Once-Daily Esomeprazole 20 mg Prevents Recurrence of Peptic Ulcer in East Asian Low-Dose Aspirin Users at Gastrointestinal Risk: the LAVENDER Study

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CONCLUSION

- **Daily esomeprazole 20 mg is efficacious and well tolerated for reducing the recurrence of peptic ulcer in East Asian patients who have a history of peptic ulcers and are taking low-dose aspirin (ASA) for cardioprotection.**

INTRODUCTION

- Clinical practice guidelines recommend the use of ASA (75–325 mg daily) for prevention of cardiovascular (CV) events in patients who have CV risk factors.[1,2]
- However, continuous long-term use of ASA has been associated with gastrointestinal (GI) problems such as upper GI symptoms[3] and peptic ulcers[4] that, in turn, may decrease patient adherence to cardiopreventive therapy.[5] Gastroprotection with a proton pump inhibitor is therefore recommended for ASA users who are at increased GI risk.[6]
- In two randomized controlled studies, esomeprazole proved efficacious and well tolerated at preventing the development of peptic ulcers in Western patients taking ASA and at high GI risk.[7,8] However, data in a comparable population of East Asian patients are scant.

AIM

- To assess the potential effects of esomeprazole in prevention of recurrent peptic (gastric and/or duodenal) ulcer in East Asian patients taking ASA for CV protection.

METHODS

Study design and patients

- The **LAVENDER** (**L**ow-dose **A**spirin-related ulcer recurrence pre**VEN**tion un**DER** esomeprazole 20 mg treatment) study[§] was a randomized, double-blind, placebo-controlled, multicenter study in East Asian (Japan, Korea, and Taiwan) patients taking prescribed ASA (81–324 mg daily) for CV prevention.
- Enrolled patients were aged ≥20 years. All participants underwent endoscopy at the time of enrollment, and were eligible for inclusion if gastric and/or duodenal ulcer scarring was visually verified. In addition to prescribed ASA, patients were randomized (1:1) to esomeprazole 20 mg daily or placebo for a maximum period of 72 weeks. All patients received gefarnate 50 mg twice daily for mucosal protection. Concomitant use of nonsteroidal anti-inflammatory drugs was not permitted.
- Patients with an active peptic ulcer, uncontrolled diabetes, unstable hypertension, serious heart failure, or history of acute coronary syndromes/stroke (within the past 3 months) were excluded from enrollment.
- As defined by the protocol, the study design incorporated an interim analysis to assess the superiority of esomeprazole relative to placebo when a minimum of 18 ulcer events had occurred in the overall patient population, and >250 patients had been randomized to treatment. An independent Data Monitoring Committee decided that the corresponding cut-off date for this analysis was 48 weeks.

Assessments and statistical analysis

- Each patient underwent planned endoscopy at 12-week intervals up to study end or upon early withdrawal (eg, because of GI bleeding). The primary end point was the time to ulcer recurrence, based on the 48-week interim analysis for the full analysis set (FAS; all randomized patients who received ≥1 dose of study medication and who had no active ulcer at baseline).
  - Data were analyzed by the Kaplan-Meier method and displayed as time-to-event curves; the log-rank test was used for statistical comparisons.
- Secondary end points include estimated ulcer-free rates along with descriptive assessment of mucosal lesion(s) by modified LANZA score, and the incidence/severity of reflux esophagitis and GI symptoms.
  - A Cox proportional hazard model was used to evaluate the effect of subgroups (gender, age, *Helicobacter pylori* status, cytochrome P450 [CYP] 2C19 genotype, and ASA treatment) on the estimated ulcer-free rate.
- Safety end points included adverse events, clinical laboratory data, and vital signs; findings are presented for the whole treatment period.

RESULTS

- A total of 364 patients comprised the 48-week FAS (esomeprazole, n=182; placebo, n=182) (Table 1). Patients were mostly men (81%), with a mean age of 67 years. The majority of patients were treated with ASA 100 mg daily (82%), and had received such treatment (mainly for secondary prevention) for >4 weeks before enrollment (89%).

Table 1. Baseline demographics (48-week full analysis set)

	Esomeprazole 20 mg (n=182)	Placebo (n=182)
Men	147 (81)	144 (79)
Mean (SD) age, years	66.1 (9.9)	68.1 (9.1)
Positive *H. pylori* status	81 (44.5)	82 (45)
Cytochrome P450 2C19 genotype[a]		
Homozygous-EM	63 (35)	66 (36)
Heterozygous-EM	93 (51)	77 (42)
Poor metabolizer	23 (13)	35 (19)
ASA dosage		
81 mg	25 (14)	22 (12)
100 mg	148 (81)	152 (83.5)
>100 mg	9 (5)	8 (4)
Duration of ASA therapy		
<2 weeks	12 (7)	22 (12)
2–4 weeks	2 (1)	4 (2)
>4 weeks	168 (92)	156 (86)
Reason for ASA therapy[b]		
Primary prevention	59 (32)	54 (30)
Secondary prevention	121 (66.5)	126 (69)

Values are n (%) unless otherwise stated.

[a]Data missing for 7 patients (esomeprazole, n=3; placebo, n=4).

[b]A total of 4 patients received ASA for other reasons (esomeprazole, n=2; placebo, n=2).

Abbreviations: ASA, low-dose aspirin; EM, extensive metabolizer; SD, standard deviation.

Ulcer recurrence

- The time to ulcer recurrence was significantly longer in the esomeprazole group compared with placebo by week 48 (hazard ratio, 0.09; 96.65% confidence interval [CI]: 0.02–0.41; p<0.001) (Figure).

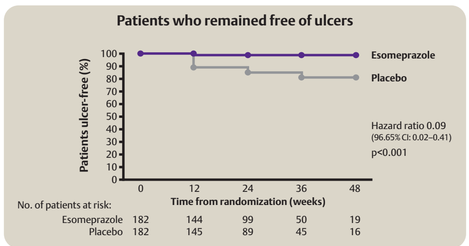

Figure. Kaplan-Meier curves of ulcer-free rates (48-week full analysis set). CI, confidence interval.

- Estimated ulcer-free rates in the FAS at week 12 were 99.3% for esomeprazole and 89.0% for placebo. Rates were high and remained steady in esomeprazole-treated patients only through week 48 (98.3% vs 81.2% for placebo).
- Sub-analysis showed superior ulcer-free rates for esomeprazole compared with placebo (Table 2).
  - Among placebo recipients, the estimated ulcer-free rate for patients aged ≤64 years (75.9%) was lower than those for other age categories (65–74 years, 88.2%; ≥75 years, 80.2%) despite advanced age being a recognized risk factor for peptic ulcer. Age did not impact ulcer-free rates with esomeprazole.
  - In the placebo group, the estimated ulcer-free rate was lower for ASA 81mg compared with the subset of patients who received the 100 mg dosage (71.9% and 83.2%, respectively). Esomeprazole protected against ulcer recurrence irrespective of ASA dose.
  - Regardless of reason for ASA treatment, the estimated ulcer-free rates were lower in the placebo group compared with esomeprazole.
- Multivariate Cox regression analysis showed that gender (p=0.026) and esomeprazole treatment (p<0.001) were the only factors significantly predictive of the time to ulcer recurrence in the FAS.

LANZA score, reflux esophagitis, and GI symptoms

- More esomeprazole-treated patients (32%, 46/144) in the 48-week FAS showed improvement in mucosal lesions by modified LANZA score compared with placebo (18%, 26/145), while a smaller proportion of patients had a worsening of scores with esomeprazole (14%, 20/144) compared with placebo (41%, 60/145) (Table 3).
- Fewer esomeprazole-treated patients than placebo recipients had endoscopic evidence of reflux esophagitis at weeks 12 (0% vs 6.5%), 24 (1.0% vs 6.8%), and 36 (0% vs 6.7%), with no cases reported at week 48.
- At baseline, the majority of patients in both treatment groups did not report GI symptoms. More placebo-treated patients without symptoms at baseline developed mild-to-severe GI symptoms by study end compared with esomeprazole recipients (data not shown).

Table 2. Estimated ulcer-free rates by subgroup (48-week full analysis set)

Subgroup	Esomeprazole 20 mg (n=182) n	Esomeprazole 20 mg (n=182) Ulcer-free rate (95% CI)	Placebo (n=182) n	Placebo (n=182) Ulcer-free rate (95% CI)
Gender				
Men	147	98.0 (95.2–100)	144	84.6 (76.6–92.6)
Women	35	100 (100–100)	38	67.1 (45.1–89.1)
Age				
≤64 years	75	97.4 (92.5–100)	62	75.9 (61.9–89.9)
65–74 years	69	98.2 (94.7–100)	72	88.2 (79.4–97.1)
≥75 years	38	100 (100–100)	48	80.2 (63.6–96.8)
H. pylori status				
Negative	94	100 (100–100)	95	84.2 (75.3–93.0)
Positive	81	96.7 (92.2–100)	82	78.4 (65.7–91.1)
CYP2C19 genotype				
Homozygous-EM	63	100 (100–100)	66	83.3 (69.8–96.9)
Heterozygous-EM	93	97.0 (92.7–100)	77	83.3 (72.7–93.9)
Poor metabolizer	23	100 (100–100)	35	72.9 (53.9–91.8)
ASA dosage				
81 mg	25	100 (100–100)	22	71.9 (50.6–93.2)
100 mg	148	99.1 (97.5–100)	152	83.2 (74.8–91.6)
>100 mg	9	83.3 (53.5–100)	8	83.3 (53.5–100)
Duration of ASA therapy				
<2 weeks	12	100 (100–100)	22	0 (0–0)
2–4 weeks	2	100 (100–100)	4	100 (100–100)
>4 weeks	168	98.2 (95.7–100)	156	83.0 (75.4–90.6)
Reason for ASA therapy				
Primary prevention	59	100 (100–100)	54	83.3 (72.1–94.6)
Secondary prevention	121	97.7 (94.6–100)	126	82.8 (74.0–91.6)

Abbreviations: ASA, low-dose aspirin; CI, confidence interval; EM, extensive metabolizer.

Table 3. Shift analysis of modified LANZA score (48-week full analysis set[a])

	Esomeprazole 20 mg (n=144)					Placebo (n=145)				
	Baseline					Baseline				
Study end	0	+1	+2	+3	+4	0	+1	+2	+3	+4
0	64	8	20	7	2	43	3	14	1	0
+1	7	1	5	2	0	5	1	4	0	0
+2	6	1	10	2	0	20	4	12	4	0
+3	1	0	3	2	0	4	0	5	2	0
+4	2	0	0	0	1	12	2	7	1	1

[a]Patients with baseline plus ≥1 subsequent measurement. Shading indicates improvement in score between baseline and study end.

Safety findings

- Treatment with esomeprazole 20 mg daily was well tolerated through the whole treatment period. The number of patients who had serious adverse events, including CV events, was similar in the two treatment groups (Table 4).
- No clinically significant changes were noted for laboratory tests and vital signs in either treatment group, and there were no new safety concerns.

Table 4. Number (%) of patients with at least one serious adverse event (SAE) other than death (safety analysis set)

	Esomeprazole 20 mg (n=182)	Placebo (n=182)
Patients with ≥1 SAE other than death	10 (5.5)	11 (6.0)
Cardiac disorders	3 (1.6)	3 (1.6)
Acute myocardial infarction	0	2 (1.1)
Angina pectoris	1 (0.5)	1 (0.5)
Arteriosclerosis (coronary artery)	1 (0.5)	0
Coronary artery stenosis	1 (0.5)	0
Nervous system disorders	2 (1.1)	1 (0.5)
Brain stem hemorrhage	1 (0.5)	0
Cerebral infarction	1 (0.5)	1 (0.5)
Gastrointestinal disorders	1 (0.5)	2 (1.1)
Erosive gastritis	0	1 (0.5)
Hemorrhagic intestinal diverticulum	0	1 (0.5)
Hemorrhoids	1 (0.5)	0
Hepatobiliary disorders	1 (0.5)	0
Acute cholangitis	1 (0.5)	0
Injury, poisoning, and procedural complications	1 (0.5)	1 (0.5)
Hip fracture	0	1 (0.5)
In-stent coronary artery restenosis	1 (0.5)	0
Neoplasms	1 (0.5)	2 (1.1)
Cardiac myxoma	0	1 (0.5)
Gastric cancer	1 (0.5)	1 (0.5)
Renal and urinary disorders	1 (0.5)	0
Renal infarct	1 (0.5)	0
Surgical and medical procedures	1 (0.5)	0
Cholecystectomy	1 (0.5)	0
Infections and infestations	0	2 (1.1)
Gastroenteritis	0	1 (0.5)
Pneumonia	0	1 (0.5)
Metabolism and nutrition disorders	0	1 (0.5)
Dehydration	0	1 (0.5)

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NOTE: The data in this poster differ slightly from those in the published abstract owing to further refinement of the analysis.

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CONFLICTS OF INTERESTS

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