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The 12-month safety profile of dexlansoprazole, a proton pump inhibitor with a dual delayed release formulation, in patients with gastro-oesophageal reflux disease

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SUMMARY

Background
Dexlansoprazole MR is a Dual Delayed Release formulation of dexlansoprazole, an enantiomer of lansoprazole, designed to extend the duration of acid suppression.

Aim
To assess the 12-month safety of dexlansoprazole MR in patients with symptomatic gastro-oesophageal reflux disease (GERD).

Methods
In this randomised open-label study, patients received dexlansoprazole MR 60 or 90 mg once-daily for 12 months. Safety was evaluated at months 1, 3, 6, 9 and 12/final visit through physical examinations, laboratory evaluations, endoscopies, gastric biopsies, fasting serum gastrin values and adverse events (AEs).

Results
Of 591 patients receiving dexlansoprazole MR 60 and 90 mg, 71% and 65%, respectively, experienced ≥1 treatment-emergent AE; the most frequent AE was upper respiratory infection (14% and 13% in the 60- and 90-mg groups). Thirty patients experienced ≥1 serious AE; a majority of serious AEs were unrelated to study drug. No clinically meaningful change in any clinical laboratory parameters was noted. As expected, serum gastrin values rose with dexlansoprazole therapy; increases were not dose related. No clinically concerning trends were identified in gastric pathology results; no endocrine cell hyperplasia, adenocarcinoma, or lymphoma were observed.

Conclusions
Twelve-month treatment with dexlansoprazole MR 60 and 90 mg was well tolerated by GERD patients in this study (Clinicaltrials.gov identifier NCT00255190).

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a common recurring medical condition that develops when reflux of stomach contents causes troublesome symptoms that can affect an individual's quality of life (QOL) and/or produce complications.[1] Proton pump inhibitors (PPIs) are the standard therapy for long-term management of GERD.[2–4]

The safety of lansoprazole has been rigorously studied. Lansoprazole has demonstrated a favourable safety profile in patients treated for up to 72 months in US clinical trials.[5, 6] High doses of lansoprazole (>60 mg/day) have been given for up to 10 years to patients with Zollinger–Ellison syndrome[7–9] and for up to 4 years to patients with duodenal ulcer[7] without significant adverse events (AEs). In a long-term study in patients with healed erosive oesophagitis, patients received lansoprazole 15–120 mg/day open-label for up to 82 months.[5] Over time, the percentage of patients with AEs did not appreciably increase in these long term-studies. Overall, AEs associated with lansoprazole use tended to occur within the first year of treatment and resolved with continued treatment.[5]

Lansoprazole is a racemic mixture of dexlansoprazole (*R*-lansoprazole) and *S*-lansoprazole of which dexlansoprazole is the major circulating enantiomer after oral administration.[10] Dexlansoprazole MR is a modified-release formulation of dexlansoprazole that employs an innovative Dual Delayed Release delivery system designed to prolong plasma concentration of dexlansoprazole and provide extended duration of acid suppression. In a phase 1 study, dexlansoprazole MR 60 and 90 mg administered once daily (QD) were shown to provide more effective acid control than a standard dose (30 mg) of lansoprazole in healthy volunteers.[11] In phase 3 studies, dexlansoprazole MR 30 mg, 60 mg and 90 mg demonstrated a safety profile comparable to those of lansoprazole and placebo in patients treated for up to 6 months.[12–14]

This work was a 12-month phase 3 safety extension study within the original dexlansoprazole MR development plan, designed to assess the safety of dexlansoprazole MR (60 and 90 mg QD) in patients with symptomatic GERD.

MATERIALS AND METHODS

Study design

This was a phase 3, open-label, multicentre, 12-month study to evaluate the safety of dexlansoprazole MR in patients with GERD (Clinicaltrials.gov identifier NCT00255190). As stated in the International Conference on Harmonisation guideline addressing exposure for drugs intended for long-term treatment of non-life-threatening conditions,[15] this study was designed to report 12-month safety results for a minimum of 100 patients exposed to the highest doses administered in phase 3 studies. Patients who were initially enrolled had completed a 4-week, placebo-controlled non-erosive reflux disease (NERD) trial in which they were randomised to placebo or dexlansoprazole MR 60 or 90 mg QD. The 60-mg and 90-mg doses selected for evaluation in this subsequent 12-month safety trial were based on the preceding 4-week symptomatic NERD efficacy trial, and their use as the highest doses studied in the phase 3 clinical program (Clinicaltrials.gov identifier NCT00251745).[12, 14]

The protocol for this study was amended (referred to as the amendment in this report) to expand the NERD population to allow enrolment of approximately 300 additional GERD patients, including those with endoscopically confirmed erosive oesophagitis (EO), who were suitable candidates for 12-month therapy.

This study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice regulations and guidance issued by the US Food and Drug Administration. Institutional Review Board approval was obtained at each study site. All patients gave written informed consent and completed Health Insurance Portability and Accountability Act authorisation forms before any study-related procedure was initiated.

Patient selection

Male or female patients aged 18 years or older were eligible to participate, regardless of *Helicobacter pylori* status. Women of child-bearing age were required to use a double barrier method of birth control. The main exclusion criteria included use of prescription or nonprescription PPIs, histamine$_2$-receptor antagonists or sucralfate; long-term use (>12 doses/month) of nonsteroidal anti-inflammatory drugs, including selective and nonselective COX-2 inhibitors (aspirin ≤325 mg daily was allowed); use of antacids (except study-supplied Gelusil); use of misoprostol or prokinetics; use of drugs with significant anticholinergic effects (unless the patient was on a stable dose for 4 weeks before dosing and continued throughout the study); evidence of uncontrolled disease; need for continuous anticoagulant therapy; cancer (except basal cell carcinoma of the skin) within 5 years of screening;

endoscopic Barrett's oesophagus and/or dysplastic changes in the oesophagus; active gastric or duodenal ulcers within 4 weeks of study entry; history of dilatation for oesophageal strictures (other than Schatzki's ring); coexisting disease affecting the oesophagus; history of Zollinger–Ellison syndrome; history of gastric, duodenal, or oesophageal surgery; acute upper gastrointestinal haemorrhage within 3 months of study entry; known hypersensitivity to any PPI; pregnancy or lactation; history of alcohol or substance abuse; and previous participation in a long-term dexlansoprazole MR clinical trial.

All patients were instructed not to alter lifestyle or behaviour for their GERD symptoms throughout the study. Study participants were allowed to receive up to 6 tablets/day of open-label Gelusil (Pfizer Inc., New York, NY, USA) as rescue medication throughout the screening and treatment periods.

Patients who completed one of the preceding NERD studies were enrolled within 7 days of the last day of the previous study. Final visit procedures from the placebo-controlled trial were considered day −1 assessments for this 12-month study. Patients enrolled under the amendment underwent a screening period that included an endoscopy with gastric biopsy and a rapid urease test (CLOtest, Kimberly Clark, Roswell, GA, USA) to determine *H. pylori* status. Those who continued to meet eligibility criteria were enrolled within 14 days of the screening evaluation.

Randomisation and patient dosing

For patients enrolled before the amendment, the randomisation schedule was generated by Takeda Global Research & Development, Inc using blocks of size 2 and implemented in an interactive voice response system (ClinPhone, Inc., Northbrook, IL, USA). The patients were enrolled by study investigators and assigned to treatment groups by the interactive voice response system. All patients enrolled after the implementation of the amendment received dexlansoprazole MR 90 mg QD. Dexlansoprazole MR 60- and 90-mg capsules were manufactured and supplied by Takeda Pharmaceutical Company Ltd. (Osaka, Japan) and were packaged by Fisher Clinical Services, Inc. (Allentown, PA, USA). Patients self-administered study drug in the morning before breakfast. Concomitant medication use was assessed by interview at each visit.

Safety assessments

The 12-month treatment period consisted of five visits at months 1, 3, 6, 9 and 12/final visit. At each visit, safety was evaluated through physical examinations, vital signs, routine laboratory evaluations, endoscopy, gastric biopsies, fasting serum gastrin values and AE assessments. An AE was defined as any untoward medical occurrence, including an abnormal laboratory result. AEs were collected whether observed by the investigator, elicited during telephone contacts and/or study visits, or spontaneously reported by the patient. The investigator evaluated event severity and potential relatedness to study drug.

A treatment-emergent AE was defined as any untoward medical event occurring after the patient signed the informed consent form through 30 days after discontinuation of study drug. Treatment-related adverse events were defined as those treatment-emergent events that the investigator considered to be possibly or definitely related to study drug. A serious AE was defined as any event that was life-threatening or resulted in death, in-patient hospitalisation (or prolongation of an existing hospitalisation), persistent or significant disability or incapacitation, a congenital anomaly or birth defect, or other medically significant event as determined by the investigator.

All routine laboratory evaluations (haematology, chemistry and urinalysis) were conducted by Covance Central Laboratory Services (Indianapolis, IN, USA). Blood samples to assess fasting serum gastrin were collected on day −1 and at months 3, 6, 9 and 12 and tested by radioimmunoassay.

Gastric biopsies were obtained during endoscopy at baseline and the month 12/final visit for all patients. For patients enrolled before the amendment, the initial biopsies were obtained at baseline of the previous NERD trials. After implementation of the amendment, baseline biopsies were taken during the screening period that immediately preceded the start of the current study. For patients enrolled under the amendment who had endoscopically confirmed EO during screening, healing status was assessed via endoscopy at months 3 and 12. Patients who were not healed at month 3 were discontinued from the study.

Four mucosal biopsies were taken from the gastric antrum and fundus/body (two from each site). Biopsies were analysed by expert gastrointestinal pathologists at the Cleveland Clinic Foundation (Cleveland, OH, USA). All biopsies were evaluated for presence of *H. pylori,* active and chronic gastritis, endocrine cell hyperplasia, reactive gastropathy and other pathologies.

Quality of life and symptom severity assessments

On day −1 (for patients enrolled before the amendment, this was the final visit of the previous study) and at each

visit, patients completed two validated questionnaires: the Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index (PAGI-QOL)[16, 17] and the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM).[18, 19]

Statistical analyses

No formal sample size calculation was performed for this study. Although statistical testing for between-group comparison was performed, in this report the focus is on within-group changes rather than between-group comparisons because of the expanded, nonrandomised patient population under the amendment. The SAS system for the UNIX operating system (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. The overall level of significance was 0.05 for demographic, safety and QOL variables. All statistical tests were two sided; *P*-values were rounded to three decimal places before determining statistical significance. All patients who received one or more doses of study drug were included in the summary of demographic data and safety analyses. All analyses were based on the actual treatment received on day 1.

Treatment-emergent and treatment-related AEs were summarised by treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 coding dictionary. Summary statistics were generated for laboratory values at baseline and post-baseline visits, and for change from baseline. Within each treatment group and each visit, the change from baseline in gastrin was also evaluated relative to no change with a one-sample paired *t*-test.

A summary of gastric biopsies tabulated the number and percentage of patients with each diagnosis by treatment group (each biopsy could have >1 diagnosis per tissue type) at baseline and final visit. The final visit summary results included the value closest to the last day of study drug after day 1 and within 14 days post-treatment. These summaries were for antrum tissue, fundus tissue and either tissue type.

Study drug compliance was determined by dividing the difference between the total number of capsules dispensed and returned by the total number of days receiving study drug. The number and percentages of patients taking each concomitant medication were summarised by treatment group for all patients who received one or more doses of study drug.

All patients who received one or more doses of study drug and had a value for 1 or more subscale at baseline and after day 1 were included in the PAGI-QOL and PAGI-SYM analyses. Summary statistics were generated for each subscale and the total score at baseline and months 1, 3, 6, 9 and 12, and for the change from baseline to each post-baseline visit.

An interim analysis was performed when all patients enrolled before the amendment completed the study. The objective of this interim analysis was to evaluate the safety and QOL and symptom severity data for inclusion in the dexlansoprazole MR New Drug Application. The conduct of the study was not affected by the results of this interim analysis.

RESULTS

Patient characteristics

This study was conducted from 7 January 2006 to 25 June 2008 at primary care and gastroenterology community practices in the United States. A total of 591 patients were enrolled and received at least one dose of study drug. Of these, 313 patients with NERD were enrolled prior to the amendment and an additional 278 GERD patients were enrolled after the implementation of the amendment. Overall NERD was diagnosed in 452 patients (76%) and EO was diagnosed in 139 patients (24%). In addition, 417 patients (71%) had participated in a previous dexlansoprazole MR phase 3 study. One hundred fifty-three patients received dexlansoprazole MR 60 mg and 438 patients received dexlansoprazole MR 90 mg (Figure 1). All patients were included in the safety analyses.

Of the 591 patients who received study drug, 105 (69%) of the patients in the dexlansoprazole MR 60-mg treatment group and 277 (63%) of the patients in the dexlansoprazole MR 90-mg treatment group completed ≥48 weeks of treatment. The median number of days on study drug was 362 and 363 days for all enrolled dexlansoprazole MR 60-mg and 90-mg treatment groups, respectively.

Baseline demographic characteristics summarised by treatment group are shown in Table 1. A majority of patients were women, white, ≥45 years of age, and had a body mass index ≥25.0 kg/m^2. *H. pylori* was detected in 84 patients (14%). The mean study drug compliance was 97% and 96% for patients receiving dexlansoprazole MR 60 and 90 mg, respectively. The use of concomitant medication was similar in both treatment groups.

Safety

Adverse events. One or more treatment-emergent AEs were experienced by 71% and 65% of patients who received dexlansoprazole MR 60 mg and 90 mg,

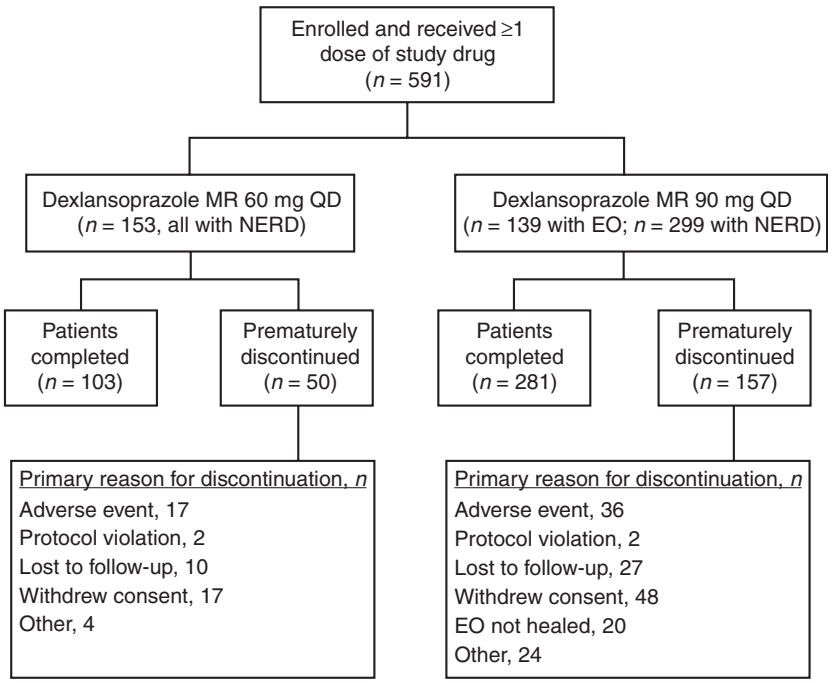

Figure 1 | Patient flow diagram. EO, erosive oesophagitis; QD, once daily.

respectively. Most of these AEs were mild or moderate in severity. Treatment-emergent AEs reported in ≥5% of patients in either treatment group are shown in Table 2a. Upper respiratory tract infection (URTI) was the most frequently reported treatment-emergent AE in both dose groups. All URTI events were assessed by the investigator as not related to study drug, except for three events (tonsillitis and upper respiratory tract infection reported by one patient on dexlansoprazole MR 60 mg and sinusitis reported by one patient on dexlansoprazole MR 90 mg). Only one of the URTIs led to premature discontinuation from the study. A majority of the patients with URTI had a history of seasonal allergies, rhinitis or sinusitis.

One or more treatment-related AEs were experienced by 25% and 20% of patients in the dexlansoprazole MR 60-mg and 90-mg treatment groups, respectively. The most frequently reported (≥2% of patients in either treatment group) treatment-related adverse events were similar between treatment groups (Table 2b).

Three patients died after completing or prematurely discontinuing the study, two dexlansoprazole MR 60 mg recipients (one each from acute promyelocytic leukaemia and acute respiratory failure) and one dexlansoprazole MR 90 mg recipient (postsurgical sepsis following fracture of right elbow). None of the deaths was considered by the investigator to be related to study drug. Twenty-seven additional patients (seven dexlansoprazole MR 60 mg; 20 dexlansoprazole 90 mg) experienced one or more nonfatal serious AEs during treatment. The investigators assessed a majority of these events to be unrelated to study drug. Seven of the serious AEs were considered to be possibly related to study drug in the 90-mg group (acute cholecystitis, cholelithiasis, anaphylactic reaction, febrile neutropenia, B-cell lymphoma of the neck, auditory hallucination and chest pain); there was no treatment-related serious AE in the 60-mg group. The percentages of patients who experienced one or more serious AEs were similar in the two treatment groups (6% and 5% of patients in the dexlansoprazole MR 60-mg and 90-mg treatment groups, respectively).

Premature discontinuation. Premature discontinuations were comparable between treatment groups [dexlansoprazole MR 60 mg, 50/153 (33%); 90 mg, 157/438 (36%)] (Figure 1). Fifty-nine patients experienced 103 AEs that led, at least in part, to premature discontinuation from the study; 53 (9%) of all patients reported AEs as their primary reason for premature discontinuation (Figure 1). Gastrointestinal disorders accounted for approximately half of the AEs that led to premature discontinuations in each treatment group (Table 3).

Clinical and laboratory evaluations. Small decreases were observed in mean haemoglobin, hematocrit and red blood cell count. These mean changes were neither dose-related nor considered to be clinically meaningful.

As expected with PPI therapy, serum gastrin concentrations increased at months 3, 6, 9 and 12 for both

Table 1 | Baseline demographics

Variable	Dexlansoprazole MR		
	60 mg QD (*n* = 153)	90 mg QD (*n* = 438)	All patients (*N* = 591)
Gender, *n* (%)			
Male	48 (31.4)	155 (35.4)	203 (34.3)
Female	105 (68.6)	283 (64.6)	388 (65.7)
Ethnicity, *n* (%)			
Hispanic or Latino	24 (15.7)	64 (14.6)	88 (14.9)
Not Hispanic or Latino	129 (84.3)	374 (85.4)	503 (85.1)
Race, *n* (%)			
American Indian or Alaskan Native	3 (2.0)	8 (1.8)	11 (1.9)
Asian	6 (3.9)	14 (3.2)	20 (3.4)
Black of African Heritage	18 (11.8)	44 (10.0)	62 (10.5)
White	126 (82.4)	366 (83.6)	492 (83.2)
Multiracial	0	6 (1.4)	6 (1.0)
Age, years			
Mean (s.d.)	47.8 (13.78)	49.0 (13.50)	48.7 (13.57)
<45, *n* (%)	65 (42.5)	158 (36.1)	223 (37.7)
45-<65, *n* (%)	71 (46.4)	237 (54.1)	308 (52.1)
≥65, *n* (%)	17 (11.1)	43 (9.8)	60 (10.2)
Body mass index, kg/m^2			
Mean (s.d.)	30.3 (7.08)	30.5 (6.98)	30.4 (7.00)
<25, *n* (%)	36 (23.5)	86 (19.6)	122 (20.6)
25-<30, *n* (%)	49 (32.0)	156 (35.6)	205 (34.7)
≥30, *n* (%)	66 (43.1)	192 (43.8)	258 (43.7)
Unknown, *n* (%)	2 (1.3)	4 (0.9)	6 (1.0)

QD, once daily.

dexlansoprazole MR treatment groups [baseline: 60 mg (mean ± s.d.), 80.0 ± 89.65 pg/mL; 90 mg, 75.9 ± 74.25 pg/mL; month 12: 60 mg, 239.9 ± 250.90 pg/mL; 90 mg, 193.2 ± 144.06 pg/mL; Figure 2]. Serum gastrin levels were generally higher in patients who tested positive for *H. pylori* at baseline compared with *H. pylori*–negative patients. Increases in serum gastrin concentrations were not dose related.

Baseline gastric biopsy results are summarised in Table 4. At baseline, 52% of patients receiving dexlansoprazole MR 60 mg had abnormal stomach biopsy results either in the antrum or fundus compared with 39% of patients receiving dexlansoprazole MR 90 mg. Chronic gastritis (in either antral or fundic tissue) was the most frequently observed abnormality and was seen in 47% and 35% of the patients in the dexlansoprazole MR 60 mg and 90 mg groups, respectively. Five to 6% of patients in each treatment group had intestinal metaplasia in either the antrum or fundus, and approximately 5% of patients in each treatment group had reactive gastropathy in either the antrum or fundus.

Of 589 patients with baseline gastric biopsy results, 412 patients had a final visit biopsy (dexlansoprazole MR 60 mg, *n* = 104; 90 mg, *n* = 308). At final visit, abnormal biopsy results were observed in 39% and 43% of dexlansoprazole MR 60 mg and 90 mg recipients, respectively. Most patients with normal gastric biopsies at baseline remained normal at final visit (Table 5).

Chronic gastritis was the most frequently observed post-treatment abnormality (dexlansoprazole MR 60 mg, 31%; 90 mg, 31%). Intestinal metaplasia was observed in 4% and 5% of patients receiving dexlansoprazole MR 60 and 90 mg, respectively at the final visit; all were negative for dysplasia. No patient had endocrine cell hyperplasia, adenocarcinoma, or lymphoma observed in gastric biopsies.

Table 2a | Most frequently reported (≥5% of patients in either treatment group) treatment-emergent adverse events

	Dexlansoprazole MR	
	60 mg QD (*n* = 153)	90 mg QD (*n* = 438)
MedDRA high level term	*n* (%)	*n* (%)
Total with ≥1 adverse event	109 (71)	284 (65)
Upper respiratory tract infections	22 (14)	59 (13)
Diarrhoea (excluding infective)	18 (12)	34 (8)
Gastrointestinal and abdominal pains (excluding oral and throat)	10 (7)	47 (11)
Nausea and vomiting symptoms	13 (8)	41 (9)
Headaches NEC	11 (7)	27 (6)
Musculoskeletal and connective tissue signs and symptoms NEC	11 (7)	23 (5)
Flatulence, bloating and distension	6 (4)	26 (6)

QD, once daily; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified.

Table 2b | Most frequently reported (≥2% of patients in either treatment group) treatment-related adverse events

	Dexlansoprazole MR	
	60 mg QD (*n* = 153)	90 mg QD (*n* = 438)
MedDRA high level term	*n* (%)	*n* (%)
Total with ≥1 adverse event	39 (25)	89 (20)
Diarrhoea (excluding infective)	8 (5)	14 (3)
Headaches NEC	7 (5)	14 (3)
Nausea and vomiting symptoms	7 (5)	19 (4)
Flatulence, bloating and distension	4 (3)	19 (4)
Gastric ulcers and perforation	4 (3)	1 (<1)
Gastrointestinal and abdominal pains (excluding oral and throat)	4 (3)	15 (3)
Gastrointestinal atonic and hypomotility NEC	4 (3)	13 (3)

QD, once daily; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified.

Quality of life and symptom severity assessments

Statistically significant improvements from baseline to each time point were observed within each treatment group in each PAGI-QOL subscale and in the total score (all $P < 0.05$). Patients receiving either dexlansoprazole MR dose experienced improved QOL from baseline to month 1, which was sustained through month 12. Patients in both treatment groups also experienced decreased symptom severity from baseline to month 1 for each subscale and total score. These improvements were statistically significant and were sustained through month 12 (all $P < 0.05$).

DISCUSSION

Non-erosive reflux disease is the most common presentation of GERD, yet there are few long-term studies evaluating PPIs in these patients.[4, 20] In this 12-month phase 3 study, the safety of dexlansoprazole MR, at doses similar to or exceeding those used in 4-week phase 3 studies was investigated. Dexlansoprazole MR 60 mg and 90 mg were well tolerated by the study population, 76% of whom were patients with NERD and 24% of whom were patients with endoscopically proven EO. Under current approval guidelines, dexlansoprazole MR 30 mg is recommended for up to 4 weeks for the treatment of symptomatic non-erosive

Table 3 | Adverse events occurring in ≥1% of patients that led to premature discontinuation

MedDRA system organ class	Dexlansoprazole MR 60 mg (*N* = 153)	Dexlansoprazole MR 90 mg (*N* = 438)	Dexlansoprazole MR Total (*N* = 591)
Gastrointestinal	7 (5%)	26 (6%)	33 (6%)
General disorders and administration site conditions	3 (2%)	3 (<1%)	6 (1%)
Nervous system	2 (1%)	6 (1%)	8 (1%)
Psychiatric	0	5 (1%)	5 (<1%)
Respiratory, thoracic and mediastinal	3 (2%)	3 (<1%)	6 (1%)
Skin and subcutaneous tissue	2 (1%)	0	2 (<1%)

MedDRA, Medical Dictionary for Regulatory Activities.

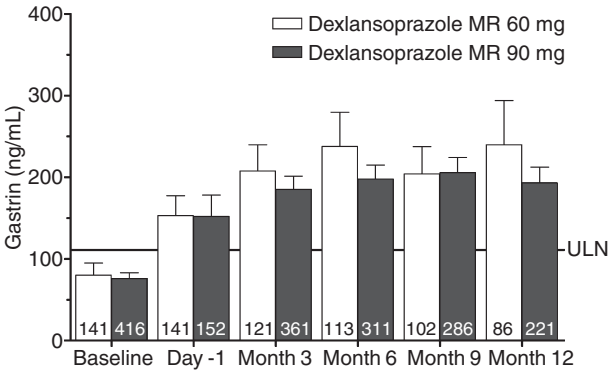

Figure 2 | Mean value of gastrin at each visit. Baseline is pre-treatment of the preceding NERD study for patients enrolled before the amendment and pre-treatment or screening for patients enrolled under the amendment. Day −1 is the last available observation from the previous NERD study and only applies to patients enrolled prior to the amendment. Error bars are 2 × s.e.m. The number of patients with available data is summarised inside each mean bar. Reference line is the upper limit of the normal range from central laboratory. ULN, upper limit of normal.

GERD, whereas the 60-mg dose has been approved for EO patients for up to 8 weeks for healing, after which patients step down to a 30-mg maintenance dose for up to 6 months.[21] Although the doses of dexlansoprazole MR administered in this study exceed the approved dosing administration for symptomatic non-erosive GERD, this safety analysis (AEs, serum gastrin and gastric biopsy findings) was consistent with that seen in previous studies of lansoprazole[5, 6, 22] as well as the 6-month EO maintenance trials and other shorter-term studies with 30-mg dose of dexlansoprazole MR.[23]

In this study, URTI was the most frequently reported treatment-emergent AEs in patients treated with dexlansoprazole MR 60 mg and 90 mg. Most of the URTI AEs were mild-to-moderate in severity and all but three were considered not to be related to treatment. A majority of patients reporting URTIs had a history of seasonal allergies, rhinitis, or sinusitis. Although some previous studies with PPIs have shown an association with lower respiratory tract infections,[24] this was not observed in this study.

The overall incidence of AEs was similar between the dexlansoprazole MR 60- and 90-mg treatment groups. There also was no dose-dependent trend observed in the number of patients who experienced serious AEs or who discontinued prematurely because of AEs. Overall premature discontinuation rates reported in other 12-month GERD studies also fell in a similar range (24% to 50%).[25–27]

Increased serum gastrin level is a physiological response to PPI treatment and is considered a marker of acid suppression.[28] The increases in serum gastrin reported in this study were consistent with other PPI studies[22, 29] and phase 3 studies of dexlansoprazole MR.[23] Serum gastrin concentrations have been shown to increase in the first 3 months of dexlansoprazole MR treatment, stabilise and remain relatively constant throughout the remainder of the treatment period; typically, serum gastrin levels return to baseline levels with cessation of treatment.[23] The observation that increases in serum gastrin concentrations were not dose related could be attributed to the fact that acid suppression with dexlansoprazole MR 90 mg was similar to that of 60 mg in previous phase 1 studies. Increased serum gastrin has not been associated with any safety issues in humans to date.[30]

In addition, no clinically concerning trend was identified in gastric biopsy results in this study. At baseline, 44% of dexlansoprazole 60-mg subjects and 56% of dexlansoprazole 90-mg subjects had normal biopsy at both antrum and fundus, whereas at the final visit, the corresponding percentages were 58% and 54%. Biopsy results

Table 4 | Baseline gastric biopsy results

	Dexlansoprazole MR					
	60 mg QD (*n* = 151) *n* (%)			90 mg QD (*n* = 438) *n* (%)		
Normal, abnormal, inadequate, or missing sample						
Diagnostic Category	Antrum	Fundus	Both†	Antrum	Fundus	Both†
Diagnostic subcategory	(*n* = 148)	(*n* = 149)	(*n* = 151)	(*n* = 413)	(*n* = 433)	(*n* = 438)
Samples inadequate for diagnosis	3	2	0‡	23	2	0‡
	Antrum	Fundus	Either§	Antrum	Fundus	Either§
	(*n* = 148)	(*n* = 149)	(*n* = 151)	(*n* = 413)	(*n* = 433)	(*n* = 438)
Number of subjects with ≥1 abnormal diagnosis	76 (51.4)	52 (34.9)	79 (52.3)	161 (39.0)*	107 (24.7)*	172 (39.3)*
Reactive gastropathy	6 (4.1)	1 (0.7)	7 (4.6)	17 (4.1)	4 (0.9)	21 (4.8)
Chronic gastritis	68 (45.9)	51 (34.2)	71 (47.0)	142 (34.4)*	104 (24.0)*	151 (34.5)*
Intestinal metaplasia	8 (5.4)	1 (0.7)	9 (6.0)	21 (5.1)	2 (0.5)	22 (5.0)
Negative for dysplasia	8 (5.4)	1 (0.7)	9 (6.0)	21 (5.1)	2 (0.5)	22 (5.0)
Adenocarcinoma	0	0	0	0	0	0
Neuroendocrine proliferation	0	0	0	0	0	0
Other abnormal¶	2 (1.4)	0	2 (1.3)	4 (1.0)	3 (0.7)	6 (1.4)
Missing one (antrum or fundus) tissue sample	0	0	NA	2	3	NA

NA, not applicable; QD, once daily.

* $P < 0.05$ between dexlansoprazole MR treatment groups.

† Patients must have both antrum and fundus showing normal stomach out of those with ≥1 subadequate or adequate tissue sample results to be counted.

‡ The number of patients with both inadequate fundus and inadequate antrum samples.

§ The number of patients with the result in antrum or fundus out of those with either an antrum or fundus subadequate or adequate result.

¶ Patients in this category had abnormalities such as parietal cell hypertrophy, eosinophils, focal active gastritis, foveola hyperplasia erosion, and ulcer.

were not summarised by baseline *H. pylori* status. Chronic gastritis was the most frequently observed abnormality before and after treatment. Final visit chronic gastritis was 31% for both treatment groups. These data are consistent with histology observed in long-term lansoprazole studies in which the aetiology of chronic gastritis is deemed unknown.[31, 32] The observation that chronic gastritis improved at the final visit is also consistent with the histology results from a 6-year lansoprazole study, irrespective of baseline *H. pylori* status.[32] The number of patients with post-treatment intestinal metaplasia was lower than that at the baseline biopsy, and neither endocrine cell hyperplasia nor carcinoid tumour was observed.

There are limitations that should be considered when evaluating this study. One such limitation is the open-label and uncontrolled study design that introduces an inherent bias due to the *a priori* knowledge that the participants are receiving active medication. In addition, the study design does not provide for the comparison of AEs to placebo or another comparator. However, as previously mentioned, the objective of the study was not a direct comparison to a control; rather, the objective was to assess safety during the development plan and comply with the ICH directive. One could also suggest that as a majority of patients participated in a previous dexlansoprazole MR study, this may contribute to selection bias as those who initially

Table 5 | Gastric biopsy results at final visit compared with baseline (all patients with final visit gastric biopsy*)

Biopsy site				
		Final visit result, *n**,‡		
Treatment group	Baseline result, *n*†,‡	Normal	Intestinal metaplasia	Others§
Antrum				
Dexlansoprazole MR 60 mg QD	Normal, 50	39	1	10
	Intestinal metaplasia, 5	2	2	1
	Others§, 47	20	1	26
Dexlansoprazole MR 90 mg QD	Normal, 175	114	4	57
	Intestinal metaplasia, 15	3	3	9
	Others§, 107	55	6	46
Fundus				
Dexlansoprazole MR 60 mg QD	Normal, 63	55	0	8
	Intestinal metaplasia, 1	1	0	0
	Others§, 39	18	0	21
Dexlansoprazole MR 90 mg QD	Normal, 233	198	0	35
	Intestinal metaplasia, 0	0	0	0
	Others§, 73	35	1	37

QD, once daily.

* The number of patients was smaller than at baseline due to reasons including premature discontinuation, absence of a final biopsy, and a final visit >14 days postdose.

† Prior to the amendment, the baseline biopsy was performed before dosing in an earlier 4-week study for symptomatic non-erosive GERD. For patients enrolled under the amendment, the baseline biopsy was performed during initial screening.

‡ Each patient was counted only once per tissue type based on the worst diagnosis.

§ Chronic gastritis or other abnormalities to include such as reactive gastropathy, adenocarcinoma (no reports), neuroendocrine proliferation, rule out mucosa-associated lymphoid tissue lymphoma or unknown (baseline assessment was not available), parietal cell hypertrophy, eosinophils, focal active gastritis, foveola hyperplasia erosion, ulcer, fundic gland polyps.

incurred issues did not enrol in the study. Another limitation that may be of particular interest for clinical practice is that the results may not be extrapolated to a 30-mg dose of dexlansoprazole MR that is approved for short-term treatment of NERD and maintenance of healed EO[21] because it was not administered in this 12-month study. As previously mentioned, the current phase 3 study included 76% patients with NERD and 24% patients with EO and was designed to capture 12-month safety results for patients exposed to the highest doses administered in phase 3 studies. Nonetheless, the 30-mg dose has been used for up to 6 months and been shown to be safe and efficacious in prevention of relapse in patients with healed EO.[13] Therefore, despite the limitation of doses required for this study, the results remain generalisable from a safety perspective. The authors acknowledge that certain AEs that have been associated with PPI therapy may require a longer duration than 12 months to detect. Lastly, premature discontinuation for a variety of reasons resulted in a lack of complete final biopsy results for 30% of study participants. Although this percentage may appear high, it is consistent with overall completion rates in studies evaluating maintenance of EO healing with other PPIs.[5, 6, 25, 26, 29, 33–38]

CONCLUSIONS

Dexlansoprazole MR 60 mg and 90 mg administered QD for up to 12 months was generally well tolerated by patients with GERD, including those with EO, in this study. No clinically significant or unexpected finding was observed for any safety parameters evaluated.

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