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The clinical safety of long-term lansoprazole for the maintenance of healed erosive oesophagitis

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SUMMARY

Background
The clinical safety of long-term lansoprazole therapy for the maintenance of healed erosive oesophagitis has not been extensively studied in clinical trials.

Aim
To assess the long-term clinical safety of dose-titrated lansoprazole as maintenance therapy for up to 82 months in subjects with healed erosive oesophagitis.

Methods
Clinical safety was assessed by monitoring adverse events (AEs), laboratory data including serum gastrin levels, and endoscopy.

Results
Mean duration (± s.d.) of lansoprazole treatment during the titrated open-label period was 56 ± 24 months (range <1–82 months). Overall, 189 of 195 (97%) subjects experienced a total of 2825 treatment-emergent AEs. Most AEs occurred during the first year of treatment, were mild-to-moderate in severity and resolved while on treatment. Of 155 serious AEs (in 74 subjects), only two (colitis and rectal haemorrhage in one subject) were considered treatment-related. Sixty-nine of 195 subjects (35%) experienced 187 treatment-related AEs, with diarrhoea (10%), headache (8%) and abdominal pain (6%) being the most common. Gastrin levels ≥400 pg/mL were seen in 9% of subjects; hypergastrinemia was not associated with gastro-intestinal AEs or nodules/polyps.

Conclusions
Lansoprazole maintenance therapy for up to 6 years is safe and well tolerated in subjects with healed erosive oesophagitis.

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INTRODUCTION

Symptoms of gastro-oesophageal reflux disease (GERD) are common in Western populations: recent pooled analyses of 10 clinical studies meeting strict inclusion criteria have estimated the prevalence of GERD (defined as at least weekly heartburn and/or acid regurgitation) to range between 10% and 20%,[1] and to have increased over the past two decades.[2] Erosive oesophagitis (EO) is a common manifestation of GERD. Patients with EO may also develop complications such as strictures and Barrett's oesophagus, as well as laryngo-respiratory complications. Limited data are available on the prevalence of EO among the general population in the western world; a recent population-based endoscopic study found that nearly 16% of a random sample of Swedish adults had EO.[3] Although short-term treatment with a proton pump inhibitor (PPI) is highly effective in healing EO,[4, 5] numerous studies confirm that unless maintenance therapy is initiated, virtually all patients will experience relapse within 1 year.[6–13]

An extensive body of literature supports the safety, tolerability and clinical efficacy of lansoprazole in preventing relapse in patients with EO.[6, 7, 14–18] The majority of these trials were of 12 months' duration, with only one European clinical trial presenting longer-term (5-year) data in subjects with GERD.[17] Efficacy, safety and pharmacoeconomic data suggest that PPIs are the preferred maintenance therapy in the management of patients with EO because of their ability to reduce the incidence of, and prolong the time to, relapse;[8] however, safety data regarding the longer-term (>1 year) use of PPIs in patients with EO are still limited, particularly in the United States.

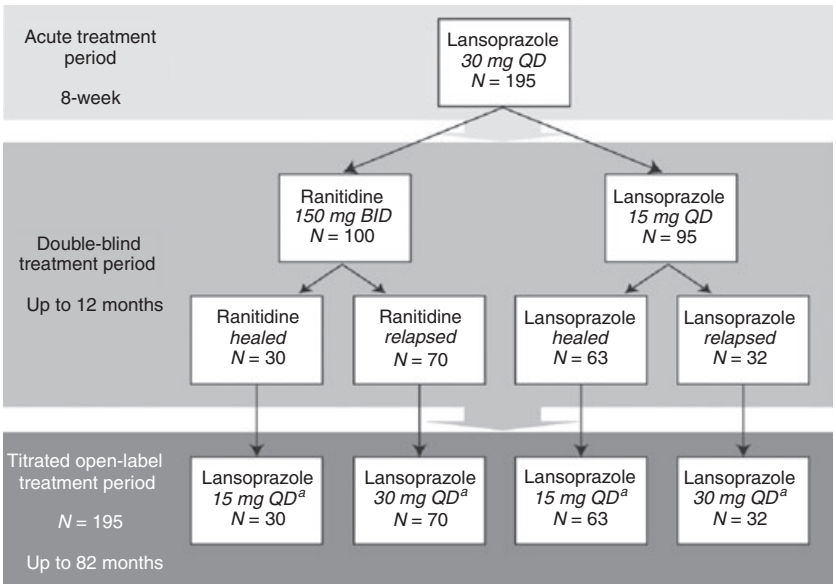
In the present study, we report the long-term safety of dose-titrated lansoprazole as maintenance therapy for healed EO in a Phase III multicentre study in the United States, in which patients received open-label lansoprazole for up to 6 years.[19]

MATERIALS AND METHODS

Study design and subjects

The M94-140 study was a Phase III parallel-group, positive-controlled, multicentre study in the United States that consisted of a 8-week open-label lansoprazole acute treatment period and a randomized, double-blind (fixed dose, lansoprazole vs. ranitidine) treatment period lasting up to 12 months, followed by a titrated open-label lansoprazole treatment period of up to 82 months (Figure 1). This article focuses on the titrated open-label portion of the study.

Subjects entering the acute treatment period were men and women aged ≥18 years with endoscopically proven EO (≥grade 2). Inclusion and exclusion criteria are summarized in Table 1. Subjects eligible for



[a] Dose at entry to the titrated open-label treatment period

Subjects who completed: N = 90
Subjects who prematurely discontinued: N = 105

Figure 1. Study design and patient disposition through the study of the 195 subjects included in the open-label treatment period. BID: twice daily; QD: once daily.

Table 1. Subject inclusion and exclusion criteria

Inclusion criteria*
≥18 years of age
Endoscopy-proven erosive reflux oesophagitis (≥grade 2)†
Negative pregnancy test and an agreement to use an appropriate means of contraception for the duration of the study in women of child-bearing potential
Exclusion criteria
Concomitant duodenal ulcer and/or gastric ulcer ≥3 mm in diameter (within 7 days prior to the initiation of treatment)
Oesophagitis due to a coexisting systemic disease
Evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurologic, or endocrine disease, Zollinger–Ellison syndrome, oesophageal varices, symptomatic pancreatobiliary tract disease, cholecystitis, rheumatoid arthritis, lupus, or malignancy (with the exception of basal cell carcinoma) requiring active treatment
Lactating women
Abnormal laboratory values
Evidence of current alcohol abuse, illegal drug use, or drug abuse in the past 12 months (by self report)
A requirement for chronic anticoagulant therapy
History of gastric, duodenal, or oesophageal surgery; evidence of current oesophageal stricture requiring dilatation (the endoscope must have passed freely into the stomach during endoscopy)
History of hypersensitivity or allergic reaction to lansoprazole, omeprazole or ranitidine
Receipt of blood products or study drug(s) within 12 weeks of initiating study medication
Requirement for more than occasional use (≤10 days per month) of any nonsteroidal anti-inflammatory drugs
Requirement for corticosteroids at dosages equivalent to >10 mg/day prednisone. Aspirin ≤325 mg/day for cardiovascular indications was acceptable
Receipt of investigational drug(s) within 12 weeks prior to the start of study treatment; receipt of a proton-pump inhibitor within 4 weeks prior to the start of treatment. Use of other anti-ulcer medications before the screening visit was allowed, but must have been discontinued at least 7 days before the screening gastrin test

* Patients who required continuous treatment with digoxin and/or theophylline derivatives could be included in the study, but required monitoring, as could those stabilized after an active gastrointestinal bleed, provided they were hemodynamically stable and able to take oral medication. Patients with Gilbert's disease or Barrett's oesophagus with no known dysplastic changes on screening were also eligible for inclusion.

† Grade ≥2 EO is defined as the patient having one or more erosion(s)/ulceration(s) involving <10% of the distal 5 cm of the oesophagus; Corresponds to Los Angeles Classification grade A.

inclusion in the titrated open-label treatment period (n = 195) were those who had completed the double-blind treatment period without relapse and those who experienced a recurrence of EO during this phase of the study. Subjects entering the titrated open-label treatment period without recurrence of EO were given lansoprazole 15 mg once daily (QD) (Figure 1). Subjects who entered the titrated open-label treatment period due to recurrence of EO began treatment with lansoprazole 30 mg QD for 8 weeks. Subjects who were not healed after 8 weeks had their dose increased until endoscopic evidence of healing was documented. Once healing occurred, subjects continued treatment with lansoprazole 15 mg QD. During the remainder of the titrated open-label treatment period, lansoprazole doses could be titrated upward to a maximum dose of 120 mg/day or downward, as required, to control symptoms.

The study was conducted according to the principles of the Declaration of Helsinki (1996 revision) and in accordance with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Food and Drug Administration guidelines, Guidelines for Good Clinical Practice governing clinical study conduct, and all applicable local regulations. Prior to initiating any study procedures, each investigator site was granted approval by its respective Institutional Review Board. Signed informed consent was obtained from each subject prior to study enrolment.

Clinical safety assessments

Physical and ophthalmology examinations were carried out and vital signs, adverse events (AEs) and laboratory data, including fasting serum gastrin levels,

were monitored at every annual visit and at the final visit.

The assessment of each reported AE included the frequency, duration, severity and relationship to study drug. AEs were coded using the COSTART dictionary.

Endoscopy was performed annually and at the final visit to evaluate healing of EO and to also monitor for the presence of Barrett's oesophagus. Gastric and duodenal nodules or polyps that were observed during upper gastrointestinal endoscopy were not routinely recorded as AEs and were documented separately. Colonic or rectal polyps observed during procedures not documented in the protocol, such as lower gastrointestinal endoscopy, were recorded as AEs. Biopsies of gastrointestinal anomalies were performed at the investigator's discretion and evaluated at local pathology laboratories. Gastric biopsies were performed annually and at the final visit of the titrated open-label period in conjunction with each endoscopy procedure and were evaluated at the Drexel University College of Medicine Pathology Diagnostic Laboratory (formerly Medical College of Pennsylvania Hahnemann University Pathology Diagnostic Laboratory) for changes in acute and chronic inflammation, endocrine cell density, intestinal metaplasia and atrophy, and *Helicobacter pylori* status.

Gastric body biopsies were obtained from the middle of the greater curvature of the gastric body, and antral biopsies were obtained from the lesser curvature, 1–2 cm proximal to the pylorus sphincter (two from each site). *Helicobacter pylori* status was determined using Warthin-Starry silver staining. If any one of the four biopsies showed the presence of *H. pylori* (grade >0; Table 2), the subject was considered positive for *H. pylori*. If none of the samples examined showed *H. pylori* organisms under at least 15 high-power fields (400 × magnification), the subject was considered negative for *H. pylori*. All slides were reviewed by independent pathologists, blinded to the clinical status of the study subjects, under the direction of M. Haber, a board-certified pathologist.

Table 2. Grading scales for the assessment of presence of *Helicobacter pylori*

H. pylori grade	
0	Negative: no organisms seen
1	Mild: one or a few organisms present in a single foveola in at least one biopsy sample, but no more than in one foveola
2	Moderate: multiple clusters of organisms in one foveola, or organisms in more than one foveoa, but less than half of the foveolae
3	Severe: numerous organisms diffusely present in half or more foveolae in a single biopsy sample

Statistical methods

All subjects who took at least one dose of lansoprazole during the titrated open-label treatment period were included in the analyses. Treatment-emergent and treatment-related (judged by investigator as at least possibly related to study drug) adverse events were tabulated for the titrated open-label treatment period overall and by COSTART term. Treatment-emergent adverse events were also summarized by time of initial onset. Adverse events reported on or after the first day of study drug dosing and within 3 days after the last dose were considered treatment-emergent events.

Summaries and descriptive statistics were performed for laboratory variables (including gastrin) and gastric biopsies collected during the titrated open-label treatment period.

RESULTS

Subject characteristics

The characteristics of the 195 subjects at open-label baseline are summarized in Table 3. A total of 176 subjects (90%) were Caucasian, 131 (67%) were male, and the mean age was 50.8 years (range 20–82).

Mean duration (± s.d.) of lansoprazole exposure for all subjects during the titrated open-label treatment period was 56 ± 24 months (range <1–82 months). The majority of subjects (120/195; 62%) received open-label treatment for ≥5 years. While some subjects were treated for up to 82 months, safety data are presented through 72 months due to the paucity of data after 72 months.

During the open-label treatment period, lansoprazole dose was increased from the maintenance dose (15 mg daily) in 65% (126/195) of subjects at least once, either due to an endoscopically documented relapse of EO or to alleviate symptoms. Daily doses of lansoprazole ranged from ≤15 mg to 120 mg, but most subjects received

Table 3. Open-label baseline characteristics of 195 subjects entering the open-label treatment period

	Number (%) of subjects
Gender	
Female	64 (33)
Male	131 (67)
Race	
Caucasian	176 (90)
Black	13 (7)
Hispanic	6 (3)
Age (years)	
Mean (s.d.)	50.8 (13.8)
Range	20–82
Erosive oesophagitis grade*	
Grade 0 (normal-appearing mucosa by endoscopy)	74 (38)
Grade 1 (mucosal edema, hyperemia, and/or friability of mucosa)	19 (10)
Grade 2 (≥1 erosion(s)/ulceration(s) involving <10% of the distal 5 cm of the oesophagus)	82 (42)
Grade 3 (erosions/ulcerations involving 10–50% of the distal 5 cm of the oesophagus or an ulcer measuring 3–5 mm in diameter)	16 (8)
Grade 4 (multiple erosions/ulcerations involving >50% of the distal 5 cm of the oesophagus or a single large ulcer >5 mm in diameter)	4 (2)
H. pylori status	
Positive	40 (21)
Negative	155 (79)

* Of the 195 subjects entering the titrated open-label period, 95 had been previously treated with lansoprazole and 100 with ranitidine.
s.d., standard deviation.

≤30 mg/day. At the final titration, the total daily dose was >30 mg lansoprazole in 19% (37/195) of subjects.

A total of 195 subjects accumulated a total of 899.6 person-years of follow-up (mean 4.6 years per person) during the study. Primary reasons for discontinuation from the study included closure of a study site (23 subjects, 12%), an AE (18 subjects, 9%), personal reasons (13 subjects; 7%), investigator decision (11 subjects, 6%) and poor compliance (nine subjects; 5%). Thirteen subjects (7%) were lost to follow-up.

Adverse events

Overall, 97% of subjects (189/195) experienced a total of 2825 treatment-emergent AEs during open-label treatment (3.14 events per subject per year). The most frequently experienced AEs were pharyngitis (87 subjects, 45%), accidental injury (76 subjects, 39%), arthralgia (68 subjects, 35%), abdominal pain (59 subjects, 30%) and headache (59 subjects, 30%). Most AEs were mild-to-moderate in severity. Serious AEs (SAEs), as defined by regulatory agencies such as the U.S. Food and Drug Administration, are discussed later in this article.

Sixty-nine of 195 subjects (35%) experienced a total of 187 AEs considered by the investigator to be at least possibly related to the study drug. Treatment-related AEs experienced by ≥2% of subjects included diarrhoea (19 subjects, 10%), headache (16 subjects, 8%) and abdominal pain (12 subjects, 6%) (Table 4). Most were mild-to-moderate in severity and resolved while subjects continued treatment.

Three cases of *C. difficile*-associated diarrhoea were reported, of which only one was considered to be treatment-related (COSTART term: colitis); this AE was also considered to be an SAE. Of the 13 cases of pneumonia recorded during the open-label treatment period (incidence rate 1.4 per 100 person-years), only 1 case was considered to be treatment-related. Other AEs that were considered treatment-related included skin disorders (seven subjects), eye disorders (four subjects) and hypertension (two subjects).

Table 4. Treatment-related and serious AEs occurring in ≥2.0% of 195 subjects during the open-label treatment period

	Treatment-related AEs *N* (%)	Serious AEs* *N* (%)
Subjects reporting any event†	69 (35.4)	74 (38.0)
Diarrhoea	19 (9.7)	0 (0)
Headache	16 (8.2)	1 (<1)
Abdominal pain	12 (6.2)	5 (2.6)
Nausea	8 (4.1)	1 (<1)
Insomnia	7 (3.6)	0 (0)
Flatulence	6 (3.1)	0 (0)
Chest pain	5 (2.6)	11 (5.6)
Vomiting	4 (2.1)	1 (<1.0)
Pruritus	4 (2.1)	0 (0)
Cataract	4 (2.1)	0 (0)
Pneumonia	1 (<1.0)	4 (2.1)
Accidental injury	0 (0)	7 (3.6)
Coronary artery disorder	0 (0)	6 (3.1)
Infection	0 (0)	5 (2.6)
Prostatic carcinoma	0 (0)	5 (2.6)
Back pain	0 (0)	4 (2.1)

* Only two serious AEs (colitis and rectal haemorrhage in the same subject) were considered treatment-related. Does not include three deaths (all considered unrelated to treatment).
† Subjects with more than one AE within the same COSTART category were counted only once.
AE, adverse events.

Twenty-three subjects discontinued the study as a result of an AE (an AE was the primary reason for discontinuation in 18). Of these subjects, seven experienced an AE that was judged by the investigator to be treatment-related. These adverse events included diarrhoea (two subjects), marrow depression, abnormal liver function tests, atrial fibrillation, depression and nervousness and headache (each one subject).

Initial onset of AEs over time

When considering the time of the first episode (initial onset) of each AE for each subject, no treatment-emergent AE demonstrated a clear increase in frequency over time. Most AEs initially occurred during the first 12 months of open-label treatment, and the number of newly occurring AEs decreased thereafter. One exception to this was the occurrence of colon/rectal polyps, which increased slightly during the third and fifth years of the titrated open-label treatment period (Table 5).

As with treatment-emergent AEs, the majority of treatment-related AEs occurred during the first year of the titrated open-label treatment period and the initial onset or rate of these events did not increase over time. Overall, treatment-related AEs were similar to treatment-emergent events in terms of onset, frequency and distribution.

A total of 17 of 195 (9%) subjects reported a total of 21 treatment-emergent benign or malignant neoplasms, none of which was considered related to treatment. The neoplasms reported included basal cell carcinoma (nine events in seven subjects), prostatic carcinoma (five events in five subjects), squamous skin cancer, meningioma, pheochromocytoma and carcinoid tumour of the colon (each in one subject). The overall percentage of subjects who developed treatment-emergent hypertension during this period was 20% (38/195).

Serious AEs

A total of 74 (38%) subjects experienced a total of 155 SAEs other than death during open-label treatment. The most frequently reported SAEs (experienced by ≥2% of subjects) are given in Table 3. SAEs of arthritis, hernia and pancreatitis were each experienced by three subjects and SAEs of angina pectoris, bradycardia, cellulitis, cholecystitis, colitis, gastroenteritis, lung

Table 5. Colon/rectal nodules or polyps by time of initial onset in subjects during the titrated open-label treatment period

	≤1 Year *N* = 195 *n* (%)	>1–2 Years *N* = 177 *n* (%)	>2 to 3 Years *N* = 164 *n* (%)	>3 to 4 Years *N* = 149 *n* (%)	>4 to 5 Years *N* = 135 *n* (%)	>5 Years *N* = 116 *n* (%)	Overall *N* = 195 *n* (%)
Colon/rectal nodules or polyps							
Treatment-emergent	2 (1.0)	2 (1.1)	3 (1.8)	3 (2.0)	7 (5.2)	3 (2.6)	20 (10.3)
Treatment-related	0	0	0	0	0	0	0

disorder, neuropathy, pulmonary embolus, prostatic disorder, skin carcinoma, urinary incontinence, urogenital disorder, uterine disorder, or vascular anomaly were each experienced by two subjects. The remaining SAEs were each experienced by one subject.

Of the 155 SAEs reported, only two (*C. difficile*-related colitis and rectal haemorrhage in the same subject) were considered related to the study drug. Ten subjects who experienced serious AEs discontinued treatment; none was considered by the site investigator to be related to the study treatment.

Additionally, there were three deaths reported during the open-label treatment period. One subject died during treatment as a result of an accidental injury and two subjects died 300 and 432 days respectively after discontinuing treatment. The causes of these deaths were cardiogenic shock secondary to an acute myocardial infarction and complications due to amyotrophic lateral sclerosis respectively. All three of these deaths were considered by the investigator to be unrelated to the study drug.

Gastrin levels

Median fasting gastrin levels increased gradually during 72 months of lansoprazole maintenance therapy, from 62 pg/mL at open-label baseline to a maximum of 120 pg/mL at 5 years, after which values reached a plateau (Figure 2). Most gastrin values remained within the normal range (25–111 pg/mL).

The highest fasting serum gastrin level seen in any subject during the open-label treatment period was 1051 pg/mL. Eighteen of 195 (9%) subjects had a gastrin level ≥400 pg/mL at any time during treatment and in only 5 (2.5%) were values ≥400 pg/mL on two or more occasions. A gastrin level ≥400 pg/mL at any time during open-label treatment was seen in a higher percentage of subjects who were *H. pylori*-positive at open-label baseline compared with those who were *H. pylori*-negative (15% [6/40] vs. 8% [12/155]). These elevated values were not associated with gastrointestinal adverse effects, including the presence of gastrointestinal polyps and neoplasms. Only one patient prematurely discontinued treatment due in part to elevated gastrin (228 pg/mL; primary reason for discontinuation: abdominal pain).

Gastric and duodenal nodules or polyps

A total of 1106 endoscopies were performed on 185 subjects over the course of the study. Overall, gastric or duodenal nodules or polyps were reported in 31% (57/185) of the study subjects (in four cases, gastric or duodenal nodules or polyps were reported as AEs and coded to the COSTART term gastrointestinal anomaly). Of these subjects, 19% (11/57) had nodules or polyps prior to open-label baseline and 46% (26/57) did not

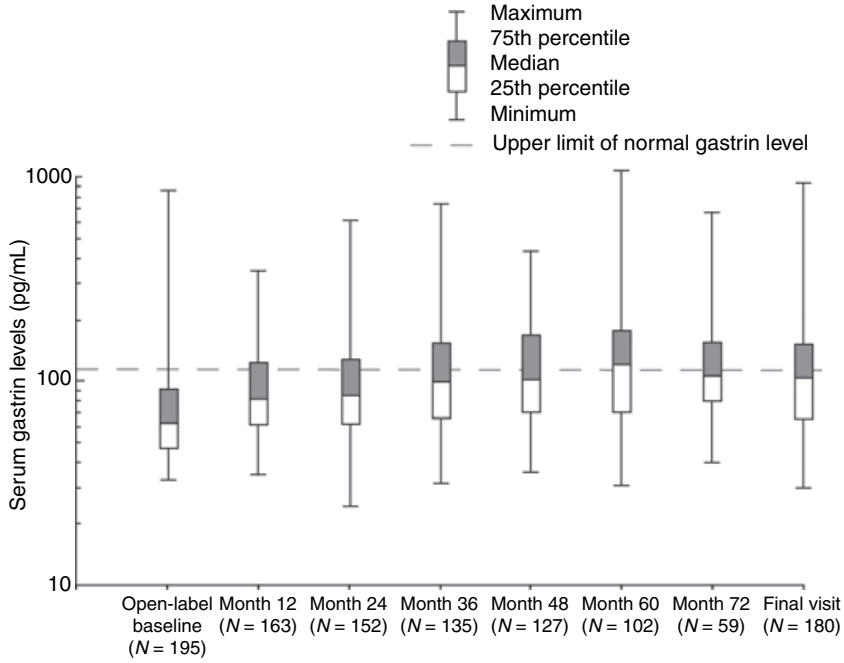


Figure 2. Box and whiskers plot of median serum gastrin levels in subjects during the titrated open-label treatment period.

have nodules or polyps at their last endoscopic evaluation. Gastric polyps were most commonly located in the gastric fundus and those biopsied were most typically fundic gland polyps. Duodenal polyps examined were most commonly determined (endoscopically) to be Brunner's gland hyperplasia. No biopsied polyp exhibited neuroendocrine proliferation, epithelial dysplasia or malignancy. Gastric nodules or polyps were found in 18% of those who were *H. pylori*-positive at baseline and 25% of those who were *H. pylori*-negative.

Barrett's oesophagus

Barrett's oesophagus was previously diagnosed (visually noted during endoscopy or biopsied) in 17%, (33/195) of subjects at or prior to the open-label baseline and the condition was first reported in 17 individuals during the open-label treatment period.

Barrett's oesophagus was confirmed in 11 subjects, five of whom were found to have low-grade dysplasia and six had no dysplasia.

Other safety assessments

Long-term lansoprazole maintenance therapy for up to 72 months did not result in clinically significant changes in laboratory parameters, vital sign measurements and physical or ophthalmologic examination results.

DISCUSSION

This study supports the long-term clinical safety of lansoprazole as maintenance therapy for up to 6 years in subjects with healed EO. To our knowledge, only one study has investigated lansoprazole as maintenance therapy with a similar duration of follow-up.[17] In this earlier study, conducted in Europe, subjects with GERD received lanzoprazole 30 mg/day for a maximum of 5 years and were discontinued from the study on relapse. In contrast, in our study, patients received the lower, recommended maintenance dose of 15 mg/day, which could be titrated to control symptoms. As a result, consistent with recent guidelines on the management of EO,[20] patients received the lowest possible effective dose of lansoprazole, thus minimizing the risk of adverse events for longer duration of the therapy. The results of both studies were supportive of the safety of long-term lansoprazole therapy. The finding that 65% of patients required an increase in lansoprazole dose to control symptoms during the titrated open-label period of the current study is in agreement with a recent report that the majority of subjects with GERD experience the recurrence of symptoms during long-term treatment with PPIs.[21] It is of note that the majority of patients experiencing recurrence during the titrated open-label period of the study achieved endoscopic healing of their EO through additional dose titration.[19]

As would be expected in a study of this length, and as seen in other studies of long-term PPI therapy for the maintenance of healed EO,[22, 23] the number of subjects reporting at least one AE was high (97%). The number of treatment-emergent AEs was 3.14 events per subject per year and most events were mild-to-moderate in severity. The constellation of AEs observed during open-label treatment was consistent with the AEs observed in other lansoprazole clinical studies and post-marketing surveillance.

Approximately one-third (35%) of subjects reported at least one AE considered to be treatment-related during the titrated open-label treatment period. Diarrhoea, headache and abdominal pain were the most frequently reported treatment-related AEs, findings consistent with the known safety profile of lansoprazole.[8, 24] The higher percentage of subjects experiencing these events relative to the data presented in the lansoprazole package insert (diarrhoea 3.8%, headache >1% and abdominal pain 2.1%) is as expected given the extended duration of this study.

As previously observed in another long-term study of PPIs in healed EO,[22] treatment with lansoprazole for up to 6 years did not increase the frequency of treatment-emergent or treatment-related AEs over time.

The overall percentage of subjects who developed hypertension during the open-label treatment period was 20%. This value is similar to the 10-year incidence of hypertension recently reported in a slightly younger cohort of generally healthy volunteers (n = 9997; aged 16–68 years, mean 37.3 years[25]); hence, the reported incidence of hypertension in the 6-year open-label treatment period of this study is in line with what would be expected in the general population.

Two recent studies concluded that long-term PPI therapy is associated with an increased risk of hip fracture in persons >50 years of age.[26, 27] One of these studies also found a dose-response relationship between the PPI dosage and risk of fracture.[27] The

demographic profile of subjects in the current study was broader than that in the study by Yang *et al.*, and included those not typically considered at increased risk of hip fracture. Hip fracture was recorded as an AE (accidental injury) in only one patient during the open-label treatment period. This incident was considered by the site investigator to be unrelated to treatment.

Studies have suggested a potential link between PPI use and an increase in the incidence of community-acquired pneumonia in adults.[28, 29] The incidence rate for pneumonia reported in the current study (1.4 per 100 person-years) is numerically lower than the reported rate in PPI users in a retrospective cohort study of general practitioner medical records involving almost one million patient-years of data (2.5 per 100 patient-years) but higher than that reported in the same study in PPI non-users (0.6 per 100 patient-years).[28] In our study, only four serious AEs of pneumonia were reported over the entire follow-up period, none of which was treatment-related (Table 4).

The results of several earlier studies have suggested a possible causal association between PPI use and the development of *C. difficile* infection in adults.[30, 31] This risk seems to be the highest in a specific population of hospitalized, older (>70 years), particularly sick patients, who are taking antibiotics or among those undergoing chemotherapy.[32, 33] In the current study, although 75% of patients took concurrent anti-infective medication at some time during the open-label treatment period, only 3 (1.5%) subjects experienced *C. difficile*-associated diarrhoea, a much lower percentage than the 9.3% reported by Dial *et al.* in a group of hospitalized patients taking antibiotics and a PPI.[31] A recent case-control study found no association between prior PPI use and community-associated *C. difficile* infection,[34] whereas a retrospective cohort study found an association between PPI use and hospital admissions for *C. difficile*-associated diarrhoea.[33] Thus, a possible link between long-term therapy with PPIs and an increase in the risk of fractures, community-acquired pneumonia and enteric infections[35] was not supported by the results of our study.

Overall, 12% (23/195) of subjects discontinued the study due to an AE, a finding consistent with previous reports of a similar duration in patients receiving long-term therapy with a PPI for the maintenance of healed EO.[20, 21, 36] Seventy-four (38%) of all enrolled subjects experienced at least one serious AE during the titrated open-label treatment period, only two of which (both occurring in the same patient) were considered possibly related to study medication. No treatment-related serious AEs led to discontinuation from the study. The three deaths that occurred in the study were not attributable to the study drug.

Lansoprazole was well tolerated during this 6-year trial, with AE rates and a discontinuation rate due to AEs similar to those seen in other long-term studies of PPIs as maintenance therapy in patients with healed EO.[20, 21, 36]

Elevated levels of serum gastrin are a known effect of long-term treatment with PPIs.[8, 20] Although the clinical significance of elevated fasting gastrin levels has not been determined, a possible link between hypergastrinemia and the development of colorectal cancer has been suggested.[37, 38] However, in the current study, elevated gastrin levels were not associated with gastric/duodenal and colon polyps and neoplasms, or with other gastrointestinal AEs in individual subjects. In this study, only 9% of patients exhibited gastrin levels ≥400 pg/mL at any time during open-label lansoprazole treatment, an incidence that compares well with the finding of elevated gastrin levels (>500 ng/L) in 11% of patients with GERD taking a long-term PPI.[39] High gastrin levels were more common in patients who were *H. pylori*-positive (compared with those who were *H. pylori*-negative) at open-label baseline, and a link between elevated gastrin levels and *H. pylori*-positive status has also been reported by other researchers during long-term PPI therapy.[22] Three recently published retrospective studies have found no association between long-term PPI use and an increased risk of developing colonic adenoma[40] or colorectal cancer.[37, 38]

The apparent gradual continued increase in median values of gastrin observed throughout the open-label treatment period, which plateaued after 5 years, contrasts with an analysis of previously reported long-term studies of acid suppression using a PPI, which found gastrin levels to plateau after 4–8 weeks of treatment.[14] However, the previous analysis looked at changes in gastrin levels only during the first year of therapy. In the current study, gastrin levels were assessed annually over the 6-year open-label treatment period, and the finding that gastrin levels appear to continue to rise with continuing PPI exposure is consistent with the findings of other long-term studies of PPIs in patients with healed EO that have also assessed gastrin levels over the entire study period.[23, 36] The

finding of a rise in gastrin levels over the open-label treatment period of this study is consistent with the pharmacology of PPIs and does not suggest an increased safety concern.

As shown in Table 5, newly identified colorectal nodules or polyps were observed in 10% of subjects with an average baseline age of 51 years. The observed incidence may be an underestimate, since colonoscopies were not a part of the study, and data were not systematically collected in a standardized manner. Although the initial onset of treatment-emergent colon/rectal nodules and polyps showed a slight rise over the course of treatment, an age-related increase in the incidence of colorectal colon nodules and polyps is to be anticipated among subjects aged 50 years or older.[41] It is noteworthy that in the current study no association was found between fasting serum gastrin levels and the occurrence of colon nodules and polyps.

One case of colon carcinoid tumour was reported in a 59-year-old man who received over 4 years of open-label lansoprazole therapy. This subject had normal gastrin levels throughout the study, was *H. pylori* negative, and completed the study. The occurrence of carcinoid tumour is rare, especially in the colon. Using data through 2000, the National Cancer Institute Surveillance Epidemiology and End Results program estimated the incidence of colon carcinoid tumour to be ~10.6 per million per year in the USA.[42] As has been seen with other forms of colon cancer, however, its incidence appears to have steadily increased in recent years.[43] There has been no demonstration of an increased risk of colon carcinoid tumours in conjunction with lansoprazole use in clinical studies.

The development of gastric or duodenal nodules/polyps is another of the known effects of PPIs. One prospective study reported that 36% (57/160) of subjects who had taken a PPI for >1 year had fundic gland polyps.[44] In one small study, fundic gland polyps associated with long-term PPI treatment were not related to the level of hypergastrinemia.[45] In our study of a much longer treatment duration than the study by Jalving *et al.*, gastric or duodenal nodules or polyps (mostly fundic gland polyps) were observed in 31% (57/185) of subjects during the open-label treatment period, with no evidence of neuroendocrine proliferation, epithelial dysplasia, or malignancy.

It is estimated that 5–15% of individuals with long-term symptoms of GERD will have Barrett's oesophagus.[13] The proportion of patients with Barrett's oesophagus over the entire open-label treatment period of this study (26%) reflects the overall severity of GERD in this patient population and compares well with a previous report that Barrett's oesophagus occurred in 37% (84/230) of patients with healed EO receiving a PPI for a mean 6.5 years.[22]

The open-label design and the consequent lack of placebo or active comparator treatment arms is one limitation of this study. However, an open-label study can be considered a more realistic approximation of clinical practice than a double-blind study and it is recognized that such studies can provide substantial information regarding the safety and tolerability of a drug.[46] Other limitations relate to the long-term nature of the trial and include the inability to ensure that gastrin measurements were obtained after the appropriate fasting period and the inability to control for any concomitant medications that patients may have been taking.

CONCLUSION

This study, the longest reported experience to date with a PPI in the United States, confirms the clinical safety profile of lansoprazole for up to 6 years, thus providing a more robust experience of clinical practice in the context of a real-world setting than previous studies of shorter duration. These findings strengthen the existing and extensive body of literature that supports the safety of long-term lansoprazole use in maintaining healing of EO.

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