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Original Article

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Efficacy and Safety of Long-Term Administration of Esomeprazole in Japanese Pediatric Patients Aged 1–14 Years with Chronic Gastric Acid-Related Disease

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ABSTRACT

Purpose: To evaluate prolonged esomeprazole use in Japanese pediatric patients for reflux esophagitis (RE) maintenance therapy and prevention of gastric (GU) and/or duodenal ulcers (DU) while using non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin (LDA).
Methods: This multicenter, open-label, parallel-group, phase III study (NCT03553563) included patients who were administered esomeprazole according to body weight (10 mg/day [Groups 1 and 3] and up to 20 mg/day [Groups 2 and 4] for patients weighing 10–20 kg and ≥20 kg, respectively). Efficacy outcomes for Groups 1 and 2 (maintenance therapy for healed RE) and Groups 3 and 4 (prevention of long-term NSAID/LDA use-associated GU/DU) were the presence/absence of RE relapse and GU/DU recurrence, respectively.
Results: Esomeprazole as maintenance therapy was associated with a low RE recurrence rate, independent of body weight or dosage. Recurrence rates of RE were 0.0% and 5.3% for Groups 1 and 2, respectively. In patients previously diagnosed with GU and/or DU due to long-term NSAID/LDA use, the recurrence rates of GU/DU during weeks 0–32 were 11.1% and 0.0% in Groups 3 and 4, respectively.
Conclusion: Long-term use of 10- or 20-mg, once-daily esomeprazole demonstrated a favorable benefit-risk balance in preventing RE and suppressing recurrence of GU and/or DU

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Conflict of Interest
The authors have no financial conflicts of interest.

secondary to NSAID or LDA therapy in Japanese pediatric patients. No new safety concerns were identified. Esomeprazole may be a viable option for managing RE and preventing GU and DU in Japanese pediatric patients.

Keywords: Anti-inflammatory agents; Non-steroidal; Child; Duodenal ulcer; Esomeprazole; Esophagitis; Peptic

INTRODUCTION

Gastric acid-related diseases arise from separate but interconnected mechanisms involving the detrimental effects of gastric acid on the protective lining of the esophagus, stomach, and duodenum [1]. Reflux esophagitis (RE), which is the inflammation of the esophageal mucosa secondary to gastroesophageal reflux disease (GERD), is commonly encountered and has markedly increased in Japan recently, even in children and adolescents [2,3]. Gastric ulcers (GU) and/or duodenal ulcers (DU) can develop due to long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin (LDA) [1,4].

As of July 2023, the only drugs approved in Japan for the initial treatment of pediatric RE are roxatidine acetate hydrochloride, an H2 receptor inhibitor, and esomeprazole, a proton pump inhibitor (PPI) [5,6]. Esomeprazole, an S-isomer of omeprazole, is approved for the treatment of RE, GU, and DU in Japanese children aged 1–14 years [6]. Patients with a body weight of <20 kg are usually administered a 10-mg oral dose, whereas those with a body weight of ≥20 kg are administered a 10–20-mg oral dose [6].

However, esomeprazole is currently not indicated for pediatric maintenance therapy and the suppression of GU/DU secondary to long-term NSAID/LDA use, and there are no other available treatments for these pediatric indications in Japan. Thus, the current study aimed to evaluate the efficacy and safety of once-daily oral esomeprazole in Japanese pediatric patients for RE maintenance therapy following initial healing therapy and for the prevention of GU/DU recurrence associated with long-term NSAID/LDA use.

MATERIALS AND METHODS

Study design

This multicenter, open-label, parallel-group, phase III study included eligible patients enrolled between July 2018 and December 2022 from 17 sites in Japan. The study design is shown in **Fig. 1**. Due to considerable individual differences in body weight among pediatric patients aged 1–14 years, patients were stratified by weight for maintenance therapy in the healed RE group and for prevention of GU/DU secondary to long-term NSAID/LDA use group. Different esomeprazole regimens were set for patients weighing ≥10 kg and <20 kg (Groups 1 and 3) and those weighing ≥20 kg (Groups 2 and 4).

Patients assigned to Group 1 were treated with esomeprazole 10 mg, and those assigned to Group 2 were treated with esomeprazole 20 mg during the RE initial healing therapy for 8 weeks. After completion of the initial healing therapy, patients who were eligible for the maintenance therapy proceeded to the maintenance phase for 24 or 44 weeks. During the maintenance therapy, all patients in Groups 1 and 2 were started on esomeprazole 10 mg.

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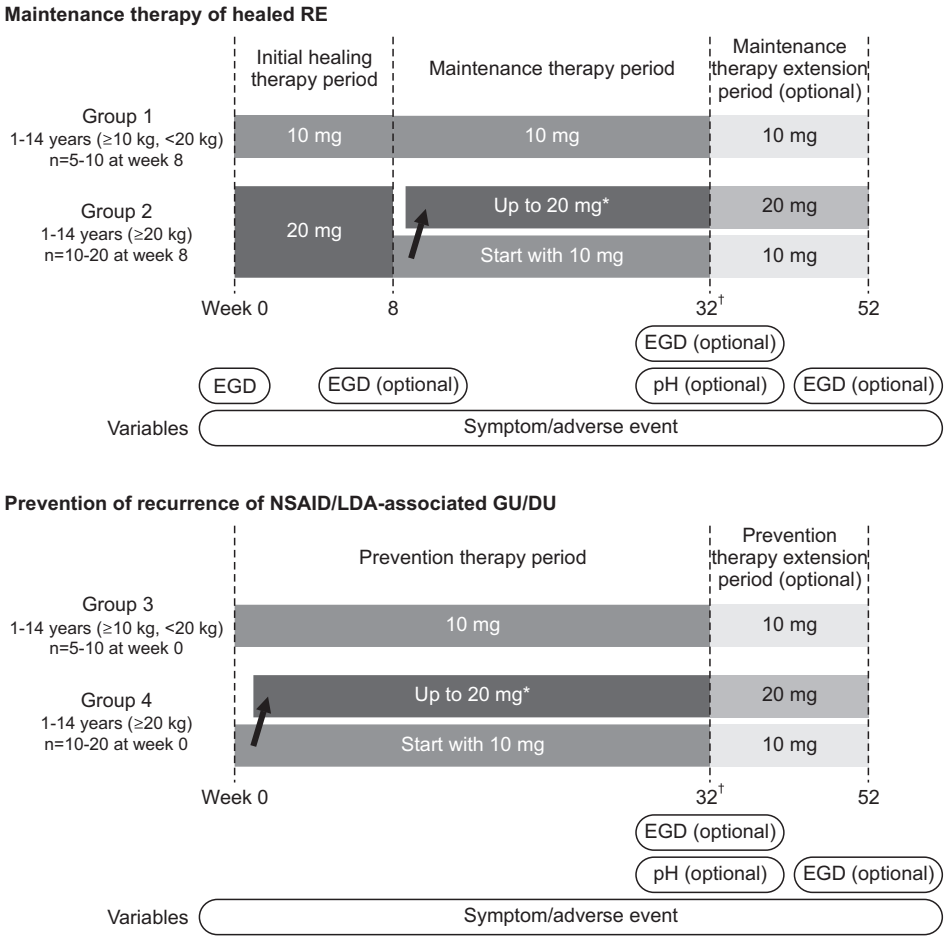

Fig. 1. Study design. RE: reflux esophagitis, EGD: esophagogastroduodenoscopy, NSAID: non-steroidal anti-inflammatory drug, LDA: low-dose aspirin, GU: gastric ulcer, DU: duodenal ulcer. *Based on the investigator's discretion. †Evaluation of the primary endpoint.

For patients in Group 2, an increase in dose to 20 mg was allowed at any visit during the treatment period based on symptoms and the investigator's discretion; however, reducing the dose back to 10 mg was not allowed. Patients assigned to Groups 3 and 4 were treated with esomeprazole 10 mg for 32 or 52 weeks. An increase in dose to 20 mg was allowed for patients in Group 4 at any visit based on the investigator's discretion, and dose reduction back to 10 mg was not allowed. Esomeprazole was administered orally once daily after breakfast to all patients. Among other measures, the time of esomeprazole administration was adjusted according to esophagogastroduodenoscopy (EGD), gastroesophageal pH monitoring, and laboratory tests. The esomeprazole drug formulation (granule or capsule) was selected for each patient based on the investigator's discretion. Mucoprotective drugs, which are usually prescribed when using NSAIDs and LDA, were prohibited during the study period.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Council for International Organization of Medical Sciences International Ethical Guidelines, Japan Good Clinical Practice Guidelines, and applicable laws and regulations.

Ethical approval for the study protocol was obtained from 17 participating institutions, including the Institutional Review Board of Tokyo Medical and Dental University Hospital

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(No. 2018-0003), and written informed consent was obtained from each patient or patient's guardian (including informed consent for genetic testing) prior to the commencement of the study. This study was registered at ClinicalTrials.gov (NCT03553563).

Patients

The study included eligible patients aged 1–14 years for whom informed consent was obtained. The inclusion criteria for the maintenance therapy for the healed RE group required patients to have endoscopically verified RE of at least Grade A (mild) according to the Los Angeles classification [7] as judged by a central evaluation committee (CEC). For initiation of the maintenance therapy phase after the initial healing therapy for 8 weeks, patients were required to have symptomatically healed RE, defined as no more than mild RE-related symptoms or with visible mucosal breaks on EGD, if performed.

The inclusion criteria for the suppression of GU/DU secondary to long-term NSAID/LDA use group required patients to have a documented medical history of GU or DU diagnosis based on upper gastrointestinal symptoms, fecal occult blood, and EGD findings. Furthermore, patients were expected to receive long-term NSAID or LDA therapy for at least 32 weeks during the study period. In addition, patients who had previously been on disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, were required to receive DMARDs for 4 weeks or longer at a constant dose before the study started.

The key exclusion criteria for both groups were as follows: body weight <10 kg, use of any other investigative compounds or participation in another clinical trial within 4 weeks prior to enrollment, significant clinical illness within 4 weeks prior to obtaining informed consent, previous total gastrectomy, and the presence of hepatic disease or other conditions that could interfere with evaluation of the study as judged by the investigators.

Efficacy analyses

For Groups 1 and 2 (maintenance therapy for healed RE outcomes), the efficacy outcome measure was the presence/absence of RE relapse from week 8 to week 32 and from week 8 to week 52 for those who continued esomeprazole treatment after week 32. The presence/absence of RE relapse was assessed using the composite endpoint (RE-related symptoms or optional EGD findings) during maintenance therapy. RE-related symptoms included heartburn, acid regurgitation, dysphagia, and epigastric pain, reported by patients and/or their guardians to investigators. The efficacy outcome measures for Groups 3 and 4 (prevention of GU/DU secondary to long-term NSAID/LDA use) were the presence/absence of GU/DU recurrence from week 0 to week 32 and from week 0 to week 52 for those who continued esomeprazole treatment after week 32. It was assessed using the composite endpoint (GU/DU-related symptoms or optional EGD findings) during prevention therapy. GU/DU-related symptoms included epigastric pain, stomach discomfort, abdominal distention/bloating, nausea/vomiting, heartburn, and anorexia, which patients and/or their guardians reported to investigators. Endoscopic assessments and RE- or GU/DU-related symptoms were evaluated as the secondary endpoints for each group.

Safety analyses

The number (%) of patients with any adverse events (AEs), causally related AEs, AEs leading to death, serious AEs (SAEs), and discontinuations of esomeprazole due to AEs were summarized for each treatment group. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 25.1, and reported by System Organ Class and Preferred Term. Changes in laboratory parameters and vital signs were also evaluated.

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For Groups 1 and 2, safety assessments were conducted from week 8 (baseline) to week 32; for participants who continued to receive the study treatment after week 32, safety assessments were continued through week 52. For Groups 3 and 4, safety assessments were performed from weeks 0 to 32, whereas for participants who continued the study treatment after week 32, corresponding safety assessments were evaluated from baseline to week 52 (baseline to 32 weeks and 32 to 52 weeks, respectively) as a secondary analysis.

Statistical analyses

The sample size for this study was not based on power calculations; rather, the sample size for maintenance therapy for the healed RE group was based on operational feasibility.

The efficacy analysis set consisted of all patients who took at least one dose of esomeprazole and had at least one efficacy assessment during the maintenance/prevention therapy period. The safety analysis set consisted of all patients who took at least one dose of esomeprazole and had at least one post-treatment assessment.

Descriptive statistics were used to summarize patients' demographic and clinical characteristics, including mean±standard deviation (SD) and median (range) for continuous data and number (%) for categorical data. The percentage of patients with RE relapse (Groups 1 and 2) and GU/DU recurrence (Groups 3 and 4) and the respective 95% confidence intervals (CIs), which were calculated using the Clopper–Pearson method, were summarized for each treatment group. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc.).

RESULTS

Patient disposition and characteristics

Figs. 2 and **3** show the patients' disposition. In Group 1, seven patients completed the initial healing therapy period, of whom six patients completed the maintenance therapy (weeks 8–32) and extended maintenance therapy (weeks 32–52) periods. In Group 2, 20 patients completed the initial healing therapy period, of whom 18 and 15 patients completed the maintenance therapy and extended maintenance therapy periods, respectively. In Group 3, nine patients completed the prevention therapy period (weeks 0–32), of whom five patients completed the prevention therapy extension period (weeks 32–52). In Group 4, 12 patients completed the prevention therapy period, of whom seven patients completed the extended prevention therapy period.

The baseline patient characteristics are shown in **Tables 1** and **2**. Patients in Group 1 had a mean±SD age of 3.7±1.7 years, and all seven patients were male with a negative *Helicobacter pylori* test result (immunoglobulin G antibody). Patients in Group 2 had a mean±SD age of 10.4±2.2 years and most were male (70.0%). Most patients (95.0%) tested negative for *H. pylori*. The most frequent EGD result (CEC assessment) at enrollment was Grade A in Groups 1 and 2.

Patients in Group 3 had a mean±SD age of 5.2±2.1 years, and 55.6% were female. All nine patients tested negative for *H. pylori*. Eight (88.9%) patients were diagnosed with GU, and one (11.1%) patient was diagnosed with DU. Patients in Group 4 had a mean±SD age of 11.3±2.4 years, and 53.8% were female. Most patients (92.3%) tested negative for *H. pylori*, and all 13 patients were diagnosed with GU. In Groups 3 and 4, the most frequent concomitant NSAIDs

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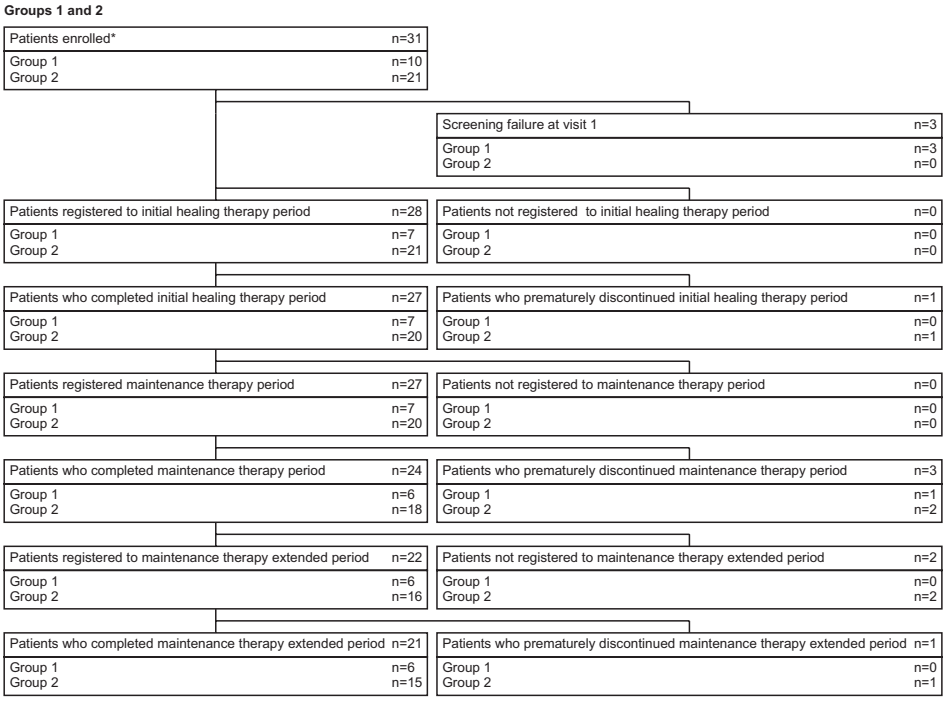

Fig. 2. Patient disposition for Groups 1 and 2 (maintenance therapy for healed RE). RE: reflux esophagitis. *Informed consent received.

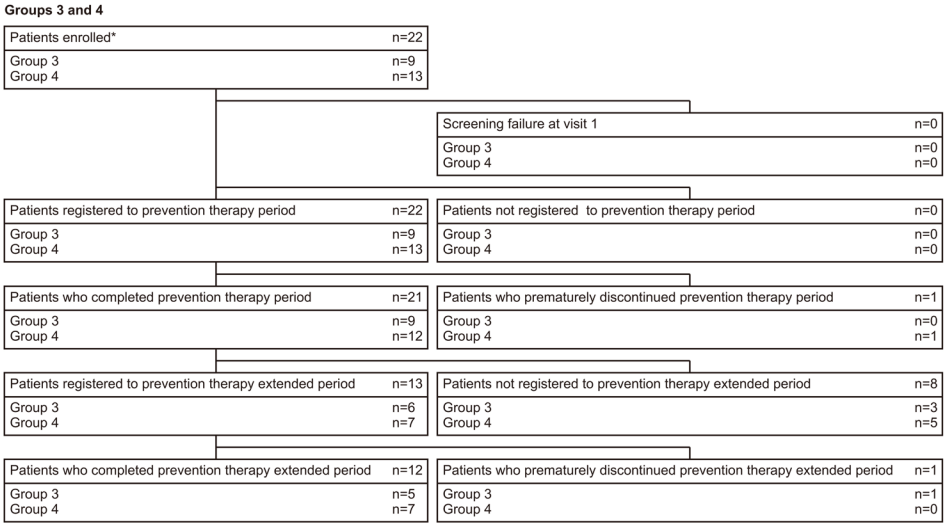

Fig. 3. Patient disposition for Groups 3 and 4 (prevention of NSAID/LDA-associated GU/DU recurrence). NSAID: non-steroidal anti-inflammatory drug, LDA: low-dose aspirin, GU: gastric ulcer, DU: duodenal ulcer. *Informed consent received.

used from weeks 0 to 32 were ibuprofen and naproxen in 36.4% and 13.6% of patients, respectively. Acetylsalicylic acid was used as concomitant LDA in 31.8% of patients in Groups 3 and 4 from weeks 0 to 32. NSAIDs were mainly administered for pediatric rheumatic diseases, and LDA was mainly administered for congenital heart diseases.

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Table 1. Baseline characteristics of patients in Groups 1 and 2 (safety analysis set, maintenance therapy for healed reflux esophagitis)

	Group 1 (n=7)	Group 2 (n=20)	Total (n=27)
Age (yr)	3.7±1.7	10.4±2.2	8.7±3.6
Male	7 (100)	14 (70.0)	21 (77.8)
Female	0 (0)	6 (30.0)	6 (22.2)
Weight (kg)	14.50±2.96	33.49±9.79	28.56±12.00
Negative *Helicobacter pylori* test (IgG antibody)	7 (100)	19 (95.0)	26 (96.3)
History of previous disease	4 (57.1)	4 (20.0)	8 (29.6)
Has concurrent disease	7 (100)	18 (90.0)	25 (92.6)
History of surgery	3 (42.9)	2 (10.0)	5 (18.5)

Values are presented as mean±standard deviation or number (%).
IgG: immunoglobulin G.

Table 2. Baseline characteristics of patients in Groups 3 and 4 (safety analysis set, prevention of NSAID/LDA-associated GU/DU recurrence)

	Group 3 (n=9)	Group 4 (n=13)	Total (n=22)
Age (yr)	5.2±2.1	11.3±2.4	8.8±3.8
Male	4 (44.4)	6 (46.2)	10 (45.5)
Female	5 (55.6)	7 (53.8)	12 (54.5)
Weight (kg)	15.48±3.35	36.61±11.18	27.96±13.74
Negative *Helicobacter pylori* test (IgG antibody)	9 (100)	12 (92.3)	21 (95.5)
History of previous disease	0 (0)	3 (23.1)	3 (13.6)
Has concurrent disease	9 (100)	13 (100)	22 (100)
History of surgery	3 (33.3)	5 (38.5)	8 (36.4)
Has GU	8 (88.9)	13 (100)	21 (95.5)
Has DU	1 (11.1)	0 (0)	1 (4.5)

Values are presented as mean±standard deviation or number (%).
NSAID: non-steroidal anti-inflammatory drug, LDA: low-dose aspirin, GU: gastric ulcer, DU: duodenal ulcer, IgG: immunoglobulin G.

Efficacy

1. Maintenance therapy for healed RE

For weeks 8–32, the percentage of patients with RE relapse in Groups 1 and 2 was 0.0% (n=0; 95% CI: 0.0–41.0%) and 5.3% (n=1, according to worsening of symptoms; 95% CI: 0.1–26.0%), respectively. For the patients in Group 1 who continued esomeprazole after week 32, the percentage of patients with RE relapse was 0.0% (n=0; 95% CI: 0.0–45.9%) for weeks 8–32 and 16.7% (n=1, detected by EGD; 95% CI: 0.4–64.1%) for both weeks 32–52 and weeks 8–52. For the patients in Group 2 who continued esomeprazole after week 32, the percentage of patients with RE relapse was 6.3% (n=1, according to worsening of symptoms; 95% CI: 0.2–30.2%) for weeks 8–32, 18.8% (n=3, according to worsening of symptoms 95% CI: 4.0–45.6%) for weeks 32–52, and 25.0% (n=4, according to worsening of symptoms; 95% CI: 7.3–52.4%) for weeks 8–52. The RE-related symptoms resolved or were unchanged during esomeprazole long-term use in most patients in both groups.

In Group 1, among the patients without the following RE-related symptoms at week 8, the symptoms at the last observation for the maintenance therapy period were as follows: heartburn, 80.0% unchanged/20.0% aggravated; acid regurgitation, 83.3% unchanged/16.7% aggravated; and dysphagia and epigastric pain, both 100.0% unchanged. Similarly, for Group 2, in patients without the following RE-related symptoms at week 8, the symptoms at the last observation for the maintenance therapy period were 86.7% unchanged/13.3% aggravated for heartburn, 92.3% unchanged/7.7% aggravated for acid regurgitation, and 100% unchanged for dysphagia and epigastric pain.

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2. Prevention of GU/DU recurrence during long-term NSAID/LDA use

For weeks 0–32, the percentage of patients with GU/DU recurrence was 11.1% (n=1, EGD by CEC; 95% CI: 0.3–48.2%) and 0.0% (n=0; 95% CI: 0.0–24.7%) in Groups 3 and 4, respectively. For patients who continued esomeprazole after week 32, the percentage of patients with GU/DU recurrence was 16.7% (n=1, EGD by CEC; 95% CI: 0.4–64.1%) for both weeks 0–32 and weeks 0–52 and 0.0% (n=0; 95% CI: 0.0–45.9%) for weeks 32–52 in Group 3, and 0.0% (n=0; 95% CI: 0.0–41.0%) for weeks 0–32, weeks 32–52, and weeks 0–52 in Group 4. In most patients in Groups 3 and 4, GU/DU-related symptoms resolved, improved, or were unchanged during long-term use of esomeprazole.

In Group 3, all patients who began week 0 without heartburn, epigastric pain, stomach discomfort, abdominal distention/bloating, or nausea/vomiting remained free of these GU/DU-related symptoms at the last observation for the prevention therapy period. Of the eight patients without anorexia at week 0, seven (87.5%) remained unchanged, and one (12.5%) reported aggravated anorexia at the last observation. In Group 4, among the patients without GU/DU-related symptoms at week 0, the symptoms were unchanged at the last observation for the prevention therapy period for 100% of patients without heartburn, epigastric pain, stomach discomfort, abdominal distention/bloating, or anorexia; of the 13 patients without nausea/vomiting at week 0, 12 (92.3%) patients remained unchanged and one (7.7%) reported aggravated symptoms at the last observation for the prevention therapy period.

Safety

1. Maintenance therapy for healed RE

Twenty-seven of 28 patients who were enrolled in the initial healing period (weeks 0–8) continued to receive esomeprazole as maintenance therapy. During the maintenance therapy period (weeks 8–32), the median durations of exposure (range) for Groups 1 and 2 were 165 (112–174) days and 164 (28–189) days, respectively. For four patients in Group 2, the daily dose was increased to 20 mg during weeks 8–52.

During the initial healing therapy period (weeks 0–8), AEs were reported in 71.4% (n=5) and 61.9% (n=13) of patients in Groups 1 and 2, respectively. The most common AE in both groups was nasopharyngitis (28.6% and 19.0% in Groups 1 and 2, respectively). No deaths or SAEs were reported. A discontinuation was reported in Group 2 and was attributed to an AE (abdominal pain) and a severe AE (gastroenteritis), both of which were judged by the investigators to be not causally related to esomeprazole.

During the maintenance therapy period, AEs were reported by all patients (n=7) in Group 1 and 80.0% (n=16) of patients in Group 2 (**Table 3**). The most common AEs were nasopharyngitis (71.4%) in Group 1 and nasopharyngitis and constipation (20.0% each) in Group 2. No deaths or discontinuations due to AEs were reported. A severe, non-fatal SAE (campylobacteriosis) was reported in Group 2, but this was judged not to be causally related to esomeprazole. No other severe AEs were reported.

AEs were reported in 83.3% (n=5) and 75.0% (n=12) of patients who continued esomeprazole after week 32 in Groups 1 and 2, respectively. The most common AEs were nasopharyngitis and pharyngitis (50.0% each) in Group 1 and nasopharyngitis (25.0%) in Group 2 during the extended maintenance therapy period. No deaths or SAEs were reported during the extended maintenance therapy period. A discontinuation due to an AE (colitis) reported in Group 2 was judged as not causally related to esomeprazole.

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Table 3. Adverse events reported in two or more patients in Groups 1 or 2 by System Organ Class and Preferred Term for weeks 8–32 (maintenance therapy period; safety analysis set)

System Organ Class/Preferred Term	Number (%) of patients*	
	Group 1 (n=7)	Group 2 (n=20)
Patients with any adverse event	7 (100)	16 (80.0)
Infections and infestations	6 (85.7)	10 (50.0)
Gastroenteritis	1 (14.3)	2 (10.0)
Influenza	2 (28.6)	2 (10.0)
Nasopharyngitis	5 (71.4)	4 (20.0)
Pharyngitis	2 (28.6)	0 (0)
Sinusitis	0 (0)	2 (10.0)
Immune system disorders	0 (0)	3 (15.0)
Seasonal allergy	0 (0)	2 (10.0)
Nervous system disorders	0 (0)	3 (15.0)
Headache	0 (0)	2 (10.0)
Respiratory, thoracic, and mediastinal disorders	0 (0)	4 (20.0)
Rhinitis allergic	0 (0)	2 (10.0)
Gastrointestinal disorders	2 (28.6)	9 (45.0)
Constipation	1 (14.3)	4 (20.0)
Stomatitis	0 (0)	2 (10.0)
Vomiting	1 (14.3)	2 (10.0)
Injury, poisoning, and procedural complications	3 (42.9)	1 (5.0)
Thermal burn	2 (28.6)	0 (0)

Medical Dictionary for Regulatory Activities, version 25.1.
*Number (%) of patients with adverse events, sorted by international order for System Organ Class and alphabetical order for Preferred Term. Patients with multiple events in the same Preferred Term were counted only once in that Preferred Term. Patients with events in >1 Preferred Term were counted once in each of those Preferred Terms. Percentages are based on the total number of patients in the treatment group (n).

2. Prevention of GU/DU recurrence during long-term NSAID/LDA use

Twenty-one of 22 patients who were enrolled in the prevention therapy period received esomeprazole for the full prevention therapy period (weeks 0–32). During this time, the median durations of exposure (range) were 219 (214–252) days and 221 (80–263) days in Groups 3 and 4, respectively. None of the patients in Group 4 had their daily dose increased during weeks 0–52.

During the prevention therapy period, AEs were reported in 88.9% (n=8) and 84.6% (n=11) of patients in Groups 3 and 4, respectively (**Table 4**). The most common AEs were gastroenteritis (33.3%) in Group 3 and nasopharyngitis (30.8%) in Group 4. No deaths or discontinuations due to AEs were reported. A non-fatal SAE (chronic recurrent multifocal osteomyelitis) was reported in Group 3, and three non-fatal SAEs (acute otitis media,

Table 4. Adverse events reported in two or more patients in Groups 3 or 4 by System Organ Class and Preferred Term for weeks 0–32 (prevention therapy period; safety analysis set)

System Organ Class/Preferred Term	Number (%) of patients*	
	Group 3 (n=9)	Group 4 (n=13)
Patients with any adverse event	8 (88.9)	11 (84.6)
Infections and infestations	8 (88.9)	8 (61.5)
Gastroenteritis	3 (33.3)	0 (0)
Nasopharyngitis	2 (22.2)	4 (30.8)
Pharyngitis	2 (22.2)	3 (23.1)
Streptococcal infection	2 (22.2)	0 (0)
Skin and subcutaneous tissue disorders	3 (33.3)	3 (23.1)
Miliaria	2 (22.2)	0 (0)

Medical Dictionary for Regulatory Activities, version 25.1.
*Number (%) of patients with adverse events, sorted by international order for System Organ Class and alphabetical order for Preferred Term. Patients with multiple events in the same Preferred Term were counted only once in that Preferred Term. Patients with events in >1 Preferred Terms were counted once in each of those Preferred Terms. Percentages are based on the total number of patients in the treatment group (n).

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polyarteritis nodosa, and skin ulcer) were reported in two patients in Group 4, which were all judged not to be causally related to esomeprazole.

During weeks 32–52, AEs were reported in 66.7% (n=4) and 42.9% (n=3) of patients in Groups 3 and 4, respectively. The most common AEs were nasopharyngitis and urticaria (33.3% each) in Group 3 and influenza (28.6%) in Group 4. Deaths or discontinuations due to AEs were not recorded; however, three non-fatal SAEs (campylobacteriosis, cyclic vomiting syndrome, and pulmonary artery atresia) were reported in two patients in Group 3, which were judged not to be causally related to esomeprazole (pulmonary artery atresia was originally diagnosed as a congenital defect prior to birth). No clinically relevant changes occurred in laboratory parameters or vital signs.

DISCUSSION

This study reports the first clinical trial involving long-term administration of a PPI in Japanese pediatric patients for maintenance therapy for RE and suppression of recurrence of GU and/or DU during the administration of NSAIDs or LDA. Younger patients weighing ≥10 kg and <20 kg (Groups 1 and 3) received a 10-mg daily dose of esomeprazole. In contrast, esomeprazole was initiated at a dose of 10 mg/day in older patients weighing ≥20 kg (Groups 2 and 4) and could be increased up to 20 mg/day according to symptoms.

Following esomeprazole initial therapy for 8 weeks, patients with symptomatic resolution of RE who continued esomeprazole as maintenance therapy showed a low recurrence rate of RE (0% and 5.3% in Groups 1 and 2, respectively), regardless of body weight or dose. For patients who continued treatment after week 32, the recurrence rates of RE for weeks 32–52 were 16.7% and 18.8% in Groups 1 and 2, respectively, suggesting that long-term esomeprazole administration may suppress the recurrence of RE in pediatric patients. Furthermore, a recent prospective study reported that PPI treatment for pediatric RE significantly improved patient quality of life, reflected by changes in the pediatric GERD symptom and quality of life questionnaire after 1 month of PPI therapy [8].

When esomeprazole was administered to pediatric patients previously diagnosed with GU and/or DU secondary to long-term NSAID/LDA use, the rates of recurrence of GU and/or DU for weeks 0–32 were 11.1% and 0.0% in Groups 3 and 4, respectively. Furthermore, the recurrence rate of GU and/or DU for weeks 32–52 was 0.0% in patients who continued administration after week 32 in all groups, suggesting that long-term administration of esomeprazole may also suppress the recurrence of GU and/or DU. Our findings are supported by those of previous studies in adult Japanese NSAID and LDA users, which reported the efficacy of esomeprazole in preventing/reducing the recurrence of peptic ulcers after long-term use [9,10].

Overall, no clinically relevant trends were identified in any laboratory values or vital signs in any treatment group in this study, and no safety concerns were raised with the long-term use of 10- or 20-mg, once-daily esomeprazole in Japanese pediatric patients. The safety profile of esomeprazole was consistent with those reported previously in another pediatric Japanese study [6], as well as pediatric studies conducted in the US and Europe [11,12]. The results of this study were as expected in the pediatric population based on the results of clinical trials in adults [9,10,13,14]. No notable differences in the type or frequency of AEs were observed between those reported in adults and those occurring in the present pediatric study.

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Limitations

The present study had a small sample size. In Japan, an estimated 24.5% of adult patients with heartburn have endoscopic Los Angeles grade A or worse erosive esophagitis [15]. Even if the prevalence rate in Japanese pediatric patients was lower than that in adults (e.g., 15%), the achievable enrollment of 150 patients would enable 22–23 patients to start in the initial healing phase, with at least 15 patients entering the maintenance phase. For the prevention of GU/DU recurrence associated with the NSAID/LDA part of the study, it was estimated that almost all enrolled patients would start treatment with esomeprazole. Therefore, enrollment of 15–30 Japanese pediatric patients was considered to allow for the registration of 15–30 patients starting treatment with esomeprazole. Another limitation is the low number of post-dose EGD evaluations. Because this was an open-label study and not a placebo-controlled comparative study, it was challenging to measure the efficacy of esomeprazole for the target pediatric patient population. Furthermore, no PPIs other than esomeprazole have been approved for pediatric use in Japan; thus, we were unable to compare our findings with data on similar drugs. Despite these limitations, we were able to make reasonable assessments supported by previous studies in Japanese adults and children, as well as overseas pediatric trials. Given the intricate nature of pediatric studies, it is customary to employ standard statistical methods to evaluate the data and consider observations that are reinforced and supplemented by comparable studies conducted on adults with the same condition [9,10,13,14].

In conclusion, this study is the first clinical trial to evaluate the long-term use of esomeprazole, a PPI, in Japanese pediatric patients for RE maintenance and prevention of GU and/or DU during long-term NSAID or LDA use. This study demonstrated that long-term administration of esomeprazole, at a daily dose of 10 or 20 mg, had a favorable benefit-risk balance to prevent RE and suppress the recurrence of GU and/or DU during NSAID or LDA administration in Japanese pediatric patients. No safety concerns were raised with the long-term use of 10- or 20-mg, once-daily esomeprazole in Japanese pediatric patients. This study's findings will enable clinicians to better manage RE and GU/DU recurrence during long-term NSAID/LDA use in pediatric patients.

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