Statistical Analysis Plan	
Study Code	D961WC00001
Edition Number	[redacted]
Date	23 January 2023

An Open Label, Parallel Group, Multi-centre, Phase III Study to Assess the Efficacy and Safety of D961H for the Maintenance Therapy Following Initial Treatment in Japanese Paediatric Patients with Reflux Esophagitis and for the Prevention of Recurrence of Gastric Ulcer or Duodenal Ulcer in Japanese Paediatric Patients Treated with Non-steroidal Anti-inflammatory Drugs or Low-dose Aspirin

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Study Statistician (CRO)	[redacted]	[redacted] Date
Japan Project Statistician (AstraZeneca)	[redacted]	[redacted]

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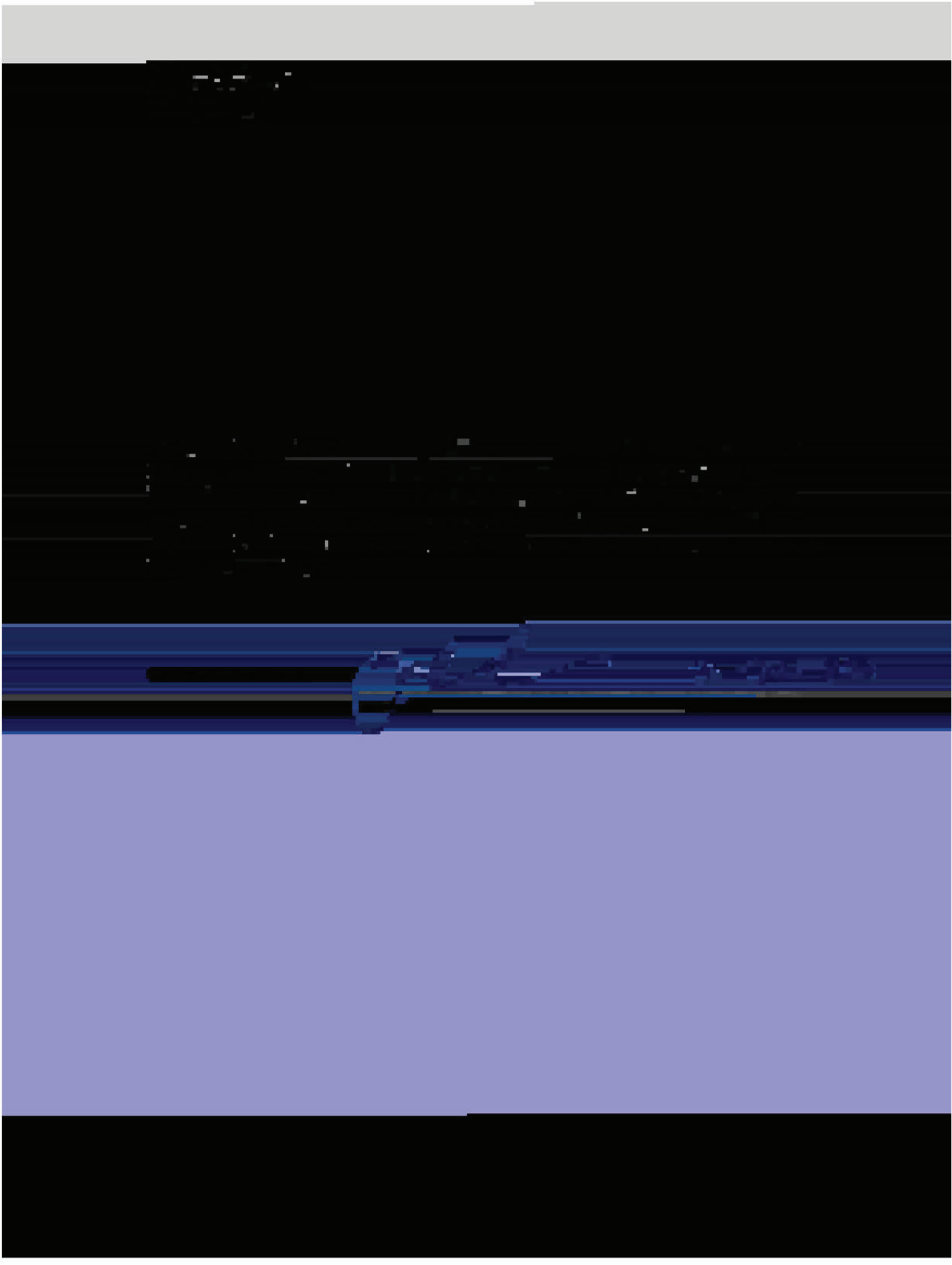

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	Confidence interval
CYP	cytochrome P450
DU	duodenal ulcer
eCRF	case report form (electronic)
EGD	esophagogastroduodenoscopy
GU	gastric ulcer
H. pylori	*Helicobacter pylori*
ICF	informed consent form
IgG	immunoglobulin G
LA classification	Los Angeles classification
LDA	low-dose aspirin
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	non-steroidal anti-inflammatory drugs
RE	reflux esophagitis
SAE	serious adverse event
SoA	schedule of activities

AMENDMENT HISTORY

Date	Brief description of change
	N/A

1 STUDY DETAILS

1.1 Study objectives

Table 1 shows the primary and secondary objectives in this study.

Table 1 Study objectives

Primary Objectives:	**Outcome Measures:**
Maintenance therapy for healed RE study part: • To assess the efficacy and safety of once-daily oral administration of D961H for the maintenance of RE healing in Japanese paediatric patients aged 1 to 14 years that have symptomatically healed RE (defined as no more than mild RE-related symptoms) and if EGD is done, no visible mucosal breaks observed.	Maintenance therapy for healed RE study part: • Presence/absence of RE relapse from 8 to 32 weeks for all subjects by assessment of the composite endpoint (RE-related symptoms or optional EGD findings) during the maintenance therapy. • Safety from 8 to 32 weeks for all subjects by the assessment of; a) AEs b) Laboratory variables c) Vital signs
Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part: • To assess the efficacy and safety of once-daily oral administration of D961H for the prevention of GU/DU recurrence in Japanese paediatric patients aged 1 to 14 years treated with long term NSAIDs/LDA therapy.	Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part: • Presence/absence of GU/DU recurrence from 0 to 32 weeks for all subjects by assessment of the composite endpoint (GU/DU-related symptoms or optional EGD findings) during the prevention therapy. • Safety from 0 to 32 weeks for all subjects by the assessment of: a) AEs b) Laboratory variables c) Vital signs

Table 1 Study objectives

Secondary Objectives:	Outcome Measures:
Maintenance therapy for healed RE study part: • To assess the efficacy of once-daily oral administration of D961H for the maintenance of symptomatically healed RE (defined as no more than mild RE-related symptoms) and if EGD is done, no visible mucosal breaks observed, from 8 to 52 weeks for subjects who continued the study treatment after Week 32. • To assess the safety of once-daily oral administration of D961H in the initial healing therapy period (0 to 8 weeks) for all subjects. • To assess the safety of once-daily oral administration of D961H for the maintenance of symptomatically healed RE (defined as no more than mild RE-related symptoms) and if EGD is done, no visible mucosal breaks observed from 8 to 52 weeks for subjects who continued the study treatment after Week 32. • To assess the RE-related symptoms during the initial healing therapy period (0 to 8 weeks) for all subjects. • To assess RE-related symptoms during the maintenance therapy from 8 to 32 weeks for all subjects, and 8 to 52 weeks for subjects who continued the study after Week 32. • To assess upper endoscopic findings during the maintenance therapy for subjects who had at least 1 EGD at post-dose. • To assess the pharmacodynamics with gastroesophageal pH monitoring during the maintenance therapy for subjects who had at least 1 pH monitoring at post-dose.	Maintenance therapy for healed RE study part: • Presence/absence of RE relapse from 8 to 52 weeks (8 to 32 weeks and 32 to 52 weeks) for subjects who continued the study treatment after Week 32 by assessment of the composite endpoint (RE-related symptoms or optional EGD findings) during the maintenance therapy. • Safety from 0 to 8 weeks for all subjects by the assessment of; a) AEs b) Laboratory variables c) Vital signs • Safety from 8 to 52 weeks (8 to 32 weeks and 32 to 52 weeks) for subjects who continued the study treatment after Week 32, by the assessment of; a) AEs b) Laboratory variables c) Vital signs • RE-related symptoms during the initial healing therapy period (0 to 8 weeks) • RE-related symptoms during the maintenance therapy • Endoscopic findings • Gastroesophageal pH measurement

Table 1 Study objectives

Secondary Objectives:	Outcome Measures:
Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part: • To assess the efficacy of once-daily oral administration of D961H for the prevention of GU/DU recurrence for 0 to 52 weeks for subjects who continued the study treatment after Week 32. • To assess the safety of once-daily oral administration of D961H for the prevention of GU/DU recurrence for 0 to 52 weeks for subjects who continued the study treatment after Week 32. • To assess GU/DU-related symptoms from 0 to 32 weeks for all subjects, and 0 to 52 weeks (0 to 32 weeks and 32 to 52 weeks) for subjects who continued the study treatment after Week 32. • To assess the endoscopic findings for subjects who had at least 1 EGD at post-dose. • To assess the pharmacodynamics with gastroesophageal pH monitoring for subjects who had at least 1 pH monitoring at post-dose.	Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part: • Presence/absence of GU/DU recurrence from 0 to 52 weeks (0 to 32 weeks and 32 to 52 weeks) for subjects who continued the study treatment after Week 32 by assessment of the composite endpoint (GU/DU-related symptoms or optional EGD findings) during the prevention therapy. • Safety from 0 to 52 weeks (0 to 32 weeks and 32 to 52 weeks) for subjects who continued the study treatment after Week 32, by the assessment of: a) AEs b) Laboratory variables c) Vital signs • GU/DU-related symptoms • Endoscopic findings • Gastroesophageal pH measurement

1.2 Study design

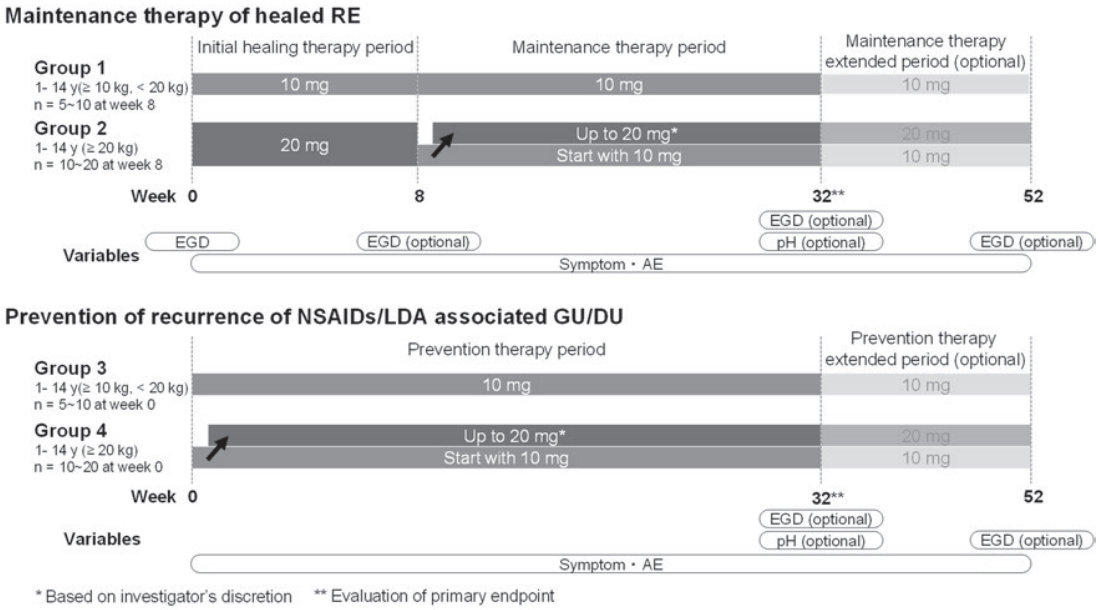
This study is an open label, parallel group, multi-centre, phase III study to assess the safety and efficacy of D961H in maintenance therapy following initial healing therapy in Japanese paediatric subjects with RE, and to assess the safety and efficacy of D961H in Japanese paediatric subjects treated with long term NSAIDs or LDA therapy who have a documented medical history of GU or DU diagnosis.

Doses of D961H in this study is set for the 2 groups (weight ≥10 kg, <20 kg and weight ≥20 kg) in the maintenance therapy for healed RE part and the prevention of GU/DU recurrence by NSAIDs/LDA part, because the individual difference in weight will be significant in paediatric subjects aged 1 to 14 years. The group of weight ≥10 kg, <20 kg

(Groups 1 and 3) and the group of weight ≥20 kg (Groups 2 and 4) should follow different regimen.

For an overview of the study design see Figure 1, Table 2, Table 3.

Figure 1 Study design



AE, adverse event; DU, duodenal ulcer; GU, gastric ulcer; EGD, esophagogastroduodenoscopy; LDA, low-dose aspirin; NSAIDs, non-steroidal anti-inflammatory drugs; RE, reflux esophagitis; y, year

Table 2 Schedule of Activities (SoA) in maintenance therapy for healed RE (Groups 1 and 2)

Activity	Informed consent ~ Registration	Initial healing therapy period		Maintenance therapy period		Maintenance therapy extended period		
	Enrolment	**Start of initial healing therapy**	**Site visits**	**Start of maintenance therapy**	**Site visits**	**Study closure 1[1)]**	**Site visit extended[2)]**	**Study closure 2[3)]**
Visit number	1	2	3	4	5, 6, 7, 8, and 9	10	11, 12, 13 and 14	15
Week	-4 ~ -1	0	4	8	12, 16, 20, 24, and 28	32	36, 40, 44, and 48	52
Day (allowance)	-28 ~ -1	1	29 (±7)	57 (±7)	85, 113, 141, 169, and 197 (±7)	225 (±7)	253, 281, 309, and 337 (±7)	365 (±7)
Informed consent/assent[4)]	X							
Registration to initial healing therapy		X[5)]						
Registration to maintenance therapy				X[6)]				
Review inclusion/exclusion criteria	X	X		X[7)]				
Demographic data	X							
Medical/surgical history		X						
Physical examination		X	X	X	X	X	X	X
Vital signs[8)]		X	X	X	X	X	X	X
Clinical laboratory tests[9)]		X		X		X		X
Urine pregnancy test[10)]		X						
H. pylori test (IgG antibody)		X						
Genetic test for CYP2C19[11)]		X						
EGD[12)]	X[13)]			(X)		(X)		(X)
Gastroesophageal 12-hour pH monitoring (optional)						(X)[14)]		
RE-related symptoms assessed by investigator[15)]		X	X	X	X	X	X	X

Activity	Informed consent ~ Registration	Initial healing therapy period			Maintenance therapy period		Maintenance therapy extended period	
	Enrolment	**Start of initial healing therapy**	**Site visits**	**Start of maintenance therapy**	**Site visits**	**Study closure 1[1)]**	**Site visit extended[2)]**	**Study closure 2[3)]**
Visit number	1	2	3	4	5, 6, 7, 8, and 9	10	11, 12, 13 and 14	15
Week	-4 ~ -1	0	4	8	12, 16, 20, 24, and 28	32	36, 40, 44, and 48	52
Day (allowance)	-28 ~ -1	1	29 (±7)	57 (±7)	85, 113, 141, 169, and 197 (±7)	225 (±7)	253, 281, 309, and 337 (±7)	365 (±7)
Dispense investigational product[16)]		X	X	X	X	X	X	
Administration of the investigational product[17)]		←	—	—	—	—	—	→
Check concomitant medication	←	—	—	—	—	—	—	→
Efficacy primary endpoint				←	—	→		
AEs and SAEs[18)]	←	—	—	—	—	—	—	→

1) Study closure visit for first period (to Week 32). Subjects who early discontinued the investigational product and/or withdrawn consent during first period (to Week 32) will be performed the activities described in Visit 10, if possible.
2) Site visits for subjects that extend treatment (after Week 32)
3) Study closure visit for extended period (after Week 32). Subjects who early discontinued the investigational product and/or withdrawn consent during extended therapy (after Week 32) will be performed the activities described in Visit 15, if possible.
4) The signed and dated informed consent form (ICF) should be obtained from the subject's legally authorised representative (including informed consent to a genetic test) prior to conducting of any study related procedure. Assent form will be signed by the subject as much as possible.
5) Perform registration whether the initial treatment is started or not; if an enrolled subject is not started initial treatment, this will be noted in the electronic case report form (eCRF).
6) Perform registration whether the maintenance therapy is started or not; if an enrolled subject is not started maintenance therapy, this will be noted in the eCRF.
7) Subjects who completed the healing therapy for 8 weeks at Visit 4 do not have any reflux esophagitis (RE)-related symptoms (none or not more than mild symptoms) on the RE-related symptom questionnaire, and if esophagogastroduodenoscopy (EGD) is done, no visible esophageal mucosal breaks, will continue into the maintenance phase.
8) Blood pressure, pulse rate and body temperature will be measured.
9) See Section 8.2.1 of protocol.
10) A urine pregnancy test will be required for all post-menarcheal female subjects, and the result must be negative at registration to the initial healing therapy. This test will be performed at each study site.

11) If the genotyping of CYP2C19 data are already available at each study site, it may be used with the consent of subject's legally authorised representative.
12) EGD should be conducted once at Visit 1. Post assessments are optional and allowed to perform anytime, and encouraged when RE relapse is suspected.
13) The EGD data within 4 weeks before the start of initial treatment could be used if available and given the consent of subject's legally authorised representative.
14) Optional evaluation. The pH monitoring is preferably done at Week 32, but is also suggested if signs of RE relapse either before (Week 8 to 32) or after (Week 32 to 52) this time point.
15) The RE-related symptom questionnaire will be provided at Visit 2 and following every visit to the subject. The subject and/or legally authorised representative will recall 1 week to date gastrointestinal symptoms and record them in the card. The card will be reviewed and collected by the investigator. The investigator will evaluate RE relapse every visit during the maintenance therapy.
16) Administration of the investigational product should be started on Day 1. Following administrations should be after breakfast. The subjects assigned to Group 1 will be treated with D961H 10 mg in the RE initial healing therapy and maintenance therapy, respectively. The subjects assigned to Group 2 will be treated with D961H 20 mg in the RE initial healing therapy, and treated with D961H 10 mg for the RE maintenance therapy. The dose may be increased to 20 mg at any visit during the RE maintenance therapy based on investigator's discretion. Dosing down back to 10 mg will not be allowed. The treatment period in both groups will be at least 32 weeks, and may be extended up to 52 weeks by investigator's discretion. The reason for the extension/no extension will be recorded in the eCRF.
17) When the subjects who assigned to Group 1 reach 20 kg after the start of investigational product administration in the maintenance therapy period, their treatment dose may be reconsidered as that of the treatment regimen for Group 2.
18) Adverse events (AEs) will be recorded from Visit 2. Serious adverse events (SAEs) will be recorded from the time of informed consent (Visit 1).

Table 3 SoA for prevention of GU or DU recurrence associated with long term NSAIDs or LDA Therapy (Groups 3 and 4)

Activity	Informed consent ~ Registration		Prevention therapy period		Prevention therapy extended period	
	Enrolment	**Start of treatment**	**Site visits**	**Study closure 1[1)]**	**Site visit extended[2)]**	**Study closure 2[3)]**
Visit number	1	2	3, 4, 5, 6, 7, 8, and 9	10	11, 12, 13 and 14	15
Week	- 4 ~ -1	0	4, 8, 12, 16, 20, 24, and 28	32	36, 40, 44, and 48	52
Day (allowance)	-28 ~ -1	1	29, 57, 85, 113, 141, 169, and 197 (±7)	225 (±7)	253, 281, 309, and 337 (±7)	365 (±7)
Informed consent/assent[4)]	X					
Registration to prevention therapy		X[5)]				
Review inclusion/exclusion criteria	X	X				
Demographic data	X					

Activity	Informed consent ~ Registration	Prevention therapy period			Prevention therapy extended period	
	Enrolment	**Start of treatment**	**Site visits**	**Study closure 1[1)]**	**Site visit extended[2)]**	**Study closure 2[3)]**
Visit number	1	2	3, 4, 5, 6, 7, 8, and 9	10	11, 12, 13 and 14	15
Week	- 4 ~ -1	0	4, 8, 12, 16, 20, 24, and 28	32	36, 40, 44, and 48	52
Day (allowance)	-28 ~ -1	1	29, 57, 85, 113, 141, 169, and 197 (±7)	225 (±7)	253, 281, 309, and 337 (±7)	365 (±7)
Medical/surgical history		X[6)]				
Physical examination		X	X	X	X	X
Vital signs[7)]		X	X	X	X	X
Clinical laboratory tests[8)]		X		X		X
Urine pregnancy test[9)]		X				
H. pylori test (IgG antibody)		X				
Genetic test for CYP2C19[10)]		X				
EGD[11)]				(X)		(X)
Gastroesophageal 12-hour pH monitoring (optional)				(X) [12)]		
GU/DU-related symptoms assessed by the investigator[13)]		X	X	X	X	X
Dispense investigational product[14)]		X	X	X	X	
Administration of the investigational product[15)]		←	—	—	—	→
Check concomitant medication	←	—	—	—	—	→
Efficacy primary endpoint		←	—	→		
AEs and SAEs[16)]	←	—	—	—	—	→

1) Study closure visit for first period (to Week 32). Subjects who early discontinued the investigational product and/or withdrawn consent during first period (to Week 32) will be performed the activities described in Visit 10, if possible.
2) Site visits for subjects that extend treatment (after Week 32)
3) Study closure visit for extended period (after Week 32). Subjects who early discontinued the investigational product and/or withdrawn consent during extended therapy (after Week 32) will be performed the activities described in Visit 15, if possible.
4) The signed and dated ICF should be obtained from the subject's legally authorised representative (including informed consent to a genetic test) prior to conducting of any study related procedure. Assent form will be signed by the subject as much as possible.
5) Perform registration whether the prevention therapy is started or not; if an enrolled subject is not started prevention therapy, this will be noted in the eCRF.
6) At Visit 2, the investigator will document the symptoms and/or signs which are considered past GU/ DU in the medical record.

7) Blood pressure, pulse rate and body temperature will be measured.
8) See Section 8.2.1 of protocol.
9) A urine pregnancy test will be required for all post-menarcheal female subjects, and the result must be negative at registration to the prevention therapy. This test will be performed at each study site.
10) If the genotyping of CYP2C19 data are already available at each study site, it may be used with the consent of subject's legally authorised representative.
11) EGD (optional) should be conducted once at Visit 10 or Visit 15. Also, allowed to perform any time when GU/DU recurrence is suspected, for instance.
12) Optional evaluation. The pH measurement is preferably done at Week 32, but is also suggested if signs of GU/DU recurrence either before (Week 0 to 32) or after (Week 32 to 52) this time point.
13) The GU/DU-related symptom questionnaire will be provided at Visit 2 and following every visit to the subject. The subject and/or legally authorised representative will recall 1 week to date gastrointestinal symptoms and record them in the card. The card will be reviewed and collected by the investigator. The investigator will evaluate GU/DU recurrence every visit during treatment.
14) Administration of the investigational product should be started on Day 1. Following administration should be after breakfast. The subjects assigned to Group 3 will be treated with D961H 10 mg throughout the treatment period. The subjects assigned to Group 4 will be treated with D961H 10 mg as a starter, and the dose may be increased to 20 mg at any visit based on investigator's discretion. Dosing down back to 10 mg will not be allowed. The treatment period in both groups will be at least 32 weeks, and may be extended up to 52 weeks by investigator's discretion. The reason for the extension/no extension will be recorded in the eCRF.
15) When the subjects who assigned to Group 3 reach 20 kg after the start of investigational product administration in the prevention therapy period, their treatment dose may be reconsidered as that of the treatment regimen for Group 4.
16) AEs will be recorded from Visit 2. SAEs will be recorded from the time of informed consent (Visit 1).

1.3 Number of subjects

The sample size of this study was selected from a feasibility point of view, while at the same time minimizing the number of subjects needed to be enrolled. The sample size of this study is not based on any power calculations.

Maintenance therapy for healed RE study part:

Group 1: aged 1 to 14 years (weight ≥10 kg, <20 kg), Maintenance phase, n=5 to 10

Group 2: aged 1 to 14 years (weight ≥20 kg), Maintenance phase, n=10 to 20

Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:

Group 3: aged 1 to 14 years (weight ≥10 kg, <20 kg), n=5 to 10 at Week 0

Group 4: aged 1 to 14 years (weight ≥20 kg), n=10 to 20 at Week 0

In treatment Groups 1 and 3, physically disabled subjects, for whom an objective assessment of symptoms or EGD findings is possible, or who are judged by the investigator to be able to report gastrointestinal symptoms, are allowed to participate in the study up to 3 subjects/treatment group. In treatment Groups 2 and 4, physically disabled subjects, for which

objective assessment of symptoms or EGD findings is possible, or that are judged by the investigator to be able to report gastrointestinal symptoms, are allowed to participate in the study up to 6 subjects/treatment group.

Rationale for the sample size:

The sample size for maintenance therapy for the healed RE study part was set based on operational feasibility perspective. In reference to Japanese epidemiology data, 24.5% of adult subjects with heartburn had endoscopic LA grade A or higher erosive esophagitis. Even if the prevalence rate in Japanese paediatrics is smaller than that in adults, for instance 15%, enrolment of achievable 150 subjects will enable 22 to 23 subjects to start the initial healing therapy. Then, at least 15 subjects will enter into the maintenance phase.

For the prevention of GU/DU recurrence associated with NSAIDs/LDA study part, it is estimated that almost all enrolled subjects will start treatment with investigational product. Therefore, it is considered that enrolment of 15 to 30 paediatric Japanese subjects will achieve registration of 15 to 30 subjects to start with the investigational product.

2 ANALYSIS SETS

2.1 Definition of analysis sets

For purposes of analysis, the following populations are defined:

Population	Description
Efficacy Analysis Set	Maintenance therapy for healed RE study part: 1. Initial healing therapy period All subjects registered to initial healing therapy who take at least 1 dose of the investigational product and have at least 1 efficacy assessment during the initial healing therapy period, and who have no major important protocol deviation. The major important protocol deviations will be defined by team review prior to the database lock. 2. Maintenance therapy period All subjects registered to maintenance therapy who take at least 1 dose of the investigational product and have at least 1 efficacy assessment during the maintenance therapy period, and who have no major important protocol deviation. The major important protocol deviations will be defined by team review prior to the database lock. 3. Maintenance therapy extended period All subjects registered to maintenance therapy who take at least 1 dose of the investigational product and have at least 1 efficacy assessment during the maintenance therapy extended period, and

	who have no major important protocol deviation. The major important protocol deviations will be defined by team review prior to the database lock. Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part: 1. Prevention therapy period All subjects who take at least 1 dose of the investigational product and have at least 1 efficacy assessment during the prevention therapy period, and who have no major important protocol deviation. The major important protocol deviations will be defined by team review prior to the database lock. 2. Prevention therapy extended period All subjects who take at least 1 dose of the investigational product and have at least 1 efficacy assessment during the prevention therapy extended period, and who have no major important protocol deviation. The major important protocol deviations will be defined by team review prior to the database lock.
Safety Analysis Set	Maintenance therapy for healed RE study part: 1. Initial healing therapy period All subjects registered to initial healing therapy who take at least 1 dose of the investigational product and have any post-treatment assessment during the initial healing therapy period. 2. Maintenance therapy period All subjects registered to maintenance therapy who take at least 1 dose of the investigational product and have any post-treatment assessment during the maintenance therapy period. 3. Maintenance therapy extended period All subjects registered to maintenance therapy who take at least 1 dose of the investigational product and have any post-treatment assessment during the maintenance therapy extended period. Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part: 1. Prevention therapy period All subjects who take at least 1 dose of the investigational product and have any post-treatment assessment during the prevention therapy period. 2. Prevention therapy extended period All subjects who take at least 1 dose of the investigational product and have any post-treatment assessment during the prevention therapy extended period.

Pharmacodynamic Analysis Set	Maintenance therapy for healed RE study part: All subjects who have at least 1 gastroesophageal pH monitoring at post-dose without any serious protocol violation or deviant that would have an impact on the pharmacodynamic evaluation in maintenance therapy period. Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part: All subjects who have at least 1 gastroesophageal pH monitoring at post-dose without any serious protocol violation or deviant that would have an impact on the pharmacodynamic evaluation.

2.2 Violations and deviations

The possible reasons for important protocol violations and deviations will be following:

Deviation from the inclusion/exclusion criteria

Noncompliant with the investigational product

Disallowed concomitant medication

Other

Important protocol violations and deviations for the exclusion from the analysis sets will be defined and documented prior to Clean File. All subjects excluded from the analysis sets will be listed, and the reasons for exclusion will be summarised with the number of subjects in each reason/category.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy assessments

3.1.1 Evaluation of efficacy composite endpoints

Maintenance therapy for healed RE study part:

Based on the following observations, the investigator will assess development and/or exacerbation of RE-related symptoms/findings and their time course, and then judge RE relapse at every visit during the maintenance therapy period.

RE relapse is to be declared if any of the following events occur during the maintenance phase of the RE study part:

1. An EGD relapse is defined as an identification of a RE with LA classification grade A to D (see Table 5)

2. A symptom relapse (defined by any of the 4 specified RE-related symptoms in the RE-related symptom questionnaire, see Section 3.1.2) is defined as any of the following:

    a) Withdrawal from the study due to RE-related symptoms; this decision is to be taken by the investigator in collaboration with the subject/subject's legally authorised representative

    b) Increasing the dose from 10 mg to 20 mg due to RE-related symptoms (only applicable in subjects weighting over 20 kg); this decision is to be taken by the investigator in collaboration with the subject/subject's legally authorised representative

Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:

Based on the following observations, the investigators will assess development and/or exacerbation of GU/DU-related symptoms/findings and their time course, and then judge GU/DU recurrence at every visit during prevention therapy period.

A GU/DU recurrence is to be declared if any of the following events occur during the prevention phase of the NSAIDs/LDA study part:

1. An EGD recurrence is defined as an identification of a GU or DU

2. A symptom recurrence (defined by any of the 6 specified symptoms in the GU/DU-related symptom questionnaire, see Section 3.1.2) is defined as any of the following:

    a) Withdrawal from the study due to GU/DU-related symptoms; this decision is to be taken by the investigator in collaboration with the subject/subject's legally authorised representative

    b) Increasing the dose from 10 mg to 20 mg due to GU/DU-related symptoms (only applicable in subjects weighting over 20 kg); this decision is to be taken by the investigator in collaboration with the subject/subject's legally authorised representative

3.1.2 Gastrointestinal symptom assessments

Maintenance therapy for healed RE study part:

The gastrointestinal RE-related symptom questionnaire will be provided at Visit 2 and following every visit of the subject. The subject and/or legally authorised representative will recall 1 week to date gastrointestinal symptoms and record them using the card. The card will be reviewed and collected by the investigator. The investigator will evaluate RE relapse at every visit during the maintenance therapy.

Heartburn: A burning feeling, rising from the stomach or lower part of the chest towards the neck

Acid regurgitation: Flow of sour or bitter fluid into mouth

Dysphagia: Difficulties in swallowing

Epigastric pain: Central upper abdominal pain

The assessment of each symptom is to include the intensity of the episode by frequency and intensity within the past 1 week.

The intensity of the symptoms will be graded by the investigators using the 4-point scale presented in Table 4 Score for intensity of upper gastrointestinal symptoms by investigator's assessment.

Table 4 Score for intensity of upper gastrointestinal symptoms by investigator's assessment

Intensity	Score	Description
None	0	No symptoms
Mild	1	Awareness of symptom, but easily tolerated
Moderate	2	Discomforting symptom sufficient to cause interference with normal activities (including sleep)
Severe	3	Incapacitating symptoms, with inability to perform normal activities (including sleep)

Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:

The gastrointestinal GU/DU-related symptom questionnaire will be provided at Visit 2 and following every visit to the subject. The subject and/or legally authorised representative will recall 1 week to date gastrointestinal symptoms and record them using the card. The card will

be reviewed and collected by the investigator. The investigator will evaluate GU/DU recurrence every visit during treatment.

Epigastric pain: Central upper abdominal pain

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

Anorexia: Having no appetite

The assessment of each symptom is to include the intensity of the most intense episode by frequency and intensity within the past 1 week.

Intensity of episode is classified are shown in Table 4 Score for intensity of upper gastrointestinal symptoms by investigator's assessment.

3.1.3 EGD

The EGD of the esophagus, stomach and duodenum, which is required for diagnosis of target disease, will be performed on the subjects with obtained informed consent from subject's legally authorised representatives. The EGD is conducted by fasting condition at least 4 hours prior to the test.

Maintenance therapy for healed RE study part:

To evaluate RE, the EGD results are assessed based on the LA classification (See Table 5). Any grades of mucosal breaks graded as A, B, C or D is considered as presence of RE.

Table 5 LA classification

Grade	Description
Grade A	One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of 2 mucosal folds.
Grade B	One (or more) mucosal break more than 5 mm long that does not extend the tops of 2 mucosal folds.
Grade C	One (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but which involve less than 75% of the circumference.
Grade D	One (or more) mucosal break which involves at least 75% of esophageal circumference.

Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:

To evaluate GU/DU, the EGD results are assessed based on the modified LANZA score (See Table 6). An ulcer is defined as a mucosal lesion with either of following features:

A base - a circular or elliptical white or grey-white punched-out defect in the mucosa that could be smooth and regular;

A margin - discrete, sharply demarcated, regular, smooth, and usually raised in relation to the ulcer base; and

Lack of an associated mass lesion or other features suggesting malignancy.

Table 6 Modified LANZA score

Score	Description
0	No visible lesions
1+	1 hemorrhage[1)] or erosion[2)]
2+	2 to 10 hemorrhages or erosions
3+	11 to 25 hemorrhages or erosions
4+	>25 hemorrhages or erosions or an invasive ulcer[3)] of any size

1) Mucosal hemorrhage with luminal bleeding.
2) Erosion is defined as a lesion producing a definite discontinuance in the mucosa but having no depth.
3) Invasive ulcer is defined as any lesion with unequivocal depth.*
*The detailed definition of an ulcer is stated as the 3 points above.

3.2 Safety assessments

Clinical safety laboratory assessments

Clinical safety laboratory tests are provided in the list (Table 7).

Table 7 The items of laboratory safety

	Items
Haematology test (quantitative, whole blood)	RBC, hemoglobin, hematocrit, WBC, leukocyte differential count (neutrophil, eosinophil, basophil, lymphocyte, monocyte), platelet count
Clinical chemistry test (quantitative, serum or plasma)	AST (GOT), ALT (GPT), ALP, γ-GTP, total bilirubin, creatinine, albumin, glucose, sodium, potassium, calcium, CK, LDH, BUN, CRP
Urinalysis (qualitative)	Occult blood, protein, glucose

3.2.1 Physical examination

General appearance, lymph node, thyroid gland, cardiovascular system, lung, abdomen, musculoskeletal/extremities, and reflex will be examined.

3.2.2 Vital signs

Blood pressure, pulse rate and body temperature will be measured.

3.2.3 Adverse Events (AEs)

AEs will be collected from the start of investigational product to the last scheduled visit or withdrawal, and will be recorded in the eCRF. SAEs will be recorded from the time of signing of ICF.

3.3 Pharmacodynamic variables

Regarding gastroesophageal pH measurement, data will be presented as:

Gastric pH: Percentages of time with intragastric pH >4 and pH >3, and median intragastric pH during 12 hours

Esophageal pH: Percentages of time with intraesophageal pH <4, number of acid reflux periods (pH <4) and number of acid reflux periods longer than 5 minutes during 12 hours

4 ANALYSIS METHODS

4.1 General principles

No imputation will be used for missing data and all of the obtained data except for obviously spurious data will be included in the planned analyses. If any of obviously spurious data is found, then the inclusion/exclusion of the data should be determined prior to the database lock. If any data is not included in an analysis, then the justification for the exclusion will be documented in the clinical study report.

Unless otherwise stated, descriptive statistics will include number of subjects, (arithmetic) mean, standard deviation, median, minimum and maximum values for continuous variables and the number and the percentage of subjects in each category for categorical variables.

For summary statistics, the following number of decimal places should generally be presented: mean, standard deviation and median to 1 more decimal places than the raw data; minimum and maximum to the same number of decimal places as the raw data. Percentages should be presented to 1 decimal place.

Ordering of maintenance therapy for healed RE study part treatment groups in summary tables should follow the general rule of Group 1 and Group 2 followed by overall subjects where applicable.GU/DU recurrence associated with long term NSAIDs/LDA therapy study part treatment groups in summary tables should follow the general rule of Group 3 and Group 4 followed by overall subjects where applicable.

All statistical analyses in this study will be performed by Statistical department in EPS Corporation using the SAS software version 9.4.

4.2 Analysis methods

4.2.1 Efficacy variables

All efficacy data will be summarised based on Efficacy Analysis Set.

4.2.1.1 Maintenance therapy for healed RE study part

(a) The percentage of subjects with RE relapse and the time to RE relapse (primary analysis)

The percentage and the exact 95% confidence levels (CIs), based on the Clopper-Pearson estimation method, of subjects with RE relapse based on the composite endpoint (RE-related symptoms or optional EGD findings) from Week 8 to Week 32 will be summarized for each treatment group. In addition, the time to RE relapse will be analyzed by the Kaplan-Meier method for each treatment group. The time to RE relapse is defined as the number of days from the start date of maintenance phase to the earliest date of satisfying the RE relapse criteria in any composite endpoints. The censored subject is defined at the last evaluable date with symptom or EGD. The Kaplan-Meier plot for time to RE relapse for each treatment group will be prepared in one figure.

(b) The percentage of subjects with RE relapse and the time to RE relapse for subjects who continued the study treatment after Week 32

The percentage and the exact 95% CIs, based on the Clopper-Pearson estimation method, of subjects with RE relapse based on the corresponding composite endpoint of the primary analysis from Week 8 to Week 52 (8 to 32 weeks and 32 to 52 weeks, respectively) will be summarized by treatment groups for subjects who continued the study treatment after Week 32. In addition, the time to RE relapse will be analyzed by the Kaplan-Meier method for each treatment group for the corresponding subjects. The Kaplan-Meier plot for time to RE relapse for each treatment group will be prepared in one figure.

(c) RE-related symptoms

RE-related symptoms will be summarised for each treatment group by frequency and intensity from baseline to Week 8 and from Week 8 to Week 32 or Week 52 separately. Baseline is defined as the last observation before the first dose of study medication during enrolment or start of initial healing therapy period.

For all subjects, the number of subjects and their percentage of disappearance, exacerbation and recurrence for each symptom will be summarised by treatment groups from baseline to Week 8 and from Week 8 to Week 32 separately.

For subjects who continued the study treatment after Week 32, the corresponding number and the percentage for each symptom will be summarised by treatment groups from Week 8 to Week 52 (8 to 32 weeks and 32 to 52 weeks, respectively).

(d) Endoscopic assessment of healed RE

The number of subjects who had RE relapse endoscopically will be summarised for all subjects who had an EGD result at pre-dose and post-dose by treatment groups. The number of subjects in each grade of the LA classification (graded A to D) for these subjects will be summarised by treatment groups.

4.2.1.2 Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part

(a) The percentage of subjects with GU/DU recurrence and the time to the recurrence (primary analysis)

For all subjects, the percentage and the exact 95% CIs, based on the Clopper-Pearson estimation method, of subjects with GU/DU recurrence based on the composite endpoint (GU/DU-related symptoms or optional EGD findings) from Week 0 to 32 will be summarized for each treatment group. In addition, the time to recurrence of GU/DU will be analyzed by the Kaplan-Meier method for each treatment group. The time to GU/DU recurrence is defined as a number of days from the start date of investigational product to the earliest date of satisfying the recurrence criteria of GU or DU in any composite endpoints. The censored subject is defined at the last evaluable date with symptom or EGD. The Kaplan-Meier plot for time to recurrence of GU/DU for each treatment group will be prepared in one figure.

(b) The percentage of subjects with GU/DU recurrence and the time to the recurrence for subjects who continued the study treatment after Week 32

The percentage and the exact 95% CIs, based on the Clopper-Pearson estimation method, of subjects with GU/DU recurrence based on the corresponding composite endpoint of the primary analysis from baseline to Week 52 (0 to 32 weeks and 32 to 52 weeks, respectively) will be summarized by treatment groups for subjects who continued the study treatment after

Week 32. In addition, the median time to recurrence of GU/DU and the 95% CIs will be analyzed by the Kaplan-Meier method for each treatment group for the corresponding subjects. The Kaplan-Meier plot for time to recurrence of GU/DU for each treatment group will be prepared in one figure.

(c) GU/DU-related symptoms

GU/DU-related symptoms will be summarised for each treatment group by frequency and intensity. Baseline is defined as the last observation before the first dose of study medication during enrolment or start of prevention therapy period.

For all subjects, the number of subjects and their percentage of disappearance, exacerbation and recurrence for each symptom will be summarised by treatment groups from baseline to Week 32 separately.

For subjects in FAS who continued the study treatment after Week 32, the corresponding number and percentage for each symptom will be summarised by treatment groups from baseline to Week 52 (baseline to 32 weeks and 32 to 52 weeks, respectively).

(d) Endoscopic assessment of GU or DU

Regarding endoscopic assessment of GU or DU and gastric erosions, the number of subjects will be summarised by treatment groups based on a clear definition of ulcer and modified LANZA score for all subjects who had EGD result at post-dose. The number of subjects with GU/DU and the number of subjects with each of the modified LANZA score (graded 0, 1+, 2+, 3+ and 4+) will be summarised by treatment groups.

4.2.2 Safety variables

All safety data will be summarised based on the safety analysis set.

Baseline is defined as the last observation before the first dose of investigational product during enrolment or either start of initial healing therapy or start of prevention therapy period.

In the maintenance therapy for healed RE study part, the safety assessments (AE, laboratory variables and vital signs) will be evaluated for all subjects in Safety Analysis Set from Week 8 as baseline to Week 32 as the primary analysis, and the corresponding safety assessment will be evaluated from baseline to Week 8 as the secondary analysis for all subject who had investigational product from baseline to Week 8. For subjects in Safety Analysis Set who continued the study treatment after Week 32, the safety measurement from Week 8 as baseline to Week 52 (8 to 32 weeks and 32 to 52 weeks, respectively) will be evaluated.

For prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part, the corresponding safety assessments will be evaluated for all subjects in Safety Analysis Set from baseline to Week 32 as the primary analysis. For all subjects in Safety Analysis Set who continued the study treatment after Week 32, the corresponding safety assessments will be evaluated from baseline to 52 (baseline to 32 weeks and 32 to 52 weeks, respectively) as the secondary analysis.

(a) AEs

All AEs will be classified by system organ class and by preferred term using the appropriate version of Medical Dictionary for Regulatory Activities (MedDRA) and those occurred before and after administration of the investigational products will be listed separately. Only AEs occurred after the start of investigational product administration will be summarised for each treatment group.

The number and proportion of subjects with AEs falling into the following categories will be summarised for each treatment group:

- Any AEs
- Causally related AEs
- AEs leading to death
- Serious AEs including events with outcome = death
- AEs leading to discontinuations of investigational product

In this summary, the number of AEs in the above categories will also be summarised for each treatment group.

The number and proportion of subjects experiencing the AEs will be presented for each treatment group as follow:

- AEs presented by system organ class and preferred term
- AEs presented by system organ class, preferred term and maximum reported intensity
- AEs presented by system organ class, preferred term and causality as judged by investigator
- SAEs presented by system organ class and preferred term
- SAEs presented by system organ class, preferred term and maximum reported intensity

- SAEs presented by system organ class, preferred term and causality as judged by investigator

- AEs leading to death presented by system organ class and preferred term

- AEs leading to discontinuation of investigational product presented by system organ class and preferred term

- AEs leading to discontinuation of investigational product presented by system organ class, preferred term and maximum reported intensity

- AEs leading to discontinuation of investigational product presented by system organ class, preferred term and causality as judged by investigator

- AEs presented by system organ class, preferred term, and time from first dose to onset of AE according to following categories: Week 8 to 16, Week 17 to 24, Week 25 to 32, Week 33 to 40, Week 41 to 48, Week 49 and after for RE for healed RE study part, Week 0 to 8,Week 9 to 16, Week 17 to 24, Week 25 to 32, Week 33 to 40, Week 41 to 48, Week 49 and after for prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part.

(b) Clinical laboratory variables

Values of laboratory tests at baseline will be determined as the values at Week 0 or before for the initial healing therapy period, and at Week 8 for the maintenance therapy period for healed RE study part, and at Week 0 or before for the prevention therapy period, and at Week 32 for the prevention therapy extended period for prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part.

For continuous variables of laboratory tests, all data at baseline and each scheduled time point of post-dose will be summarised for each treatment group using descriptive statistics. Changes from baseline to each scheduled time point of post-dose will also be summarised using descriptive statistics. For clinical chemistry and hematology data, line plots showing the individual absolute values over time will be made for each treatment group.

For categorical variables of laboratory tests, the frequency and percentage in each category of the item at baseline and each scheduled time point of post-dose will be calculated for each treatment group.

Each laboratory test result will be classified into the three categories (Normal, High, or Low) using a standard reference range (or normal range). Shift tables comparing the classification at baseline with the classification at last time point of post-dose data will be made for each combination of laboratory variables and treatment groups.

(c) Vital signs

Values of vital signs at baseline will be determined as the values at Week 0 or before for the initial healing therapy period, and at Week 8 for the maintenance therapy for healed RE study part, and at Week 0 or before for the prevention therapy period, and at Week 32 for the prevention therapy extended period for prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part.

All data at baseline and each scheduled time point of post-dose will be summarised for each treatment group using descriptive statistics. Changes from baseline to each scheduled time point of post-dose will also be summarised using descriptive statistics. Line plots showing the individual absolute values over time will be made for each treatment group.

4.2.3 Pharmacodynamic variables

For the analyses of this variable, the Pharmacodynamic Analysis Set will be used.

(a) Gastric pH

Percentages of time with intragastric pH >4 and pH >3 and median intragastric pH during 12 hours will be summarised for each treatment group using descriptive statistics.

(b) Esophageal pH

Percentages of time with intraesophageal pH <4, number of acid reflux periods (pH <4) and number of acid reflux periods longer than 5 minutes during 12 hours will be summarised for each treatment group using descriptive statistics.

4.2.4 Demographic data and other subject characteristics

The analysis will be performed by the following demographic data and other subject characteristics in the Safety analysis set. Similar analyses will be performed in Efficacy Analysis Set as well.

The following baseline information (Visit 1) will be summarised by treatment group using frequencies and percentages.

Sex (Male, Female)

Race (Asian)

Age at enrolment (– 3, 4 – 5, 6 – 7, 8 – 9, 10 –11, 12 – 14)

Height (cm) (< 90, 90 – < 110, 110 – < 120, 120 – < 130, 130 – < 140, 140 – < 150, >=150)

Weight (kg) (10 – < 15, 15 – < 20, 20 – < 25, 25 – < 30, 30 – < 35, 35 – < 40, >= 40)

H. pylori test (IgG antibody) (Negative, Positive)

CYP2C19 genotype (homo EM, hetero EM, PM, Unknown)

Primary disease (Gastric ulcer, Duodenal ulcer, Reflux esophagitis)

Medical history on RE (No, Yes) for Group 1 and 2

Medical history on GU / on DU (No, Yes) for Group 3 and 4

Concurrent disease (No, Yes)

History of surgery (No, Yes)

In addition, age at enrolment, height, body weight will be summarised for each treatment group using descriptive statistics.

4.2.5 Subject disposition

The number of enrolled subjects in this study will be summarised.

The number of subjects who were enrolled but not registered will be summarised in total and by reasons of discontinuation from the study.

The numbers of registered subjects, subjects who completed the study and subjects who discontinued the study will be summarised in total and by each treatment group. In addition, the number of subjects who discontinued the study will be summarised by reasons of discontinuation.

The number of subjects who had at least one important protocol violation or deviation will be summarised in total and by each treatment group. In addition, reasons of the protocol violation or deviation will be summarised with the number of subjects in each reason.

For all registered subjects, the numbers of subjects who were included in each analysis set and were excluded from each analysis set will be summarised in total and by treatment group. The number of subjects who were excluded from each analysis set will be summarised by reasons of exclusion.

4.2.6 Exposure to investigational product

Extent of exposure to investigational product (in days) will be determined for each subject and summarised for each treatment group in the Safety Analysis Set using descriptive statistics.

The number and proportion of subjects who had an extent of exposure to investigational product during a specified period in the safety analysis set will be calculated by 4-week interval (i.e., Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52) for each treatment group. The number of subjects with 10 mg and with 20 mg dose of investigational product are counted by 4-week interval for each Group of 2 and 4.

4.2.7 Investigational product compliance

The investigational product compliances (< 75%, >= 75%) by period (initial healing (Week 0 to Week 8), maintenance therapy (Week 8 to Week 32), Maintenance therapy extended (Week 32 to Week 52) and prevention therapy (Week 0 to Week 32), prevention therapy extended (Week 32 to Week 52)) will be summarised in total and by treatment group based on Safety Analysis Set.

4.2.8 Prior and Concomitant medications

The number of subjects who took the following medications / therapies will be summarized using frequency tables presented by World Health Organization Drug Dictionary (WHO-DD). Medications classified as NSAIDs or LDA are counted specifically.

- Medications that started and stopped before the start of investigational product administration.
- Medications that started at or before the end date of investigational product administration, excluding medications that stopped before the start date of investigational product administration - during Week 0 and Week 8 for Group 1 and 2.
- Medications that started at or before the end date of investigational product administration, excluding medications that stopped before the start date of investigational product administration - during Week 8 and Week 32 for Group 1 and 2, during Week 0 and Week 32 for Group 3 and 4.
- Medications that started at or before the end date of investigational product administration, excluding medications that stopped before the start date of investigational product administration - during Week 8 and Week 52 for Group 1 and 2, during Week 0 and Week 52 for Group 3 and 4.

5 INTERIM ANALYSES

There is no plan to have any interim analyses.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Not Applicable.

7 REFERENCES

Not Applicable.

8 APPENDIX

Not Applicable.