and by preferred term using MedDRA and those occurred at baseline and after administration of the investigational products will be summarised in separate lists. AEs occurred after administration of the investigational products will be classified by system organ class and by preferred term using MedDRA. Data on drug-related AEs will be collected in the same manner, as required. The number of subjects who developed AEs, drug-related AEs, SAEs, and AEs led to withdrawal from the

study will be summarised, together with the total number of AEs, drug-related AEs, SAEs and AEs led to withdrawal from the study.

(b) Clinical laboratory values

Quantitative data of clinical laboratory values will be summarised for each measurement using descriptive statistics. Descriptive statistics of the changes from baseline (at screening) will also be summarised. Qualitative data will be summarised for each measurement using frequency table. Values before baseline and values of each measurement will be summarised in cross tables.

(c) Vital signs

Quantitative data of vital signs will be summarised for each measurement using descriptive statistics. Descriptive statistics of the changes from baseline (at screening) will also be summarised.

6.4.2 Secondary variables

Secondary variables, the efficacy variables, will be analysed using the FAS . For presence/absence of gastric and/or duodenal ulcer, the analysis based on PPS will be also performed.

6.4.2.1 Gastric and/or duodenal ulcer free status

The following two methods will be used to calculate each proportion of subjects without gastric and/or duodenal ulcer (ulcer-free rate) in FAS and PPS. The population excluding subjects who are declared not to have an ulcer scar by the central evaluation committee at baseline will be evaluated (see Section 6.7). In this analysis, the evaluation of the central committee for the presence/absence of gastric and/or duodenal ulcer after dosing will be used.

[Ulcer-free rate by the Kaplan-Meier method]

It will be defined as an event if gastric and/or duodenal ulcer is observed by EGD and the plots to show the period from the date of initial administration to the date of event occurred will be constructed using the Kaplan-Meier method. Data obtained from the subjects who have not developed ulcer throughout the study period will be cut off on the day of the last test with EGD. Ulcer free rates of gastric and/or and duodenal ulcer at Week 4, 12, 24 and 52 and its 95% confidence intervals will be calculated by the constructed Kaplan-Meier plots.

[Ulcer-free rate by EGD performed at each measurement]

Subjects who remained gastric and/or duodenal ulcer-free status confirmed by the EGD at Weeks 4, 12, 24 and 52 after the initial administration or those who discontinued the study by reason that gastric and/or duodenal ulcer-free status was confirmed before performing the EGD at each measurement will be considered as ulcer-free subjects and the proportion of the ulcer-free subjects will be calculated against the entire number of the subjects included in the

analysis population, and its 95% confidence intervals will be calculated. The proportion of the ulcer-free subjects will be stratified by the following factors to calculate the percentages for each subgroup.

- Sex (Male, Female)
- Age (<65, 65-74, 75≤)
- Hp positive/negative
- Number of types of NSAID (one or more types)
- Use of steroidal agent(s) (Yes or No)
- Genotypes of CYP2C19 (homo EM, hetero EM, PM)
- Underlying diseases (e.g., osteoarthritis, rheumatoid arthritis, lumbago)
- Degree of gastric mucosa atrophy (positive or negative)
  Positive: Concentration of pepsinogen I is 70.0 ng/mL or below and pepsinogen I/II is 3.0 or below
  Negative: Concentration of pepsinogen I is 70.1 ng/mL or above or pepsinogen I/II is 3.1 or above
- Extension of gastric mucosa atrophy (no atrophy, C-1, C-2, C-3, O-1, O-2, O-3)

6.4.2.2 Severity of gastric mucosal lesion by modified LANZA score

Severity of gastric mucosal lesion will be evaluated using the modified LANZA score based on the results of EGD at pre-dose and at Weeks 4, 12, 24 and 52 after initial administration. Descriptive statistics of the modified LANZA score at each time point of measurement will be calculated. Descriptive statistics of the changes from baseline will also be calculated.

6.4.2.3 NSAID-associated GI symptoms assessed by the investigator(s)

NSAID-associated GI symptoms, i.e., epigastric pain, discomfort in the stomach, abdomen enlarged feeling, nausea/vomiting, heartburn and anorexia, will be assessed for each patient every 4 weeks from Week 4 to Week 52 after initial administration on the 4-point scale ‘None’, ‘Mild’, ‘Moderate’ and ‘Severe’. For each of the 6 NSAID-associated GI symptoms, a cross table of the severities at pre-dose and each time point of measurement after administration will be prepared. For patients who have ‘None’ for a symptom at pre-dose, the percentage of the patients who have the symptom at the subsequent time points will be calculated at each time point of measurement after administration, and for patients who have a symptom at pre-dose, the percentage of the patients whose symptoms are resolved will be calculated at each time point of post-dose.

6.5 Determination of sample size

'The Size of Population and Treatment Period to Assess Safety at Clinical Study Phase for Drugs Intended for Long-Term Treatment of Non-life-threatening Conditions' (PMSB Notification No.592 dated 24 May 1995), which reflects ICH E1 guideline mentions that safety data of at least 300 subjects with 6-month treatment need to be included in submission data for new drug application, and that safety data of 100 subjects with 1-year treatment will be ultimately needed. The safety data of subjects receiving D961H 20 mg once daily for 6 months are planned to include data of approximate 155 subjects from ongoing Phase III study and 180 from a clinical study of maintenance treatment in subjects with gastroesophageal reflux disease. Therefore, 130 patients will be enrolled in this study to collect safety data of 100 or more subjects with 1-year treatment considering the discontinuation or the withdrawal from the study.

6.6 Interim analyses

Data up to 24-week administration will be summarised, analysed and submitted for application for approval. Data up to 52-week administration will be summarised and analysed to additionally submit before approval.

Data analysis will be performed after 24-week treatment data are locked, and the results will be included in the application. The final data analysis will be performed after all data (up to 52 weeks) of all subjects are locked. The set of patients for 24-week data analysis will consist of patients who received treatment and were discontinued from study treatment by the 24-week data is locked as well as patients who completed 24-week treatment.

6.7 Central evaluation committee

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

The board will review the findings of the baseline EGD that was judged as the scar of ulcer and EGD images taken before screening and used for eligibility assessment due to unclear scar at baseline, and EGD images by which the investigator(s) confirmed gastric and/or duodenal ulcer after initial administration as needed, and report the results of the review to AstraZeneca K.K..

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

7. STUDY MANAGEMENT

7.1 Monitoring

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

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

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigator(s) and study collaborators are adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (e.g., clinic charts).
- Perform source verification of the genetic consent of participating subjects and ensure that the investigational team is adhering to the specific requirements of this genetic test

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

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

7.1.1 Direct access to source data in Japan

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

The monitor(s) will verify data from the eCRFs against source data to ensure accuracy and completeness of documentation. When the data in the eCRF are changed or modified, the

monitor will confirm the amended part (and the reason for amendment) with the investigator(s).

7.2 Audits and inspections

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

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

7.3 Training of staff

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

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

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

7.4 Changes to the protocol

If a protocol amendment is required, the revised version of the protocol must be submitted to the head of the study centre to obtain an approval from the IRBs. If applicable, AstraZeneca K.K. should submit a notification to the regulatory before it is implemented.

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

If an administrative change is required, AstraZeneca will distribute it to IRB. If applicable, the approval of the local regulatory authority will be needed.

7.5 Study agreements

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

7.6 Study timetable and end of study

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

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site
- Approval of the study in written form by the IRB
- The head of Medical Institution Approval Letter
- Approval of the study, if applicable, by the regulatory authority

7.6.1 Planned duration of the study

Study period: October 2007 – June 2009

Registration period: October 2007 – June 2008

7.6.2 Discontinuation or suspension of the whole study programme

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

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

7.6.3 Completion of the study

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

7.6.4 Deviations from the protocol and the recording

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

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

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

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

7.6.5 Archiving of records at the study centre

7.6.5.1 Filing of study related materials

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

7.6.5.2 Archiving period

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

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

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

In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These essential documents should be retained for a longer period however if needed by AstraZeneca, 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.

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, and eCRF must be approved or given a favourable opinion in writing by an IRB as appropriate. The IRB must approve all advertising used to recruit patients for the study, if planned. The head of the medical institute must submit a copy of the written approval and documents describing decision of the head of the study centre along with the institutions related to the approval to AstraZeneca. A valid contract between the medical institution and AstraZeneca KK must be signed before the investigator(s) can enrol any patient into the study.

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

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

8.2 Ethical conduct of the study

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

For studies including genetic tests special precautions are taken as described in Section 4.9.

8.3 Informed consent

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

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

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

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

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

8.4 Subject data protection

The informed consent form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with Japanese data legislation. All data computer processed by AstraZeneca will be identified by enrolment code.

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

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

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

The results of the genetic test will be informed to AstraZeneca K.K. and the investigator(s) after the database is locked. In the case the subjects wished to be informed of the test results, the relevant information will be disclosed to the subject after the database is locked. However,

the result will be disclosed to the subject immediately even before the database is locked only when the subject requests to do so during the study period.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

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

Role in the study	Name	Address & telephone number
Monitors	See Supplement A	
Study Delivery Team Leader		AstraZeneca K.K. 1-88, 1-chome, Ohyodo-naka, Kita-ku, Osaka 531-0076 Tel: +81-6-6453-7442 Fax: +81-6-6453-7840
Study Delivery Team Physician		AstraZeneca K.K. 1-88, 1-chome, Ohyodo-naka, Kita-ku, Osaka 531-0076 Tel: +81-6-6453-8534 Fax: +81-6-6453-8562

9.2 Procedures in case of medical emergency

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

9.3 Procedures in case of overdose

Overdose is defined as taking 6 capsules or more of the investigational product a day.

Since there is no antidote for overdose of D961H, standard symptomatic therapy should be performed and monitor the status of vital signs in the event of overdose or when overdose is suspected.

Overdose must be reported as described below:

- An overdose associated with SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRFs.

- An overdose associated with non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

- An overdose without associated symptoms will not be recorded as an AE in the eCRFs. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

9.4 Procedures in case of pregnancy

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

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

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