| **Clinical Study Protocol** | |
|---|---|
| Drug Substance | D961H |
| Study Code | D961WC00001 |
| Version | [redacted] |
| Date | 6-Sep-2022 |

# 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

**Sponsor:**

AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

# VERSION HISTORY

| **Version 1,** [redacted] |
|---|
| Initial creation |
| **Version 2,** [redacted] |
| [redacted] (SoA): Annotation on the timing of genetic test was added.<br><br>- 5.2 Exclusion criteria 13 Erlotinib wad added to drugs known to have drug-drug interactions with D961H.<br><br>- 6.5 Table5: Erlotinib wad added to drugs known to have drug-drug interactions with D961H.<br><br>- 8. Visit 1: Demographic data was arranged (add age, delete birth date).<br>Visit 2: Annotation on the timing of genetic test was added.<br><br>- Appendix A8: Definitions of source data was changed. |
| **Version 3,** [redacted] |
| - 1.1 Schedule of Activities (SoA): Annotation about start of treatment in the prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part wad added.<br><br>- 1.2 Synopsis: Secondary objectives were modified.<br><br>- 1.2 Synopsis: The definition of Efficacy Analysis Set was added instead of FAS.<br><br>- 3. Secondary objectives were modified.<br><br>- 5.2 Exclusion criteria 13: Annotation about usage of gastrointestinal drug was clarified.<br><br>- 6.4: Starting date for data collection was changed.<br><br>- 6.5: Starting date for data collection was changed.<br><br>- 6.5 Table 5: Annotation about usage of gastrointestinal drug was clarified.<br><br>- 7.1: Contents regarding follow-up and any further evaluation at the withdrawal from the stuyd were deleted.<br><br>- 7.1.1: Contents regarding follow-up and any further evaluation at the withdrawal from the study were deleted.<br><br>- 7.3: Contents regarding follow-up and any further evaluation at the withdrawal from the study were deleted. |

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| - 8.3.8: The requirement in potential Hy's Law was changed.<br><br>- 8.6: A standardized diet during pH monitoring was deleted.<br><br>- 9.3: The definition of Efficacy Analysis Set was added instead of FAS.<br><br>- Appendix E: The requirement in potential Hy's Law was changed. |
| **Version 4.[redacted]** |
| - 1.2: Analysis methods of efficacy analyses were modified.<br><br>- 2.3: Wording was corrected.<br><br>- 9.3: The definition of each analysis population was described separately for each study part and treatment period.<br><br>- 9.4.1: Analysis methods of efficacy analyses were modified. |

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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# 1. PROTOCOL SUMMARY

## 1.1 Schedule of Activities (SoA)

**Table 1 Schedule of Activities (SoA) in maintenance therapy for healed reflux esophagitis (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)] | | |

| 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) |
| RE-related symptoms assessed by investigator[15)] | | X | X | X | X | X | X | X |
| 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 patient's guardian (including informed consent to a genetic test) prior to conducting of any study related procedure. Assent form will be signed by the patient 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.

10) A urine pregnancy test will be required for all post-menarcheal female patients, 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 guardian. According to the subject's body weight, it is possible to do it at Visit 3 or after for the purpose of reducing blood collection volume of Visit 2.
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 guardian.
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 guardian 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 2 Schedule of Activities (SoA) for prevention of gastric ulcer (GU) or duodenal ulcer (DU) recurrence associated with long term non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin (LDA) Therapy (Groups 3 and 4)**

| Activity | Informed consent ~ Registration | Prevention therapy period | | | Prevention therapy extended period | |
|---|---|---|---|---|---|---|
| | Enrolment | Start of treatment[17)] | 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 ~ 0 | 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 | | | | | |
| 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)] | | |

| Activity | Informed consent ~ Registration | Prevention therapy period | | | Prevention therapy extended period | |
|---|---|---|---|---|---|---|
| | **Enrolment** | **Start of treatment[17)]** | **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 ~ 0 | 1 | 29, 57, 85, 113, 141, 169, and 197 (±7) | 225 (±7) | 253, 281, 309, and 337 (±7) | 365 (±7) |
| 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 patient's guardian (including informed consent to a genetic test) prior to conducting of any study related procedure. Assent form will be signed by the patient 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 gastric ulcer (GU) or duodenal ulcer (DU) in the medical record.
7) Blood pressure, pulse rate and body temperature will be measured.
8) See Section 8.2.1.
9) A urine pregnancy test will be required for all post-menarcheal female patients, 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 guardian. According to the subject's body weight, it is possible to do it at Visit 3 or after for the purpose of reducing blood collection volume of Visit 2.
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 guardian 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).
17) Start of treatment (Visit 2) can be performed on the same day as informed consent (Visit 1).

## 1.2 Synopsis

**Co-ordinating investigator or principal investigators**

The details of co-ordinating investigator or principal investigators refer to the Addendum A.

**Protocol Title:**

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

**Rationale:**

D961H is considered a medical need, not only in adults but also, in children for:

- Maintenance therapy after the initial reflux esophagitis (RE) healing therapy
- Prevention of gastric ulcer (GU) or duodenal ulcer (DU) recurrence in children treated with non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin (LDA)

It is considered appropriate to evaluate the safety, tolerability and efficacy of treatment for 32 or 52 weeks with once-daily oral administration of D961H for both the maintenance of RE healing and for the prevention of GU/DU recurrence when treated with NSAIDs or LDA in Japanese paediatric patients.

**Study Objectives:**

| **Primary Objectives:** | **Outcome Measures:** |
|---|---|
| Maintenance therapy for healed RE study part:<br>• 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 esophagogastroduodenoscopy (EGD) is done, no visible mucosal breaks observed. | Maintenance therapy for healed RE study part:<br>• 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.<br>• Safety from 8 to 32 weeks for all subjects by the assessment of;<br>a) Adverse events (AEs)<br>b) Laboratory variables<br>c) Vital signs |
| Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:<br>• 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:<br>• 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.<br>• Safety from 0 to 32 weeks for all subjects by the assessment of;<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs |

| Secondary Objectives: | Outcome Measures: |
|---|---|
| Maintenance therapy for healed RE study part:<br>• 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, for 8 to 52 weeks for subjects who continued the study treatment after Week 32.<br>• To assess the safety of once-daily oral administration of D961H in the initial healing therapy period (0 to 8 weeks) for all subjects.<br>• 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 for 8 to 52 weeks for subjects who continued the study treatment after Week 32.<br>• To assess the RE-related symptoms during the initial healing therapy period (0 to 8 weeks) for all subjects.<br>• To assess the 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.<br>• To assess upper endoscopic findings during the maintenance therapy for subjects who had at least 1 EGD during the maintenance therapy .<br>• To assess the pharmacodynam ics with gastroesophageal pH monitoring during the maintenance therapy for subjects who had at least 1 pH monitoring during the maintenance therapy . | • Maintenance therapy for h ealed RE study part:<br>• 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.<br>• Safety from 0 to 8 weeks for all subjects by the assessment of;<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs<br>• 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;<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs<br>• RE-related symptoms during the initial healing therapy period (0 to 8 weeks)<br>• RE-related symptoms during the maintenance therapy<br>• Endoscopic findings<br>• Gastroesophageal pH measurement |

| Secondary Objectives: | Outcome Measures: |
|---|---|
| Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:<br>• 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.<br>• 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.<br>• 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.<br>• To assess the endoscopic findings for subjects who had at least 1 EGD at post-dose.<br>• 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:<br>• 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.<br>• 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;<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs<br>• GU/DU-related symptoms<br>• Endoscopic findings<br>• Gastroesophageal pH measurement |

**Overall design:**

This 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 patients with RE, and to assess the safety and efficacy of D961H in Japanese paediatric patients treated with long term NSAIDs or LDA therapy who have a documented medical history of GU or DU diagnosis.

**Study Period:**

Estimated date of first subject enrolled: April 2018

Estimated date of last subject completed: December 2022

**Number of Subjects:**

**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

Physically disabled patients are allowed to participate in the study up to 3 subjects/group in Groups 1 and 3, and up to 6 subjects/group in Groups 2 and 4, respectively.

**Treatments and treatment duration:**

**Maintenance therapy for healed RE study part:**

- Group 1: Initial healing phase (8 weeks), D961H 10 mg once-daily; Maintenance phase (24 or 44 weeks), D961H 10 mg once-daily
- Group 2: Initial healing phase (8 weeks), D961H 20 mg once-daily; Maintenance phase (24 or 44 weeks) starts with D961H 10 mg once-daily, and may be increased to 20 mg once-daily based on investigator's discretion

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

- Group 3: D961H 10 mg once-daily (32 or 52 weeks)
- Group 4: D961H starts with 10 mg once-daily, and may be increased to 20 mg once-daily based on investigator's discretion (32 or 52 weeks)

When the subjects who assigned to Group 1 or 3 reach 20 kg after the start of investigational product administration in the maintenance/prevention therapy period, their treatment dose may be reconsidered as that of the treatment regimen for Group 2 or 4. However, during initial RE healing period of Group 1, the dose of D961H should not be changed.

**Statistical methods:**

**Efficacy Analysis:**

All efficacy analyses will be performed on Efficacy Analysis Set, which consists of all subjects who take at least 1 dose of investigational product and have at least 1 efficacy datum assessment during the maintenance/prevention therapy period, and who have no important protocol deviation.

**Maintenance therapy for healed RE study part:**

For all subjects in Efficacy Analysis Set who have at least 1 efficacy assessment during the maintenance therapy period, the percentage of subjects with RE relapse and the time to RE

relapse will be analysed by the Kaplan-Meier method for each treatment group by assessing any composite endpoint (RE-related symptoms or optional EGD findings) from Week 8 to 32 as a primary analysis. 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.

For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the percentage of subjects with RE relapse and the time to RE relapse will be analysed by the Kaplan-Meier method for each treatment group by assessing the similar composite endpoint of the primary analysis from Week 8 to 52 (8 to 32 weeks and 32 to 52 weeks, respectively).

RE-related symptoms (heartburn, acid regurgitation, dysphagia and epigastric pain) will be summarised by frequency and intensity from Week 0 to 8, and from Week 8 to 32 or 52, separately. For all subjects in Efficacy Analysis Set, the number of subjects and their percentage of disappearance, exacerbation and recurrence for each symptom will be summarised by group from Week 0 to 8 and from Week 8 to 32 separately. For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the similar number and percentage for each symptom will be summarised by group from Week 8 to 52 (8 to 32 weeks and 32 to 52 weeks, respectively).

Regarding endoscopic assessment of healed RE, the number of subjects who had RE relapse endoscopically will be summarised for all subjects in Efficacy Analysis Set who had an EGD result at post-dose by group. The number of subjects with each grade of the Los Angeles (LA) classification (graded A to D) for these subjects will be summarised by group.

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

For all subjects in Efficacy Analysis Set, the percentage of subjects with GU/DU recurrence and the time to the recurrence will be analysed by the Kaplan-Meier method for each treatment group by assessing any composite endpoint (GU/DU-related symptoms or optional EGD findings) from Week 0 to 32 as a primary analysis. 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.

For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the percentage of subjects with GU/DU recurrence and the time to the recurrence will be analysed by the Kaplan-Meier method for each treatment group by assessing the similar composite endpoint of the primary analysis from Week 0 to 52 (0 to 32 weeks and 32 to 52 weeks, respectively).

GU/DU-related symptoms (epigastric pain, discomfort in the stomach, abdomen enlarged feeling, nausea/vomiting, heartburn and anorexia) will be summarised by frequency and intensity. For all subjects in Efficacy Analysis Set, the number of subjects and its percentage of disappearance, exacerbation and recurrence of each symptom will be summarised by group from

Week 0 to 32. For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the same number and percentage for each symptom will be summarised by group from Week 0 to 52 (0 to 32 weeks and 32 to 52 weeks, respectively).

Regarding endoscopic assessment of GU or DU and gastric erosions, the number of subjects will be summarised by group based on a clear definition of ulcer and modified LANZA score for all subjects in Efficacy Analysis Set 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 group.

**Safety analysis:**

All safety analyses will be performed on Safety Analysis Set, which consists of all subjects who take at least 1 dose of investigational product and have any post-treatment assessment.

Frequency and incidence rate of AEs, serious adverse events (SAEs), discontinuation of investigational product due to adverse events (DAEs) and other significant adverse events (OAEs) will be presented by System Organ Class (SOC) and Preferred Term (PT) in International Council on Harmonisation (ICH) Medical Dictionary for Regulatory Activities (MedDRA) for each group. In addition, summaries of AEs will be further broken down by maximum intensity and relationship to the investigational product as assigned by investigators.

Clinical laboratory variables and vital signs will be summarised by group with descriptive statistics using values and changes from Week 8 as baseline to Week 32 for the maintenance therapy for healed RE study part, and changes from Week 0 as baseline to Week 32 for prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part. Qualitative data will be presented by group in terms of frequency and percentage, and changes from baseline will be presented using shift tables. The distribution of subject with values below and above the reference range will be provided.

In 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 similar safety assessments will be evaluated from Week 0 as baseline to Week 8 as the secondary analysis. 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 same safety assessments will be evaluated for all subjects in Safety Analysis Set from Week 0 as baseline to Week 32 as the primary analysis. For all subjects in Safety Analysis Set who continued the study treatment after Week 32, the same safety assessments will be evaluated from Week 0 to Week 52 (0 to 32 weeks and 32 to 52 weeks, respectively) as the secondary analysis.

**Pharmacodynamic analysis:**

Regarding gastroesophageal pH measurement, data will be presented as:

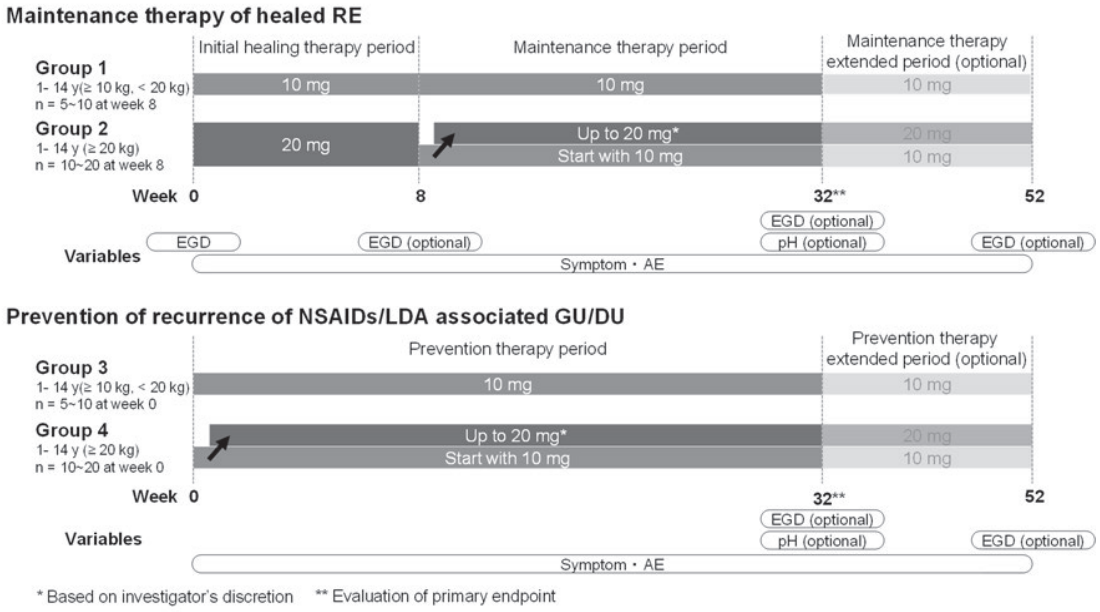
- Gastric pH: Percentages of time with intragastric pH >4 and pH >3, and median intragastric pH during 12 hours

- 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

## 1.3 Schema

The general study design is summarised in Figure 1.

**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

# 2. INTRODUCTION

## 2.1 Study rationale

D961H is considered a medical need, not only in adults but also, in children for:

- Maintenance therapy after the initial RE healing therapy

- Prevention of GU/DU recurrence in children treated with NSAIDs or LDA

It is considered appropriate to evaluate the safety, tolerability and efficacy of treatment for 32 or 52 weeks with once-daily oral administration of D961H for both the maintenance of RE healing and for the prevention of GU/DU recurrence when treated with NSAIDs or LDA in Japanese paediatric patients.

## 2.2 Background

Proton pump inhibitors (PPIs), including D961H (the trade name in Japan, Nexium capsule 10 mg and Nexium capsule 20 mg; the trade name in overseas, Nexium®; Active ingredient, esomeprazole), are widely used for the treatment of gastrointestinal acid related diseases.

D961H has been developed as a drug containing only a single enantiomer (*S*-body) of omeprazole. After approval in Sweden in 2000, it has been approved in more than 125 countries including EU, the US and Asia.

In Japan, repeated dose studies (5 days of repeated D961H doses at 10 mg, 20 mg and 40 mg) have demonstrated that D961H has strong gastric antisecretory activity in Japanese healthy volunteers (SHQBE-0098 study, Nagashima H and Ikushima I 2011). In a phase III study using D961H for the initial treatment of RE in Japanese adult patients (D961HC00002 study), once-daily administration of 20 mg D961H showed high healing rates of 87.3%. In another phase III study using D961H for maintenance of healed RE in Japanese adult patients (D961HC00006 study), once-daily administration of 20 mg or 10 mg D961H showed maintenance rates of 92.0% and 87.5%, respectively. Lastly, another study demonstrated that NSAIDs related peptic ulcer recurrence was prevented in Japanese adult patients receiving 20 mg D961H once-daily, with a 96.0% ulcer-free rate (D961HC00001 study).

Based on the results of these studies, etc., D961H was approved in Japan on July 1st, 2011 for the indication for GU, DU, Anastomotic Ulcer, RE, Non-Erosive Reflux Disease (Nexium capsule 10 mg only), Zollinger-Ellison syndrome, prevention of GU and DU recurrence in patients treated with NSAIDs/LDA and adjunct for eradication of *Helicobacter pylori* (*H. pylori*) in GU, DU, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura and metachronous development of gastric cancer after endoscopic resection of early gastric cancer and *H. pylori* gastritis (approved in February, 2013), and are widely used for the treatment of gastrointestinal acid related diseases.

However, so far PPIs including D961H are approved with gastrointestinal acid related diseases for adult only and not approved for children. Therefore, the phase I/III study for gastrointestinal acid related diseases (D961TC00002 study) was conducted to develop an initial paediatric development program for D961H in Japan. In this study, the safety, tolerability and efficacy of D961H for gastrointestinal acid related diseases in children was confirmed.

Among gastrointestinal acid related diseases, RE is a chronic, relapsing disease that is associated with a range of potentially serious complications. Some paediatric patients experience repeated relapses of RE. The current treatment available for these patients is a continuous use of acid inhibitors such as PPIs or $H_2$-receptor antagonists, similar to the initial treatment. Especially, RE in children having physical disabilities has characteristics such that it is frequently refractory, and that natural healing is less anticipated.

NSAIDs or LDA are available agents for treatment of paediatric chronic inflammatory diseases (eg, paediatric idiopathic arthritis, systemic lupus erythematosus, paediatric dermatomyositis, and Kawasaki disease). However, NSAIDs and LDA are known to cause mucosal erosions on the upper gastrointestinal tract, which could progress to ulcerations and bleeding, as well as

upper gastrointestinal symptoms. To counteract the negative effect of NSAIDs/LDA on the gastrointestinal tract, these drugs are often given together with antacids, cytoprotective agents or gastric acid reducing medications. Treatment of paediatric patients with chronic inflammatory diseases is often continued over an extended period, and upper gastrointestinal symptoms caused by NSAIDs/LDA may cause discontinuation of treatment of the underlying disease, resulting in poor control and disease exacerbation.

A detailed description of the chemistry, pharmacology, efficacy, and safety of D961H is provided in the Investigator's Brochure or Development Safety Update Report.

## 2.3 Benefit/risk assessment

D961H was approved in Japan on July 1st, 2011 for the indication for the treatment of adults with gastrointestinal acid related disease. It has been widely used in clinical practice and the efficacy and safety of the drug have been well established. In overseas, pharmacokinetics, efficacy and safety of paediatric patients with gastroesophageal reflux disease (GERD) had been already confirmed, dosage for paediatric patients aged 1 to 11 years with GERD and erosive esophagitis had been approved in the US. D961H is commercially available in the EU and other worldwide markets. The phase I/III study (D961TC00002) demonstrated safety, tolerability and efficacy of 10- and 20-mg D961H treatment for 8 weeks in Japanese children.

Based on the available safety data and benefit of Japanese children getting access to D961H for RE maintenance therapy and prevention of NSAIDs/LDA related peptic ulcers recurrence, it is AstraZeneca´s judgement that the benefit risk assessment is positive.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of D961H may be found in the Investigator's Brochure, or Development Safety Update Report.

# 3. OBJECTIVES AND ENDPOINTS

Table 3 shows the primary and secondary objectives in this study.

**Table 3 Study objectives**

| Primary Objectives: | Outcome Measures: |
|---|---|
| Maintenance therapy for healed RE study part:<br>• 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:<br>• 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.<br>• Safety from 8 to 32 weeks for all subjects by the assessment of;<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs |
| Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:<br>• 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:<br>• 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.<br>• Safety from 0 to 32 weeks for all subjects by the assessment of:<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs |

**Table 3 Study objectives**

| Secondary Objectives: | Outcome Measures: |
|---|---|
| Maintenance therapy for healed RE study part:<br>• 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.<br>• To assess the safety of once-daily oral administration of D961H in the initial healing therapy period (0 to 8 weeks) for all subjects.<br>• 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.<br>• To assess the RE-related symptoms during the initial healing therapy period (0 to 8 weeks) for all subjects.<br>• 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.<br>• To assess upper endoscopic findings during the maintenance therapy for subjects who had at least 1 EGD during the maintenance therapy .<br>• To assess the pharmacodynam ics with gastroesophageal pH monitoring during the maintenance therapy for subjects who had at least 1 pH monitoring during the maintenance therapy . | • Maintenance therapy for h ealed RE study part:<br>• 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.<br>• Safety from 0 to 8 weeks for all subjects by the assessment of;<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs<br>• 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;<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs<br>• RE-related symptoms during the initial healing therapy period (0 to 8 weeks)<br>• RE-related symptoms during the maintenance therapy<br>• Endoscopic findings<br>• Gastroesophageal pH measurement |

**Table 3 Study objectives**

| Secondary Objectives: | Outcome Measures: |
|---|---|
| Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:<br>• 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.<br>• 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.<br>• 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.<br>• To assess the endoscopic findings for subjects who had at least 1 EGD at post-dose.<br>• 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:<br>• 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.<br>• 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:<br>a) AEs<br>b) Laboratory variables<br>c) Vital signs<br>• GU/DU-related symptoms<br>• Endoscopic findings<br>• Gastroesophageal pH measurement |

# 4. STUDY DESIGN

## 4.1 Overall design

This 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 patients with RE, and to assess the safety and efficacy of D961H in Japanese paediatric patients 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 group and the prevention of GU/DU recurrence by NSAIDs/LDA group, 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, Section 1.3; Table 1 and Table 2, Section 1.1. For details on treatments given during the study, see Section 6.1 Treatments administered and Section 8 Study Assessments and Procedures.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints and Section 8.1 Efficacy assessments.

## 4.2 Scientific rationale for study design

**Rationale for treatment duration:**

RE study part: The duration of initial healing therapy in this study was set to 8 weeks, based on the durations in the previous phase I/III study for Japanese paediatric subjects and the approved duration of treatment with D961H for adult patients with RE. The duration of maintenance therapy for healed RE in this study was set to 24 weeks, based on the duration in the previous study of Japanese adult subjects with healed RE showing the efficacy and safety of D961H for 24 weeks. Further, this study was designed to evaluate the long term efficacy and safety of D961H for a maximum of 52 weeks, in consideration of the medical needs for long term PPI treatment.

NSAIDs/LDA study part: The treatment duration for prevention of GU recurrence in paediatric patients who need long term treatment of NSAIDs/LDA was set to 32 weeks, based on 2 studies of Japanese adult subjects with NSAIDs showing the efficacy and safety of D961H for 24 weeks and 52 weeks, respectively. Further, this study was designed to evaluate the long term efficacy and safety of D961H for a maximum of 52 weeks, in consideration of the medical needs for long term PPI treatment.

**Rationale for not selecting comparator groups:**

There is no comparator in this study, because the use of placebo is judged unethical.

**Rationale for a genetic test:**

D961H is primarily metabolised by cytochrome P450 (CYP) subtype CYP2C19, an enzyme with known gene and corresponding functional polymorphism. Individuals can be classified based on their genotype of CYP2C19 either as functionally poor metabolisers (PMs) or as functionally extensive metabolisers (EMs). Subjects that are CYP2C19 PM will metabolize D961H more slowly, with the plasma concentration of D961H higher than that in subjects that are CYP2C19 EM. Based on the estimated difference in pharmacokinetics, and potential differences in pharmacodynamics and safety, there is a rationale to investigate the genotypes of CYP2C19 in the subjects of this study.

**Rationale for EGD:**

EGD is the most common method to evaluate esophageal reflux disease, as well as GU/DU and erosions. However, EGD is known to be linked to a physical burden especially in children. Therefore, it was decided that EGD is only mandatory to confirm eligibility for the maintenance therapy for healed RE. As indicated in Figure 1, for other study visits in the RE maintenance

therapy study part and NSAIDs/LDA study part, evaluation with EGD is encouraged but optional, and will be done only upon agreement from patient/patient's guardian to participate in this examination.

**Rationale for gastroesophageal pH monitoring:**

The gastric pH monitoring is the standard test to investigate gastric antisecretory activity. Esophageal pH monitoring is used to evaluate this effect in the distal esophagus. The intragastric/esophageal cut off at pH 4 is generally correlated to clinical effect in the treatment of acid related diseases. Therefore, it was decided to conduct gastroesophageal pH monitoring as a complement to evaluate pharmacodynamics as a measure of gastric antisecretory activity; the gastroesophageal pH monitoring for 12 hours is an optional test considering subjects' burden.

**Rationale for an *H. pylori* test:**

Although it is known that GU and DU are mostly caused by infection with *H. pylori*, GERD (including RE) is also cited as one of the 'diseases investigated for the significance of *H. pylori* eradication' by the *H. pylori* infection diagnosis and treatment guideline (The Japanese Society for *Helicobacter* Research 2016). Therefore, it was decided to collect information on the presence or absence of *H. pylori* infection in this study.

**Rationale for assessment of upper gastrointestinal symptoms:**

GERD (including RE) is associated with upper gastrointestinal symptoms, such as heartburn, acid regurgitation, dysphagia and epigastric pain. This is mainly due to reflux of acidic gastric content into the esophagus.

Intake of NSAIDs/LDA is associated with GU/DU-related upper gastrointestinal symptom such as epigastric pain, stomach discomfort, bloating, nausea/vomiting, heartburn and anorexia.

Therefore, it was decided to obtain these relevant data (upper gastrointestinal symptoms) and to evaluate upper gastrointestinal symptoms in detail from the questionnaire (Addendum B).

## 4.3 Justification for dose

The dosage for paediatric patients aged 1 to 11 years with GERD and erosive esophagitis has been approved in the US (Symptomatic GERD, 10 mg once-daily up to 8 weeks; Erosive esophagitis, 10 mg once-daily up to 8 weeks for weights <20 kg, or 10 mg or 20 mg once-daily up to 8 weeks for weights ≥20 kg).

The results of the phase I/III study (D961TC00002 study), which was conducted with the approved dosage in the US, showed the safety, tolerability and efficacy of 8 weeks D961H treatment in Japanese paediatric subjects with gastrointestinal acid related disease. When 20 mg D961H was administered to the paediatric subjects aged 1 to 11 years weighting ≥20 kg, higher exposure was observed compared to that of 20 mg D961H in adult subjects. Similar exposure was also observed in some paediatric subjects compared to that of 40 mg in the adult subjects.

Based on the study results above dose is considered justified:

RE study part: Subjects assigned to Group 1 will be treated with 10 mg D961H and subjects assigned to Group 2 will be treated with 20 mg D961H during the RE initial healing therapy for 8 weeks. Subjects who entered in the maintenance therapy period will be treated with 10 mg as a starter. The dose in the subjects weighting ≥20 kg may be increased to 20 mg at any visit during the treatment period based on investigator's discretion.

NSAIDs/LDA study part: The subjects assigned to Group 3 will be treated with 10 mg D961H throughout the treatment period. The subjects assigned to Group 4 will be treated with 10 mg D961H as a starter. The dose in the subjects weighting ≥20 kg may be increased to 20 mg at any visit during the treatment period based on investigator's discretion.

## 4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed his/her last visit.

See Appendix A 6 for guidelines for the dissemination of study results.

# 5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to registration/assigned to start treatment with the investigational product (D961H). Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, "enrolled" subjects/subject's guardians are defined as those who sign informed consent.

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

## 5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

**Maintenance therapy for healed RE study part:**

For initiation of the initial healing therapy phase, the study patients should fulfil the following criteria (1 to 3):

1. Provision of signed written informed consent from the patient's guardian (including informed consent to a genetic test) prior to conducting of any study-related procedure. Signed assent obtained from the patient as much as possible.

2. Patients aged 1 to 14 years inclusive at the time of informed consent.

3. Endoscopically verified RE, Grade A or higher according to the LA classification as judged by central evaluation committee (CEC). Endoscopic image taken within 4 weeks prior to initiation of the treatment with D961H could also be used for evaluation of eligibility. The EGD data prior to informed consent are also applicable if the consent of patient's guardian is obtained.

For initiation of the maintenance therapy phase after the initial healing therapy for 8 weeks, the study subjects should fulfil the following criteria (4):

4. Symptomatically healed RE, defined as no more than mild RE-related symptoms. If EGD is done, no visible mucosal breaks observed.

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

For inclusion, the study patients should fulfil the following criteria:

1. Provision of signed written informed consent from the patient's guardian (including informed consent to a genetic test) prior to conducting of any study-related procedure. Signed assent forms will be obtained from the patient as much as possible.

2. Patients aged 1 year to 14 years inclusive at the time of informed consent.

3. Patients with documented medical history of GU or DU diagnosis based on upper gastrointestinal symptoms, fecal occult blood, EGD finding, etc.

4. Expected to require a long term NSAIDs/LDA therapy (same dose is preferable) for at least 32 weeks during the study treatment.

5. If the patient has been taken disease modifying anti-rheumatic drug (DMARD) (such as methotrexate), the drugs should be taken for 4 weeks or longer before start of study treatment at the constant dose.

## 5.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled. The criteria are applicable for both the maintenance therapy for healed RE study part and the prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part.

1. Patients less than 10 kg in weight.

2. Use of any other investigational compounds or participations in another clinical trial within 4 weeks prior to the enrolment.

3. Significant clinical illness within 4 weeks prior to the informed consent, eg, unintentional weight loss, gastrointestinal bleeding requiring abstinence from food, jaundice, or any other signs indicating serious or malignant diseases.

4. Presence of hepatic diseases or other conditions that could interfere with evaluation of the study as judged by investigators.

5. Positive pregnancy urinary test result for post-menarcheal or lactating female patients.

6. Previous total gastrectomy.

7. Any conditions that are predicted to require a surgery during the study period (from the day of informed consent to the day of the last scheduled visit or discontinuation).

8. Prior treatment in this study.

9. Patients with diseases/symptoms allowing no administration of investigational products, such as known or suspected allergy or sensitivity to PPIs.

10. History of drug addiction or alcoholism within 12 months prior to the informed consent.

11. Involvement in the planning and conduct of the study, such as sponsor staff or staff at the study site (this applies to family of patients).

12. Anticipated need for *H. pylori* eradication therapy during the study period.

13. Anticipated need for concomitant therapy with any of the following after enrolment in this study*

    - PPIs (except for the investigational products)
    - $H_2$-receptor antagonists
    - Anticholinergic agents for gastrointestinal related diseases or symptoms
    - Antacids drugs (except for magnesium oxide for constipation)
    - Prostaglandin analogue indicated for peptic ulcers (eg, Misoprostol)
    - Gastrointestinal promotility drugs
    - Mucosal protectants

    *All the subjects are allowed to use any gastrointestinal drug until the day before the first dosing of investigational product (D961H) including the subjects during transit

CEC judgement on endoscopic image on condition of not changing dose and administration.

*Gastrointestinal drugs (Chinese medicines, etc.) other than the drugs above and drugs that have no indication as the gastrointestinal drugs will be allowed.

– Any drugs known to have drug-drug interactions with D961H (eg, atazanavir sulphate, rilpivirine hydrochloride, diazepam, phenytoin, cilostazol, high-dose methotrexate, warfarin, tacrolimus hydrate [except external use], digoxin, methyldigoxin, itraconazole, gefitinib, nilotinib, erlotinib, voriconazole, clopidogrel, nelfinavir mesilate, saquinavir mesilate, rifampicin and St. John's wort, etc.)

– Anticancer drugs (DMARD, eg, methotrexate is a “anticancer drug” that could be used for non-cancer Rheumatic disease treatment are allowed)

– Continuous therapy of NSAIDs (oral, intravenous, intramuscular, suppository more than 8 days) - for subjects enrolled in the maintenance therapy for healed RE study part only

14. Inability or unwillingness to take the study medication according to the dosing instructions, as judged by the investigators. For physically disabled patients, this applies if objective assessment of symptoms or EGD findings by investigators is not possible, or investigators judge that they are not able to report gastrointestinal symptoms.

15. Patients who, for whatever reason are unlikely to comply with study requirements as judged by the investigators.

## 5.3 Lifestyle restrictions

Subjects must follow the following restrictions during the study period:

- Refrain from eating and drinking, except for water, for at least 4 hours before the laboratory tests, EGD and gastroesophageal pH monitoring.
- Post-menarcheal patients must maintain effective contraception from informed consent day to the last day of scheduled visit or day of discontinuation.
- Refrain from *H. pylori* eradication therapy during the study period.
- Refrain from taking any of the concomitant therapy specified in the exclusion criterion No. 13 during the study period.
- If subject has been taking DMARD (such as methotrexate), the dose is expected to be taken at the constant dose during the period from start of study treatment to the day of the last scheduled visit or withdrawal.

## 5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form (ICF) to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. Subjects who discontinued before the initial study treatment do not need tests for the study discontinuation.

These subjects should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

Individuals who do not meet the RE Grade criteria according to the LA classification for participation in this study (screen failure) may be rescreened at another episode. Rescreened subjects should not be assigned the same subject number (E code) as for the initial screening. However, rescreening should be documented so that its effects on study results, if any, can be assessed.

# 6. STUDY TREATMENTS

Study treatment is defined as any investigational products (including marketed product comparator and placebo) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to D961H.

All study treatments will be given orally once-daily after breakfast.

**Maintenance therapy for healed RE study part:**

- Group 1: Initial healing phase (8 weeks), D961H 10 mg once-daily; Maintenance phase (24 or 44 weeks), D961H 10 mg once-daily
- Group 2: Initial healing phase (8 weeks), D961H 20 mg once-daily; Maintenance phase (24 or 44 weeks) starts with D961H 10 mg once-daily and may be increased to 20 mg once-daily based on investigator’s discretion

The subjects assigned to Group 1 will be treated with 10 mg D961H and the subjects assigned to Group 2 will be treated with 20 mg D961H during the RE initial healing therapy for 8 weeks.

The subjects who are eligible for the maintenance therapy (see Section 5.1) at the completion of the initial healing therapy will be moved to the maintenance phase for 24 or 44 weeks. During the maintenance therapy, all subjects in Groups 1 and 2 will start with 10 mg D961H. For the subjects assigned to Group 2, the dose may be increased to 20 mg at any visit during the treatment period based on investigator’s discretion. Dosing down back to 10 mg will not be allowed.

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

- Group 3: D961H 10 mg once-daily (32 or 52 weeks)
- Group 4: D961H starts with 10 mg once-daily, and may be increased to 20 mg once-daily based on investigator's discretion (32 or 52 weeks)

The subjects assigned to Group 3 will be treated with 10 mg D961H for 32 or 52 weeks.

The subjects assigned to Group 4 will be treated with 10 mg D961H for 32 or 52 weeks, 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.

However, the time of D961H administration and eating time around D961H administration in the scheduled visit will be adjusted according to test items (EGD, gastroesophageal pH monitoring, laboratory test, etc.). The drug formulation of D961H (granule or capsule) will be selected for each subject based on investigator's discretion.

The D961H sachet 10 mg will be dispersed in 15 mL of water in a cup prior to use. The contents will be stirred and left for a few minutes to thicken. The suspension will then be administered orally. An additional 15 mL of water will be used to suspend any esomeprazole granules remaining in the cup, and will be administered orally to the subjects. The suspension will be administered within 30 minutes from the stir, and stirred immediately before administration if there is more than a few minutes delay between re-constitution and administration.

## 6.1 Treatments administered

### 6.1.1 Investigational products

Choice of granule or a capsule is to be decided by investigator's discretion.

**Table 4 Study treatments**

| **Study treatment name:** | **D961H granule for suspension 10 mg** | **D961H capsule 10 mg** |
|---|---|---|
| **Dosage formulation:** | Granule containing 10 mg of Esomeprazole (11.1 mg of Esomeprazole Magnesium Hydrate) as entire coated pellets and granule of additive agent in single use aluminium sachet. | Hard capsule containing 10 mg of Esomeprazole (11.1 mg of Esomeprazole Magnesium Hydrate) as entire coated pellets in HMPC capsule. |
| **Route of administration:** | Oral | |
| **Dosing instructions:** | Refer to Section 6 | |
| **Packaging and labelling:** | The investigational products will be provided as the box for the D961 granule (include 35 packages/box) or the bottle for the D961 capsule (include 35 capsules/bottle). Each package will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. | |
| **Provider:** | AstraZeneca Sweden Operations Drug Product Supply | |

HMPC: Hydroxypropyl methyl cellulose

## 6.2 Preparation/handling/storage/accountability

The head of the medical institution or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the ‘Procedures for drug accountability’ and ‘Procedures for drug dissolution and usage’.

## 6.3 Measures to minimise bias: randomisation and blinding

This is an open label study.

If a subject withdraws from the study, then his/her enrolment/randomisation code (E code) cannot be reused. Withdrawn subjects will not be replaced.

## 6.4 Treatment compliance

The administration of all drugs (including investigational products) should be recorded in the appropriate sections of the eCRF from 7 days before Visit 2 to the last scheduled visit or withdrawal (except for drugs used for pre-treatment of EGD and gastroesophageal pH monitoring).

The investigational product is prescribed every 4 weeks in principle from Visits 2 to Visit 14. The subject's guardian is instructed to return all unused investigational products and used bottles/boxes. The quantity of returned investigational products is confirmed to check the compliance status.

If the subject's compliance rate is low due to missing doses, etc., the investigator will instruct subject's guardian (or the subject, if properly) to comply with the treatment.

## 6.5 Concomitant therapy

Other medications considered necessary for the subject's safety and wellbeing may be given at the discretion of the investigator. The use of all medications including investigational products and over-the-counter drugs during the study period (from 7 days before Visit 2 to the last scheduled visit or withdrawal) must be recorded in the appropriate sections of the eCRF. However, drugs used for pre-treatment of EGD and gastroesophageal pH monitoring (eg, anticholinergic agents, anti-anxiety agents, etc.) will not be recorded in the eCRF.

After starting the investigational product treatment, the drugs and treatments shown in Table 5 are prohibited since these may affect interpretation of results of the investigational products or result in general complications (eg, gastrointestinal bleeding).

For the subjects enrolled in the prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part, NSAIDs or LDA is recommended to be received at the constant dose from 4 weeks before the initial study treatment to the last visit or study discontinuation. If the subject has received DMARD (methotrexate, etc.), the drugs is expected to be received at the constant dose from 4 weeks before the initial study treatment to the last visit or study discontinuation.

**Table 5 Prohibited medications**

| Prohibited medication/class of drug: |
|---|
| − PPIs (except for the investigational products) * |
| − $H_2$-receptor antagonists* |
| − Anticholinergic agents for gastrointestinal related diseases or symptoms* |
| − Antacids drugs (except for magnesium oxide for constipation) * |
| − Prostaglandin analogue indicated for peptic ulcers (eg, Misoprostol) * |
| − Gastrointestinal promotility drugs* |
| − Mucosal protectants* |
| − Any drugs known to have drug-drug interactions with D961H (eg, atasanavir sulphate, rilpivirine hydrochloride, diazepam, phenytoin, cilostazol, high-dose methotrexate, warfarin, tacrolimus hydrate [except external use], digoxin, methyldigoxin, itraconazole, gefitinib, nilotinib, erlotinib, voriconazole, clopidogrel, nelfinavir mesilate, saquinavir mesilate, rifampicin and St.John's wort, etc.) |
| − Anticancer drugs (DMARD, eg, methotrexate is a "anticancer drug" that could be used for non-cancer Rheumatic disease treatment are allowed) |
| − Continuous therapy of NSAIDs (oral, intravenous, intramuscular, suppository more than 8 days treatment)- for subjects enrolled to the maintenance therapy for healed RE study part only |

*All the subjects are allowed to use any gastrointestinal drug until the day before the first dosing of investigational product (D961H ) including The subjects during transit CEC judgement on endoscopic image on condition of not changing dose and administration.

*The gastrointestinal drugs (Chinese medicines, etc.) other than the drugs above and the drugs that have no indication as the gastrointestinal drugs will be allowed.

### 6.5.1 Other concomitant therapy

Other medications considered necessary for the subject's safety and wellbeing may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

## 6.6 Dose modification

**Maintenance therapy for healed RE study part:**

The maintenance therapy dose for subjects assigned to Group 2 may be increased from 10 mg to 20 mg upon investigator's discretion that it is necessary due to development and/or persistence of RE-related symptoms or findings. If it is the case, investigators will clarify the reasons in the eCRF, citing the symptoms and/or findings, time course, and intensity. Dosing down back to 10 mg will not be allowed.

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

The prevention therapy dose for subjects assigned to Group 4 may be increased from 10 mg to 20 mg upon investigator's discretion that it is necessary due to development and/or persistence of GU/DU-related symptoms or findings. If it is the case, investigators will clarify the reasons in the eCRF, citing the symptoms and/or findings, time course, and intensity. Dosing down back to 10 mg will not be allowed.

When the subjects who assigned to Group 1 or 3 reach 20 kg after the start of investigational product administration in the maintenance/prevention therapy period, their treatment dose may be reconsidered as that of the treatment regimen for Group 2 or 4. However, during initial RE healing period of Group 1, the dose of D961H should not be changed.

## 6.7 Treatment after the end of the study

Not Applicable.

# 7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

## 7.1 Discontinuation of study treatment

Subjects may be discontinued from investigational product in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Subject or subject's guardians' decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Not fulfilling the criteria for continuation into the RE maintenance phase at Week 8
- AE
- Severe non-compliance with the Clinical Study Protocol as judged by investigator (s) and/or AstraZeneca and/or designee
- Incorrect registration, ie, the subject does not meet the required inclusion/exclusion criteria for the study, except for when the study team physician and the investigator agree with continuation through discussion
- Subject lost to follow-up
- Pregnancy
- Others as judged appropriate by the investigators (reasons for discontinuation must be recorded in the eCRF)

See the Schedule of Activities (SoA) (Table 1 and Table 2) for data to be collected at the time of study discontinuation that need to be completed.

### 7.1.1 Procedures for discontinuation of a subject from investigational product

The investigator should instruct the subject/subject's guardian to contact the study site before or at the time if study treatment is stopped. A subject/subject's guardian that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment should

be returned by the subject/subject's guardian at their next on-site study visit or unscheduled visit. Subjects permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the investigator.

## 7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject/subject's guardian and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject/subject's guardian or next of kin by eg, repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- Efforts to reach the subjects/subject's guardian should continue until the end of the study. Should the subject/subject's guardian be unreachable at the end of the study the subject should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

## 7.3 Withdrawal from the study

A subject/subject's guardian may withdraw from the study (eg, withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment. A subject who discontinued from administration of investigational product will withdraw from the study as well.

If the subject/subject's guardian withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject/subject's guardian withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject/subject's guardian who withdraws consent will always be asked about the reason (s) and the presence of any AEs. The investigator will follow-up subjects as medically indicated.

See SoA, Table 1 and Table 2, for data to be collected at the time of study discontinuation that need to be completed. All study treatment should be returned by the subject/subject's guardian.

# 8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timings are summarised in the SoA (Table 1 and Table 2).

The following will be assessed, measured or performed.

**Visit 1 (Week -4 to -1; Enrolment within 28 days prior to initial treatment):**

1. The signed and dated ICF should be obtained from the patient's guardian (including informed consent to a genetic test) prior to conducting of any study related procedure. Assent form will be signed by the patient as much as possible. The procedure for informed consent refers to Appendix A (A 3 'Informed consent process').

2. Assign a unique enrolment code (E code), beginning with 'E' to the potential subject whose signed ICF has been submitted. The E code (EXXXXYYY) is composed of 4 digits (XXXX) of study site number and 3 digits (YYY) of consecutive numbers in the order of informed consent at each study site. For study site number, see Addendum A 'Investigators and Study Administrative Structure'. E codes of subjects who failed screening or subjects who withdrew from this study after the registration to initial treatment should not be reused. At the time of the informed consent, the E code with consecutive number will be assigned.

3. Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2).

4. EGD will be performed to check EGD eligibility as judged by the CEC (for RE study part only). The EGD data within 4 weeks before the start of initial treatment could be used if available and given the consent of subject's guardian.

5. The following will be assessed, measured or performed.

    - Demographic data (sex, age, race, date of signature of informed consent, height and weight)

6. Check concomitant medication (at the time of informed consent)

7. Collection of SAEs (after informed consent has been obtained)

**Visit 2 (Week 0; Day of registration, initial treatment):**

1. Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2).

2. The following will be assessed, measured or performed:

    - Medical/surgical history (eg, a condition which a subject has had in the past and which has been declared cured)
      At Visit 2, the investigator will document the symptoms and/or signs which is considered past GU or DU in the medical record (for NSAIDs/LDA study part only)

- Physical examination (see Section 8.2.2)
- Vital signs (blood pressure, pulse rate and body temperature, see Section 8.2.3)
- Clinical laboratory tests (hematology, biochemistry and urinalysis, see Section 8.2.1)
- Urine pregnancy test
  A urine pregnancy test will be required for all post-menarcheal female patients, and the result must be negative at registration to the study treatment. This test will be performed at each study site.
- *H. pylori* test (immunoglobulin G [IgG] antibody) (see Section 8.2.1)
- Genetic test for CYP2C19 (see Section 8.7)
  If the genotyping data of CYP2C19 is already available at the study site, it may be used with the consent of subject's guardian. According to the subject's body weight, it is possible to do it Visit 3 or after for the purpose of reducing blood collection volume of Visit 2.

3. Symptom assessment by the investigator: RE-related symptoms (for RE study part) or GU/DU-related symptoms (for NSAIDs/LDA study part) (see Section 8.1.2)

4. Registration to the initial healing therapy (for RE study part) or to the prevention therapy (for NSAIDs/LDA study part).
   Subjects who meet all of the inclusion criteria and none of the exclusion criteria for this study should be registered to initial healing therapy (for RE study part) and prevention therapy (NSAIDs/LDA study part). Subjects who do not fulfill the criteria should not be registered for the initial healing/prevention phase, but will be noted in the eCRF as screen failures.

5. Dispense/Administration of the investigational product

6. Check concomitant medication

7. Evaluation of efficacy composite endpoint (for NSAIDs/LDA study part only) (see Section 8.1.1)

8. Collection of AEs (after the investigational product administration) and SAEs (after the informed consent)

**Visits 3 and 5 to 9 (Weeks 4 and 12 to 28):**

1. The following will be assessed, measured or performed:

   - Physical examination (see Section 8.2.2)
   - Vital signs (blood pressure, pulse rate and body temperature, see Section 8.2.3)

2. Symptom assessment by the investigator: RE-related symptoms (for RE study part), or GU/DU-related symptoms (for NSAIDs/LDA study part) (see Section 8.1.2)

3. Dispense/Administration of the investigational product

4. Check concomitant medication

5. Evaluation of efficacy composite endpoint: Visits 5 to 9 (for RE study part) or Visits 3 and 5 to 9 (for NSAIDs/LDA study part) (see Section 8.1.1)

6. Collection of all AEs and SAEs

**Visit 4 – For RE study part only (Week 8; Day of initial treatment for RE maintenance therapy):**

1. Review inclusion/exclusion criteria for registration to the RE maintenance therapy. Subjects who completed the healing therapy for 8 weeks and evaluated to have symptomatically healed RE (defined as no more than mild RE-related symptoms) at Visit 4, or if an EGD is done, no visible mucosal breaks observed.

2. The following will be assessed, measured or performed.

   - Physical examination (see Section 8.2.2)
   - Vital signs (blood pressure, pulse rate and body temperature, see Section 8.2.3)
   - Clinical laboratory tests (hematology, biochemistry and urinalysis, see Section 8.2.1)
   - EGD (optional)
   - RE-related symptom assessment by the investigator (see Section 8.1.2)

3. Registration for maintenance therapy
   Subjects who meet the criteria for entering the RE maintenance phase should be registered for maintenance therapy. Subjects who do not meet the criteria for entering the RE maintenance phase should not be registered for maintenance therapy but be noted in the eCRF. For these subjects, this will be the last visit (Study closure visit).

4. Dispense/Administration of the investigational product

5. Check concomitant medication

6. Evaluation of efficacy composite endpoint (see Section 8.1.1)

7. Collection of all AEs and SAEs

**Visit 4 (Week 8; for NSAIDs/LDA study part only):**

Same as Visits 3, and 5 to 9.

**Visit 10 (Week 32; Study Closure 1, Day of end of the first study period and start of the initial treatment for extension therapy):**

Subjects who discontinue from investigational product treatment and/or withdraw during maintenance/prevention phase before Week 32 will be performed the activities described in Visit 10, if possible:

A) Data from the first study period will be collected.

1. The following will be assessed, measured or performed.

   - Physical examination (see Section 8.2.2)
   - Vital signs (blood pressure, pulse rate and body temperature, see Section 8.2.3)
   - Clinical laboratory tests (hematology, biochemistry and urinalysis, see Section 8.2.1)
   - EGD (optional)
   - Gastroesophageal 12-hour pH monitoring (optional) (see Section 8.6)

2. Symptom assessment by the investigator: RE-related symptoms (for RE study part), or GU/DU-related symptoms (for NSAIDs/LDA study part) (see Section 8.1.2)

3. Check concomitant medication

4. Evaluation of efficacy composite endpoint (see Section 8.1.1)

5. Collection of all AEs and SAEs

B) The treatment period in all groups may be extended up to 52 weeks upon investigator's discretion. The reason for the extension will be recorded in the eCRF.

6. Dispense/Administration of the investigational product (in case of extension of the treatment)

**Visits 11 to 14 (Weeks 36 to 48; Extended period):**

Same as Visits 3, and 5 to 9.

**Visit 15 (Week 52; Study Closure 2, Day of end of extended period):**

Subjects who discontinue from investigational product treatment and/or withdraw during the maintenance/prevention phase after Week 32 will be performed the activities described in Visit 15, if possible:

1. The following will be assessed, measured or performed:
   - Physical examination (see Section 8.2.2)
   - Vital signs (blood pressure, pulse rate and body temperature, see Section 8.2.3)
   - Clinical laboratory tests (hematology, biochemistry and urinalysis, see Section 8.2.1)
   - EGD (optional)
2. Symptom assessment by the investigator: RE-related symptoms (for RE study part), or GU/DU-related symptoms (for NSAIDs/LDA study part) (see Section 8.1.2)
3. Check concomitant medication
4. Evaluation of efficacy composite endpoint (see Section 8.1.1)
5. Collection of all AEs and SAEs

The investigator will ensure that data are recorded on the eCRF. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, vital signs) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1 and Table 2).

## 8.1 Efficacy assessments

The primary endpoints are shown in Table 3.

### 8.1.1 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:

1. An EGD relapse is defined as an identification of a RE with LA classification grade A to D (see Table 6)

2. A symptom relapse (defined by any of the 4 specified RE-related symptoms in the RE-related symptom questionnaire, see Section 8.1.2) 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 guardian

    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 guardian

For subjects who are judged as having RE relapse, record the reason (symptoms and/or findings, time course, and intensity, etc.) in the eCRF.

**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 8.1.2) 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 guardian

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 guardian

For subjects who are judged as having GU/DU recurrence, record the reason (symptoms and/or findings, time course, and intensity, etc.) in the eCRF.

### 8.1.2 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 guardian 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.

Intensity of episode is classified as follows:

- None - No symptoms
- Mild - Awareness of symptom, but easily tolerated
- Moderate - Discomforting symptom sufficient to cause interference with normal activities (including sleep)
- Severe - 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 guardian 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 as follows:

- None - No symptoms
- Mild - Awareness of symptom, but easily tolerated
- Moderate - Discomforting symptom sufficient to cause interference with normal activities (including sleep)
- Severe - Incapacitating symptoms, with inability to perform normal activities (including sleep)

### 8.1.3 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 guardians. The EGD is conducted by fasting condition at least 4 hours prior to the test.

The EGD is performed by the method usually employed at each study site. The drug used for the pre-treatment of EGD is not recorded in the eCRF.

Subjects who get more symptoms during the maintenance therapy period (especially if they leave the study) should be encouraged to do an EGD, whenever possible.

**Maintenance therapy for healed RE study part:**

To evaluate RE, the EGD results are assessed based on the LA classification (Lundell et al 1999) (See Table 6). Any grades of mucosal breaks graded as A, B, C or D is considered as presence of RE.

Photo documentation from the EGD will be judged by the CEC, which consists of gastrointestinal specialist(s) who will be appointed for this study to validate the diagnosis for inclusion by investigators based on the EGD findings. If investigators find any suspicious findings of RE on the EGD during the study, all suspicious finding photos should be sent to CEC for review. The CEC will report the review results to the investigators and the sponsor. When the results are inconsistent between the central and local assessments, the central assessment will be used for judgement of the enrolment. For the EGD on Visit 1, if the EGD data within 4 weeks before the initial treatment are available, they may be used with the consent of subject's guardians even though these are the results of the test conducted before obtaining informed consent.

**Table 6 LA classification**

| | |
|---|---|
| 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 (Lanza et al 1988) (See Table 7). If investigators find any suspicious findings of GU/DU on the EGD during the study, all suspicious finding photos should be sent to CEC for review. The CEC will report the review results to the investigators and the sponsor. The presence of an ulcer is separately collected in the eCRF. 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 7 Modified LANZA score**

| | |
|---|---|
| 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.

## 8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 2).

### 8.2.1 Clinical safety laboratory assessments

See Table 8 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA. The date of collecting samples for the laboratory tests must be recorded in the eCRF. These tests will be performed in fasting condition at least 4 hours before test at each study site. The urinalysis is not required if the subjects have no ability to autonomously excrete urine.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at study site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

**Table 8 The items of laboratory safety**

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

**NB.** In case a subject shows an AST **or** ALT ≥3 x upper limit normal (ULN) together with total bilirubin ≥2 x ULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

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

The total volume of blood that will be drawn from each subject in this study is as follows (Table 9). All the laboratory tests except for urine pregnancy test will be performed at the central laboratory.

The urine pregnancy test will be performed at each study site by using dipstick provided from the central laboratory.

At Visit 2 (Week 0), blood sample (1 mL) will be collected to measure IgG antibody to determine the presence or absence of *H. pylori* infection.

**Table 9 Volume of blood to be drawn from each subject**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| Characteristic of subject | *H. pylori* test | 1 | 1 | 1 |
| Safety | Hematology | 2 | RE study part: 3 (or 4*)<br>NSAIDs/LDA study part: 2 (or 3*) | RE study part: 6 (or 8*)<br>NSAIDs/LDA study part: 4 (or 6*) |
| | Biochemistry | 5 | RE study part: 3 (or 4*)<br>NSAIDs/LDA study part: 2 (or 3*) | RE study part: 15 (or 20*)<br>NSAIDs/LDA study part: 10 (or 15*) |
| Pharmacogenetics | CYP2C19 | 2 | 1 | 2 |
| Total | | | | RE study part: 24 (or 31*)<br>NSAIDs/LDA study part: 17 (or 24*) |

* In case of the subjects continue the study after Visit 11.

### 8.2.2 Physical examination

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

### 8.2.3 Vital signs

At the Visit 2 and the all subsequent visits, blood pressure, pulse rate and body temperature will be measured.

## 8.3 Collection of AEs

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

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs see Section 8.3.3.

### 8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

### 8.3.2 Time period and frequency for collecting AE and SAE information

AEs will be collected from the start of investigational product (Visit 2) 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 (Visit 1).

Hospitalisation for investigations defined in this protocol (eg, EGD, gastroesophageal pH monitoring) is not considered as SAE.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

### 8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, explanation of the event, or the subject is lost to follow-up.

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

### 8.3.4 AE data collection

'The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not

- Investigator causality rating against the investigational product(s) (yes or no)
- Action taken with regard to investigational product(s)
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

### 8.3.5 Causality collection

The investigator will assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

### 8.3.6 AEs based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study site staff: *'Have you/the child had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other

signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 8.3.7 AEs based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline (Visit 2) in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment (Visit 2) will be reported as an AE unless unequivocally related to the disease under study, see Section 8.3.9.

### 8.3.8 Hy's law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x upper limit normal (ULN) together with total bilirubin ≥ 2 x ULN need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

### 8.3.9 Disease under study

**EGD findings of disease under the study:**

The EGD findings due to target illness (see Section 8.1.3) are not reported as the AEs except for those that correspond to the SAE definition (see Appendix B), or those whose aggravation resulted in discontinuation of study.

**Symptoms of disease under the study:**

Symptoms due to target illness (see Section 8.1.2) are not reported as the AEs except for those that correspond to the SAE definition (see Appendix B), or those whose aggravation resulted in discontinuation of study.

## 8.4 Safety reporting and medical management

### 8.4.1 Reporting of SAEs

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the WBDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

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

### 8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study subject has received any investigational product

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

#### 8.4.2.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

#### 8.4.2.2 Paternal exposure

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented.

If the subject's partner gets pregnant, despite prevention, state that the partner will be asked to sign an Inform Consent for pregnant partners and be collected the information.

### 8.4.3 Overdose

No subject in this study is scheduled to receive a dose higher than 20 mg within 1 calendar day. Therefore, an overdose will be any dose greater than 20 mg taken in a 24-hour period. The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

If an overdose occurs, the following actions should be taken:

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

If an overdose on an AstraZeneca investigational drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

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

For overdoses associated with SAE, standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting should be done to the AstraZeneca patient safety data entry site within 30 days.

### 8.4.4 Medication Error

If an medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B 8.

## 8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

## 8.6 Pharmacodynamics

The gastroesophageal pH will be measured during 12 hours as an indicator of gastric antisecretory activity (optional).

The gastroesophageal pH monitoring is preferably done at Visit 10 (Week 32), but is also suggested if signs of RE relapse or GU/DU recurrence either before (Week 8 to 32) or after (Week 32 to 52) this time point. The date of performing the pH monitoring must be recorded in the eCRF.

A combined catheter with 2 pH sensors will be introduced and gastroesophageal pH will be measured during 12 hours. The pH probe will be inserted nasally with the esophageal sensor positioned 3 cm above the lower esophageal sphincter, and the gastric sensor within the central part of the stomach. The precise location of the tip will be confirmed. The subject should be in fasting condition at least 4 hours before pH monitoring. The gastroesophageal pH will be recorded every 10 seconds. The results of pH monitoring (electronic data) will be submitted to AstraZeneca or designee. Data extraction, storage and sending will be performed according to the manual.

The gastroesophageal pH monitoring will be performed in the subjects obtained informed consent from subject’s guardians.

## 8.7 Genetics

The purpose of the genetic research is to investigate the genotype of CYP2C19, a metabolising enzyme of D961H known to have 2 genotypes. These genotypes are named 'Extensive, Metaboliser (EM)' (EM homozygotes- and EM heterozygotes- types) and 'poor metaboliser (PM)'. Since changes in blood D961H concentrations showed different tendency between the 2 metabolisers and as a different in pH time might be seen, they will be examined accordingly. Subjects will be categorized using the 2 mutated alleles, CYP2C19*2 and CYP2C19*3. The wild-type allele (CYP2C19*1) will be defined if these mutation are not detected. EM homozygote types (homo-EMs) are to be homozygous for the wild-type allele (CYP2C19*1/*1); EM heterozygote types (hetero-EMs) are to be heterozygous for the CYP2C19*2 allele without CYP2C19*3 (CYP2C19*1/*2) or the CYP2C19*3 without CYP2C19*2 (CYP2C19*1/*3), PMs are to be homozygous or heterozygous for either variant allele (CYP2C19*2/*2, *3/*3, *2/*3).

This test will be conducted in the central laboratory. If results of the CYP2C19 genotype are already available at the study site, they will be provided to AstraZeneca with the consent of subject's guardian and an additional analysis will not be required.

### 8.7.1 Collection of mandatory genetic samples

The blood sample (2 mL) for genetic research of CYP subtype CYP2C19 will be obtained from the subjects at Visit 2. Only 1 sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the procedure manual.

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 of informed consent is provided:

- Written informed consent to a genetic test must be provided by each subject's guardian.
- 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 sites and AstraZeneca or designee 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 assigned to treatment groups in the study will be destroyed immediately by central laboratory.

- If the genetic test for the sample of the subject who is not assigned to treatment groups in the study was completed, the results of the test and the records will be destroyed immediately by central laboratory.

- In the case the subject's guardian in concern wishes a release of the genetic test results, the results will be disclosed to subject's guardian via investigator (s) after the database of this study is locked. However, the results will be disclosed to subject's guardians immediately even before the database is locked only when the subject's guardian 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 after completion of the CYP2C19 genotyping by central laboratory.

### 8.7.2 Optional exploratory genetic sample

Paediatric subject samples will not be collected for optional genetic research.

### 8.7.3 Storage and destruction of genetic samples

The samples will be used up or disposed according to the following rules:

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

The principal investigator at each study site keeps full traceability of collected biological samples from the subjects while in storage at the study site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

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

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

The principal investigator:

- Ensures subject's guardian withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.

- Ensures the laboratory holding the samples are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.

- Ensures that subject's guardian and AstraZeneca are informed about the sample disposal.

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

## 8.8 Biomarkers

Biomarkers are not evaluated in this study.

## 8.9 Health economics

Health economics parameter is not evaluated in this study.

# 9. STATISTICAL CONSIDERATIONS

## 9.1 Statistical hypotheses

Not applicable because no formal statistical analysis is planned in this study.

## 9.2 Sample size determination

**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 patients, 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/group. In treatment Groups 2 and 4, physically disabled patients, 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/group.

**Rationale for the sample size:**

The sample size of this study is not based on any power calculations.

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 (Ohara et al 2005), 24.5% of adult patients with heart burn had endoscopic LA grade A or higher erosive esophagitis. Even if the prevalence rate in Japanese paediatrics was 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 15 to 30 registration of subjects to start with the investigational product.

## 9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Efficacy Analysis Set | Maintenance therapy for healed RE study part:<br>1. Initial healing therapy period<br>All subjects registered to initial healing therapy who take at least 1 dose of the investigational product and have at least 1 efficacy datum assessment during the initial healing therapy period, and who have no important protocol deviation.<br>2. Maintenance therapy period<br>All subjects registered to maintenance therapy who take at least 1 dose of the investigational product and have at least 1 efficacy datum assessment during the maintenance therapy period, and who have no important protocol deviation.<br>3. Maintenance therapy extended period<br>All subjects registered to maintenance therapy who take at least 1 dose of the investigational product and have at least 1 efficacy datum assessment during the maintenance therapy extended period, and who have no important protocol deviation.<br><br>Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:<br>1. Prevention therapy period<br>All subjects who take at least 1 dose of the investigational product and have at least 1 efficacy datum assessment during the prevention therapy period, and who have no important protocol deviation.<br>2. Prevention therapy extended period<br>All subjects who take at least 1 dose of the investigational product and have at least 1 efficacy datum assessment during the prevention |

| Population | Description |
|---|---|
| | therapy extended period, and who have no important protocol deviation. |
| Safety Analysis Set | Maintenance therapy for healed RE study part:<br>1. Initial healing therapy period<br>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.<br>2. Maintenance therapy period<br>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.<br>3. Maintenance therapy extended period<br>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.<br><br>Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:<br>1. Prevention therapy period<br>All subjects who take at least 1 dose of the investigational product and have any post-treatment assessment during the prevention therapy period.<br>2. Prevention therapy extended period<br>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:<br>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.<br><br>Prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part:<br>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. |

## 9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused,

and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

### 9.4.1 Efficacy analyses

Efficacy analyses are intended for Efficacy Analysis Set.

**Maintenance therapy for healed RE study part:**

For all subjects in Efficacy Analysis Set who have at least 1 efficacy assessment during the maintenance therapy period, the percentage of subjects with RE relapse and the time to RE relapse will be analysed by the Kaplan-Meier method for each treatment group by assessing any composite endpoint (RE-related symptoms or optional EGD findings) from Week 8 to 32 as a primary analysis. 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.

For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the percentage of subjects with RE relapse and the time to RE relapse will be analysed by the Kaplan-Meier method for each treatment group by assessing the similar composite endpoint of the primary analysis from Week 8 to 52 (8 to 32 weeks and 32 to 52 weeks, respectively).

RE-related symptoms (heartburn, acid regurgitation, dysphagia and epigastric pain) will be summarised by frequency and intensity from Week 0 to 8 and from Week 8 to 32 or 52 separately. For all subjects in Efficacy Analysis Set, the number of subjects and their percentage of disappearance, exacerbation and recurrence for each symptom will be summarised by group from Week 0 to 8 and from Week 8 to 32 separately.

Definitions of the disappearance, exacerbation and recurrence are given below:

- Disappearance: the symptom disappeared during the period for subjects who had the corresponding symptom at the start of the period
- Exacerbation: the symptom worsened during the period for subjects who had the corresponding symptom at the start of the period
- Recurrence: the symptom occurred during the period for subjects who did not have the corresponding symptom at the start of the period

For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the similar number and percentage for each symptom will be summarised by group from Week 8 to 52 (8 to 32 weeks and 32 to 52 weeks, respectively).

Regarding endoscopic assessment of healed RE, the number of subjects who had RE relapse endoscopically will be summarised for all subjects in Efficacy Analysis Set who had an EGD result at post-dose by group. The number of subjects in Efficacy Analysis Set in each grade of the LA classification (graded A to D) for these subjects will be summarised by group.

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

For all subjects in Efficacy Analysis Set, the percentage of subjects with GU/DU recurrence and the time to the recurrence will be analysed by the Kaplan-Meier method for each treatment group by assessing any composite endpoint (GU/DU-related symptoms or optional EGD findings) from Week 0 to 32 as a primary analysis. 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.

For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the percentage of subjects with GU/DU recurrence and the time to the recurrence will be analysed by the Kaplan-Meier method for each treatment group by assessing the similar composite endpoint of the primary analysis from Week 0 to 52 (0 to 32 weeks and 32 to 52 weeks, respectively).

GU/DU-related symptoms (epigastric pain, discomfort in the stomach, abdomen enlarged feeling, nausea/vomiting, heartburn and anorexia) will be summarised by frequency and intensity. For all subjects in Efficacy Analysis Set, the number of subjects and its percentage of disappearance, exacerbation and recurrence of each symptom will be summarised by group from Week 0 to 32.

Definitions of the disappearance, exacerbation and recurrence are given below:

- Disappearance: the symptom disappeared during the period for subjects who had the corresponding symptom at the start of the period
- Exacerbation: the symptom worsened during the period for subjects who had the corresponding symptom at the start of the period
- Recurrence: the symptom occurred during the period for subjects who did not have the corresponding symptom at the start of the period

For subjects in Efficacy Analysis Set who continued the study treatment after Week 32, the same number and percentage for each symptom will be summarised by group from Week 0 to 52 (0 to 32 weeks and 32 to 52 weeks, respectively).

Regarding endoscopic assessment of GU or DU and gastric erosions, the number of subjects will be summarised by group based on a clear definition of ulcer and modified LANZA score for all subjects in Efficacy Analysis Set 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 group.

### 9.4.2 Safety analyses

All safety analyses will be performed on the Safety Analysis Set.

Frequency and incidence rate of AEs, SAEs, DAEs and OAEs will be presented by MedDRA SOC and PT for each group. In addition, summaries of AEs will be further broken down by maximum intensity and relationship to the investigational product as assigned by investigators.

Clinical laboratory variables and vital signs will be summarised by group with descriptive statistics using values and changes from Week 8 as baseline to Week 32 for the maintenance therapy for healed RE study part, and changes from Week 0 as baseline to Week 32 for prevention of GU/DU recurrence associated with long term NSAIDs/LDA therapy study part. Qualitative data will be presented by group in terms of frequency and percentage, and changes from baseline will be presented using shift tables. The distribution of subject with values below and above the reference range will be provided.

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 similar safety assessment will be evaluated from Week 0 as baseline to Week 8 as the secondary analysis. 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 same safety assessments will be evaluated for all subjects in Safety Analysis Set from Week 0 as baseline to Week 32 as the primary analysis. For all subjects in Safety Analysis Set who continued the study treatment after Week 32, the same safety assessments will be evaluated from Week 0 to 52 (0 to 32 weeks and 32 to 52 weeks, respectively) as the secondary analysis.

### 9.4.3 Pharmacodynamic analyses

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

## 9.5 Interim analyses

There is no plan to have any interim analyses.

# 10. REFERENCES

**The Japanese Society for *Helicobacter* Research 2016**
The Japanese Society for *Helicobacter* Research. The guideline for diagnosis and treatment of *H. pylori* infection (revised version, 2016).

**Lanza et al 1988**
Lanza FL, Aspinall RL, Swabb EA, Davis RE, Rack MF, Rubin A. Double-blind, placebo-controlled endoscopic comparison of the mucosal protective effects of misoprostol versus cimetidine on tolmetin-induced mucosal injury to the stomach and duodenum. Gastroenterology. 1988;95(2):289-94.

**Lundell et al 1999**
Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45(2):172-80.

**Nagashima H and Ikushima I 2011**
Nagashima H, Ikushima I. Evaluation of pharmacodynamics and pharmacokinetics of esomeprazole 10, 20 and 40 mg and omeprazole 10 and 20 mg in Japanese healthy male subjects. Japanese Journal of Therapeutics & Medicines. 2011;27(10):735-46.

**Ohara et al 2005**
Ohara S, Kouzu T, Kawano T, Kusano M. Nationwide epidemiological survey regarding heartburn and reflux esophagitis in Japanese. Journal of JSGE. 2005;102(8):1010-24.

# 11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, ethical and study oversight considerations

### A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable Japan Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/ independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The head of the study site will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of applicable guidelines, the IRB/IEC, and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

### A 2 Financial disclosure

Not applicable.

### A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of local regulations, applicable guidelines and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

Subjects who are rescreened are required to sign a new ICF.

## A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to investigators.

## A 6 Dissemination of clinical study data

A description of this clinical trial will be available on *http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov* as will the summary of the study results when they are available. The clinical trial and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 7 Data quality assurance

All subject data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, Japan GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

## A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data are any data generated as a result of the subject's inclusion in the study and includes all related medical examinations and other records and may also include past/current medical records.

## A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multi-centre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B AE definitions and additional safety information

## B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

## B 2 Definitions of SAE

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- 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 treatment to prevent one of the outcomes listed above.

## B 3 Life threatening

‘Life-threatening’ means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

## B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

## B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

## B 6 Intensity rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

## B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality considers the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca investigational product that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred

- was identified and intercepted before the participant received the drug

- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed
- Wrong participant received the medication (excluding interactive voice response system [IVRS]/interactive web response system [IWRS] errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

# Appendix C Handling of Human Biological Samples

## C 1 Chain of custody of biological samples

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

The investigator at each study site keeps full traceability of collected biological samples from the subjects while in storage at the study site until shipment or disposal (where appropriate).

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

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

## C 2 Withdrawal of Informed Consent for donated biological samples

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

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The investigator:

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

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

## C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

## LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

# Appendix D Genetics

Not applicable.

# Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

## E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases.It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## E 2 Definitions

**Potential Hy's Law (PHL)**

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

**Hy's Law (HL)**

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Central laboratories being used:**

When a subject meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (and also to the AstraZeneca representative). The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

**Local laboratories being used:**

Not applicable.

## E 4 Follow-up

### E 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

### E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central study team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the subject's condition
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.

  Subsequent to this contact the investigator will:

  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician.This includes deciding which the tests available in the Hy's law lab kit should be used
  - Complete the three Liver CRF Modules as information becomes available

# A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

## E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate. According to the outcome of the review and assessment, the investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF

- If the alternative explanation is an AE/SAE, update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## E 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

Not applicable.

## E 7 Actions required for repeat episodes of potential Hy's Law

Not applicable.

## E 8 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory . For studies using a local laboratory, the list may be modified based on clinical judgement. If required, additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded in the CRF.

**Hy's Law recommended tests**

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>IgM and IgG anti-HBc<br>HBsAg<br>HBV DNA<br>IgG anti-HCV<br>HCV RNA*<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM & IgG anti-CMV<br>IgM & IgG anti-HSV<br>IgM & IgG anti-EBV |
| Alcoholic hepatitis | Carbohydrate deficient transferrin (CD-transferrin) |
| Autoimmune hepatitis | Antinuclear antibody (ANA)<br>Anti-Liver/Kidney Microsomal Ab (Anti-LKM)<br>Anti-Smooth Muscle Ab (ASMA) |
| Metabolic diseases | alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive.

**References**

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’

# Appendix F Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| CEC | central evaluation committee |
| CIOMS | Council for International Organizations of Medical Sciences |
| CONSORT | Consolidated Standards of Reporting Trials |
| CYP | cytochrome P450 |
| DAE | discontinuation of investigational product due to adverse event |
| DILI | drug induced liver injury |
| DMARD | disease modifying anti-rheumatic drug |
| DU | duodenal ulcer |
| eCRF | case report form (electronic) |
| EGD | esophagogastroduodenoscopy |
| EM | extensive metaboliser |
| EU | European Union |
| GCP | Good Clinical Practice |
| GERD | gastroesophageal reflux disease |
| GU | gastric ulcer |
| HL | Hy's Law |
| *H. pylori* | *Helicobacter pylori* |
| IATA | International Airline Transportation Association |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| IEC | independent ethics committee |
| IgG | immunoglobulin G |
| IRB | institutional review board |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| LA classification | Los Angeles classification |
| LDA | low-dose aspirin |

| Abbreviation or special term | Explanation |
|---|---|
| MALT | mucosa-associated lymphoid tissue |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NSAIDs | non-steroidal anti-inflammatory drugs |
| OAE | other significant adverse event |
| PHL | potential Hy's Law |
| PM | poor metaboliser |
| PPI | proton pump inhibitor |
| PT | preferred term |
| RE | reflux esophagitis |
| SAE | serious adverse event |
| SoA | schedule of activities |
| SOC | system organ class |
| TBL | total bilirubin |
| ULN | upper limit normal |
| US | United States |
| WBDC | web based data capture |