Clinical Study Report Synopsis

Drug Substance D961H

Study Code D961WC00001

Edition Number [redacted]

[redacted]

NCT Number NCT03553563

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

Study dates:

First subject enrolled: [redacted]

Last subject last visit: [redacted]

The analyses presented in this report are based on a clinical data lock date of [redacted]

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator:

[redacted]

Sponsor's Responsible Medical Officer:

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This multi-centre study was conducted at a total of [redacted] sites in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

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

Table S1 Objectives and Endpoints

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

Table S1 Objectives and Endpoints

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

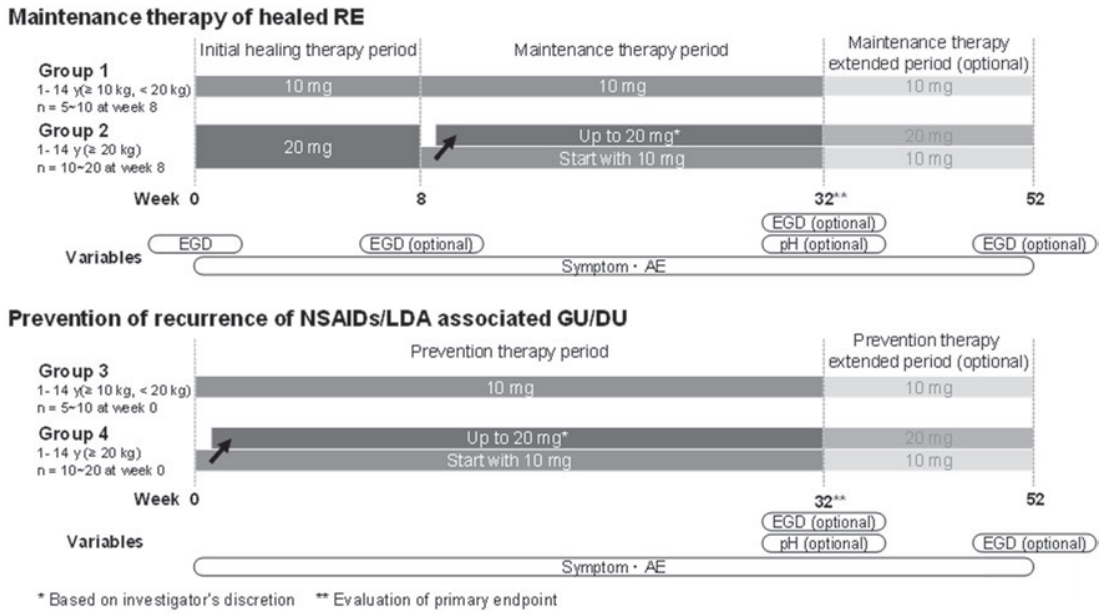
AE: adverse event, DU: duodenal ulcer, EGD: esophagogastroduodenoscopy, GU: gastric ulcer, LDA: low-dose aspirin, NSAIDs: non-steroidal anti-inflammatory drugs, RE: reflux esophagitis

Study design

This was an open label, parallel group, multi-centre, phase III study to assess the safety and efficacy of D961H in maintenance therapy following initial 8 weeks healing therapy in Japanese paediatric patients with reflux esophagitis (RE), and to assess the safety and efficacy of D961H in Japanese paediatric patients treated with long term non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin (LDA) therapy who had a documented medical history of gastric ulcer (GU) or duodenal ulcer (DU) diagnosis.

Doses of D961H in this study were 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 would 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) followed different regimen.

Figure S1 Study design



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

Target population and sample size

Maintenance therapy for healed RE study part

- Patients aged 1 to 14 years, with endoscopically verified RE, Grade A or higher according to the Los Angeles (LA) classification as judged by central evaluation committee (CEC).
- For initiation of the maintenance therapy phase after the initial healing therapy for 8 weeks, patients with symptomatically healed RE, defined as no more than mild RE-related symptoms. If esophagogastroduodenoscopy (EGD) was done, no visible mucosal breaks had been observed.

Sample size:

- 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 during long term NSAIDs/LDA treatment part

- Patients aged 1 to 14 years with documented medical history of GU/DU diagnosis based on upper gastrointestinal symptoms, faecal occult blood, EGD finding, etc.
- Patients expected to require a long term NSAIDs/LDA therapy (same dose is preferable) for at least 32 weeks during the study treatment.

- 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.

Sample size:

- 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 were 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.

Investigational product (IP) and comparator(s): dosage, mode of administration and batch numbers

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.
Batch numbers	AAAC, AAAH, AAAN, AAAY	L009558, L012624, DAAE
Route of administration:	Oral	
Provider:	AstraZeneca Sweden Operations Drug Product Supply	

HMPC: hydroxypropyl methyl cellulose

Duration of treatment

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) started with D961H 10 mg once-daily, and could be increased to 20 mg once-daily based on investigator's discretion

Prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part

- Group 3: D961H 10 mg once-daily (32 or 52 weeks)
- Group 4: D961H started with 10 mg once-daily, and could 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 reached 20 kg after the start of IP administration in the maintenance/prevention therapy period, their treatment dose could 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 analyses

All efficacy analyses were performed on Efficacy Analysis Set, which consists of all subjects who took at least 1 dose of IP and had at least 1 efficacy assessment during the maintenance/prevention therapy period, and who had no major important protocol deviation.

Maintenance therapy for healed RE study part

As a primary endpoint, for all subjects in Efficacy Analysis Set who had at least 1 efficacy assessment during the maintenance therapy period, the percentage of subjects with RE relapse by assessing any composite endpoints (RE-related symptoms or optional EGD findings) from Week 8 to Week 32 and its exact 95% confidence interval (CI) using the Clopper-Pearson method were summarised for each treatment group, and the time to RE relapse was analysed by the Kaplan-Meier method for each treatment.

As a secondary endpoint, the percentage of subjects with RE relapse from Week 8 to Week 52 (8 to 32 weeks and 32 to 52 weeks, respectively) and its exact 95% CI were summarised and analysed using the same methods for the primary endpoint.

The other secondary endpoints (RE-related symptoms and endoscopic assessments) were summarised for each treatment group.

Prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part

As a primary endpoint, for all subjects in Efficacy Analysis Set, the percentage of subjects with GU/DU recurrence by assessing any composite endpoints (GU/DU-related symptoms or optional EGD findings) from Week 0 to Week 32 and its exact 95% CI using the Clopper-Pearson method were summarised for each treatment group, and the time to GU/DU recurrence were analysed by the Kaplan-Meier method for each treatment group.

As a secondary endpoint, the percentage of subjects with GU/DU recurrence from baseline to Week 52 (baseline to 32 weeks and 32 to 52 weeks, respectively) and its exact 95% CI were summarised and analysed using the same methods for the primary endpoint.

The other secondary endpoints (GU/DU-related symptoms and endoscopic assessments) were summarised for each treatment group.

Safety analyses

All safety analyses were performed on Safety Analysis Set, which consists of all subjects who took at least 1 dose of IP and have any post-treatment assessment.

The numbers of any adverse events (AEs), causally related AEs, AEs leading to death, serious adverse events (SAEs), and discontinuations of IP due to adverse event (DAEs), and the numbers and proportions of subjects with those AEs were summarised for each treatment group. The numbers and proportions of subjects with AEs, SAEs, and DAEs were presented by System Organ Class (SOC) and Preferred Term (PT) in Medical Dictionary for Regulatory Activities (MedDRA) for each treatment group.

For continuous clinical laboratory variables and vital signs, all data at baseline and each post-dose time point were summarised for each treatment group using descriptive statistics. For categorical results of laboratory tests, the frequency and percentage in each category of the item at baseline and each post-dose time point were calculated for each treatment group.

In the maintenance therapy for healed RE study part, the safety assessments (AEs, laboratory variables, and vital signs) were evaluated for all subjects in Safety Analysis Set from Week 8 as baseline to Week 32 as the primary analysis.

For prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part, the corresponding safety assessments were evaluated for all subjects in Safety Analysis Set from baseline to Week 32 as the primary analysis.

Pharmacodynamic analyses

Regarding gastroesophageal pH measurement, Pharmacodynamic Analysis Set was used:

The results of gastric and esophageal pH were summarised.

Study population

The subjects were enrolled from 17 sites in Japan.

Maintenance therapy for healed RE study part

Out of 31 enrolled subjects, 3 were not registered due to screen failures, and 28 were registered to the initial healing therapy period. All 28 registered subjects received the IP so that they were included in Safety Analysis Set and in Efficacy Analysis Set in the initial healing therapy period. Twenty seven subjects were registered to the maintenance therapy period. All 27 subjects received the IP and were included in Safety Analysis Set. One of the 27 subjects was excluded from Efficacy Analysis Set because the CEC judged the RE as not healed at Week 8, hence 26 subjects were included in Efficacy Analysis Set in the maintenance therapy period. Three subjects discontinued the maintenance therapy period because of physician decision (2 subjects) and failure to meet continuation criteria (1 subject

with not healed RE after the initial healing therapy period). Two subjects were not registered to the maintenance therapy extended period because of physician decision. Twenty two subjects were registered to the maintenance therapy extended period. All 22 subjects received the IP and were included in Safety Analysis Set and Efficacy Analysis Set in the maintenance therapy extended period.

Prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part

Of 22 enrolled subjects, all 22 subjects were registered to the prevention therapy period. All 22 registered subjects received the IP so that they were included in Safety Analysis Set and Efficacy Analysis Set in the prevention therapy period. One subject discontinued the prevention therapy period because of withdrawal by parent/legally authorised representative. Thirteen subjects were registered to the prevention therapy extended period. Eight subjects were not registered to the prevention therapy extended period because of physician decision (5 subjects) and withdrawal by parent/legally authorised representative (3 subjects). All 13 subjects received the IP and were included in Safety Analysis Set and Efficacy Analysis Set in the prevention therapy extended period.

Summary of efficacy results

Maintenance therapy for healed RE study part

In most subjects in Groups 1 and 2, RE relapses were prevented during the long term therapy with D961H.

- The percentages of subjects with RE relapse from Week 8 to Week 32 were 0.0% (0 of the 7 subjects, 95%CI: 0.0, 41.0) in Group 1 and 5.3% (1 of the 19 subjects, 95%CI: 0.1, 26.0) in Group 2.
- For the subjects who continued the study treatment after Week 32, the percentages of subjects with RE relapse were 0.0% (0 of the 6 subjects, 95%CI: 0.0, 45.9) from Week 8 to Week 32, and 16.7% (1 of the 6 subjects, 95%CI: 0.4, 64.1) from both Week 32 to Week 52 and Week 8 to Week 52 in Group 1.
  The percentages of subjects with RE relapse were 6.3% (1 of the 16 subjects, 95% CI: 0.2, 30.2) from Week 8 to Week 32, 18.8% (3 of the 16 subjects, 95% CI: 4.0, 45.6) from Week 32 to Week 52, and 25.0% (4 of the 16 subjects, 95% CI: 7.3, 52.4) from Week 8 to Week 52 in Group 2.

In most subjects in Groups 1 and 2, the RE-related symptoms disappeared or were unchanged during the long term therapy with D961H.

Prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part

In most subjects in Groups 3 and 4, GU/DU recurrences were prevented during the long term therapy with D961H.

- The percentages of subjects with GU/DU recurrence from Week 0 to Week 32 were 11.1% in Group 3 (1 of the 9 subjects, 95%CI: 0.3, 48.2) and 0.0% in Group 4 (0 of the 13 subjects, 95%CI: 0.0, 24.7).
- For the subjects who continued the study treatment after Week 32, the percentages of subjects with GU/DU recurrence were 16.7% (1 of the 6 subjects, 95%CI: 0.4, 64.1) from both Week 0 to Week 32 and Week 0 to Week 52, and 0.0% (0 of the 6 subjects, 95%CI: 0.0, 45.9) from Week 32 to Week 52 in Group 3, and 0.0% (0 of the 7 subjects, 95%CI: 0.0, 41.0) from Week 0 to Week 32, Week 32 to Week 52, and Week 0 to Week 52 in Group 4.

In most subjects in Groups 3 and 4, the GU/DU-related symptoms disappeared, improved, or were unchanged during the long term therapy with D961H.

Summary of pharmacodynamic results

In 1 subject in Group 3, a gastroesophageal pH measurement was performed at Week 32. The result was as follows;

Table S2 Individual pH monitoring data (Pharmacodynamic Analysis Set)

Percentages of time (Intragastric pH >4)	Percentages of time (Intragastric pH >3)	Median Intragastric pH during 12 hours	Percentages of time (Intra-esophageal pH >4)	Number of acid reflux periods (Intra-esophageal pH <4)	Number of acid reflux periods longer than 5 minutes
[redacted]					

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Summary of safety results

No safety concerns were raised in this study. D961H at a dose of 10 or 20 mg once daily was safe in Japanese paediatric patients.

Maintenance therapy for healed RE study part.

All 28 subjects registered to the initial healing period (Week 0 to Week 8) received the IP in the maintenance therapy for healed RE study part. In the maintenance therapy period (Week 8 to Week 32), the median durations of exposure (range) from Week 8 to Week 32 were 165.0 (112 to 174) days in Group 1 and 164.0 (28 to 189) days in Group 2. The daily dose was increased to 20 mg in 4 subjects in Group 2 from Week 8 to Week 52.

Maintenance therapy period (Week 8 to Week 32)

- During the maintenance therapy period, AEs were reported in 7 of the 7 subjects (100.0%) in Group 1 and 16 of the 20 subjects (80.0%) in Group 2. The most common AEs were nasopharyngitis (71.4%) in Group 1, nasopharyngitis and constipation (20.0% each) in Group 2 during this period.

- During the maintenance therapy period, no deaths or DAEs were reported. A non-fatal SAE (campylobacter gastroenteritis) was reported in Group 2. This SAE was judged by the investigator as severe and not causally related to the IP. No other severe AEs were reported.

Initial healing therapy period (Week 0 to Week 8)

- During the initial healing therapy period (Week 0 to Week 8), AEs were reported in 5 of the 7 subjects (71.4%) in Group 1 and 13 of the 21 subjects (61.9%) in Group 2. The most common AE was nasopharyngitis in both Group 1 (28.6%) and Group 2 (19.0%) during this period.
- During the initial healing therapy period, no deaths or SAEs were reported. A DAE (abdominal pain) was reported in Group 2 and judged by the investigator as not causally related to the IP.
- During the initial healing therapy period, an AE (gastroenteritis) reported as severe in intensity in Group 2 were judged by the investigators as not causally related to the IP.

Maintenance therapy period and maintenance therapy extended period (Week 8 to Week 52)

- For the subjects who continued the study treatment after Week 32, AEs were reported in 5 of the 6 subjects (83.3%) in Group 1 and 12 of the 16 subjects (75.0%) in Group 2 during the maintenance therapy extended period (Week 32 to Week 52). The most common AEs were nasopharyngitis and pharyngitis (50.0% each) in Group 1 and nasopharyngitis (25.0%) in Group 2 during the maintenance therapy extended period.
- During the maintenance therapy extended period, no deaths or SAEs were reported. A DAE (colitis) was reported in Group 2 and judged by the investigator as not causally related to the IP.

<u>Prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part</u>

All 22 subjects registered to prevention therapy period (Week 0 to Week 32) received the IP in the prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part. In the prevention therapy period, the median durations of exposure (range) from Week 0 to Week 32 were 219.0 (214 to 252) days in Group 3 and 221.0 (80 to 263) days in Group 4. The daily dose was not increased in any subject in Group 4 from Week 0 to Week 52.

Prevention therapy period (Week 0 to Week 32)

- During the prevention therapy period, AEs were reported in 8 of the 9 subjects (88.9%) in Group 3 and 11 of the 13 subjects (84.6%) in Group 4. The most common AEs were gastroenteritis (33.3%) in Group 3, and nasopharyngitis (30.8%) in Group 4 during this period.

- During the prevention therapy period, no deaths or DAEs were reported. A non-fatal SAE (chronic recurrent multifocal osteomyelitis) was reported in Group 3, and 3 non-fatal SAEs (otitis media acute, polyarteritis nodosa, and skin ulcer) were reported in 2 subjects in Group 4. These SAEs were judged by the investigator as not causally related to the IP.

Prevention therapy period and prevention therapy extended period (Week 0 to Week 52)

- For the subjects who continued the study treatment after Week 32, AEs were reported in 4 of the 6 subjects (66.7%) in Group 3 and 3 of the 7 subjects (42.9%) in Group 4 during the prevention therapy extended period (Week 32 to Week 52). The most common AEs were nasopharyngitis and urticaria (33.3% each) in Group 3, and influenza (28.6%) in Group 4 during the prevention therapy extended period.
- During the prevention therapy extended period, no deaths or DAEs were reported. Three non-fatal SAEs (campylobacter gastroenteritis, cyclic vomiting syndrome, pulmonary artery atresia) were reported in 2 subjects in Group 3. These SAEs were judged by the investigator as not causally related to the IP.
- During the prevention therapy extended period, an AE (pulmonary artery atresia) reported as severe in intensity in Group 3 was judged by the investigators as not causally related to the IP.

There were no clinically relevant trends identified in any laboratory values or vital signs in any treatment group in this study.

Conclusion(s)

Maintenance therapy for healed RE study part

- The primary efficacy endpoint, the percentages of subjects with RE relapse by assessing any composite endpoints (RE-related symptoms or optional EGD results) from 8 to 32 weeks were 0.0% to 5.3% indicating RE relapses were prevented in most subjects.
- As the primary safety endpoint, the maintenance therapy with D961H after the initial healing therapy up to 32 weeks was safe in Japanese paediatric subjects with healed RE.
- In most subjects, the RE-related symptoms disappeared or were unchanged during the long term therapy with D961H.
- No safety concerns were raised during the long term therapy with D961H up to Week 52.

Prevention of GU/DU recurrence during long term NSAIDs/LDA treatment part

- The primary efficacy endpoint, the percentages of subjects with GU/DU recurrence by assessing any composite endpoints (GU/DU-related symptoms or optional EGD results) from 0 to 32 weeks were 0.0% to 11.1% indicating GU/DU recurrences were prevented in most subjects.
- As the primary safety endpoint, the prevention therapy with D961H up to 32 weeks was safe in Japanese paediatric subjects with long term NSAIDs/LDA treatment who had a medical history of GU/DU.

- In most subjects, the GU/DU-related symptoms disappeared, improved, or were unchanged during the long term therapy with D961H.
- No safety concerns were raised during the long term therapy with D961H up to Week 52.

Overall, RE relapses or GU/DU recurrences were prevented during the long term treatment with D961H at a dose of 10 or 20 mg once daily in Japanese paediatric subjects, and no new safety concern was raised in this study.