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CLINICAL TRIAL

Clinical Trial: Dose-Finding Study of Linaprazan Glurate, A Novel Potassium-Competitive Acid Blocker, Versus Lansoprazole for the Treatment of Erosive Oesophagitis

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ABSTRACT

Background: Linaprazan glurate, a potassium-competitive acid blocker, is in development for the treatment of erosive oesophagitis and other acid-related diseases.

Aim: To evaluate the 4-week healing rate and safety of four linaprazan glurate dosing regimens in patients with erosive oesophagitis.

Methods: This double-blind, dose-finding study compared linaprazan glurate to lansoprazole. We included patients with endoscopically confirmed erosive oesophagitis (validated by a central review board) if they had Los Angeles (LA) grade C/D or LA grade A/B with partial response to at least 8 weeks of proton pump inhibitor therapy. Patients were randomised to 4 weeks of linaprazan glurate (25, 50, 75 or 100 mg twice daily) or lansoprazole (30 mg once daily), followed by 4 weeks of open-label lansoprazole.

Results: Of 248 patients randomised, central review confirmed erosive oesophagitis in 182 at screening endoscopy. Across all doses, linaprazan glurate achieved a 4-week healing rate of 71.1% in intention-to-treat (ITT) analysis and 80.9% in per protocol (PP) analysis. In comparison, lansoprazole achieved healing rates of 60.6% (ITT) and 59.1% (PPS). The best performing linaprazan glurate dosing group outperformed lansoprazole by 28% in patients with LA grade A/B with partial PPI response and by more than 50% in patients with LA grade C/D.

Conclusions: Linaprazan glurate demonstrated high 4-week healing rates compared to lansoprazole, with a good safety profile, supporting its further development.

Trial Registration: ClinicalTrials.gov: NCT05055128; EudraCT: 2020-003319-91

1 | Introduction

Gastro-oesophageal reflux disease (GORD) is a common chronic disorder, with an increasing global prevalence [1]. The highest prevalence is seen in North America and northern Europe, where weekly reflux symptoms are reported by 10% to 30% of the population [2]. A noticeable increase has also been observed in developing countries [3]. GERD is the result of the reflux of stomach contents into the oesophagus causing troublesome symptoms and/or mucosal injuries and long-term complications such as peptic stricture and Barrett's oesophagus, the latter being a risk factor for oesophageal adenocarcinoma [4].

According to the Rome consensus criteria, the presence of mucosal erosions at endoscopy divides GERD into erosive GERD and symptomatic non-erosive GERD. Erosive GERD accounts for approximately one-third to one-half of all chronic GERD cases [5, 6]. The LA classification system of erosive GERD, is the most widely used and validated scoring system to describe the endoscopic appearance of erosive GERD and grade its severity extending from grade A, characterised by small mucosal breaks (< 5 mm), to grade D, characterised by mucosal breaks that involve at least 75% of the oesophageal circumference [6].

The initial goals of management for erosive GERD are endoscopic healing of the erosions and resolution of GERD-related symptoms. Intragastric acid control is a robust predictor of erosive GERD healing. The duration of acid suppression, defined as a gastric pH > 4, achieved over a 24-h period correlates well with the rates of endoscopic healing and symptomatic remission in patients with erosive GERD [7]. Proton-pump inhibitors (PPIs) are currently used as the standard first-line treatment; however, a significant proportion of patients with GERD respond only partially to PPIs [8], possibly due to insufficient reduction in gastric acid secretion [9].

Patients with severe erosive oesophagitis (EO), grades C and D, experience more persistent and severe acid reflux, requiring more aggressive acid suppression to heal. Achieving a high level of gastric acid suppression is crucial for healing EO. This unmet medical need cannot be fully addressed by double dose PPIs [10].

A gastric pH above 4 is necessary for minimising acid exposure to the damaged oesophageal tissue and promoting effective healing. A recent mathematical model of the relationship between pH holding time and erosive oesophagitis healing rates, concludes that P-CABs provide the longest duration with intragastric pH > 4 and, accordingly, the highest healing rates of erosive oesophagitis [11].

P-CABs belong to a class of molecules that inhibit gastric H^+, K^+ -ATPase by K^+-competitive binding, that differentiates them from PPIs [9]. Recent clinical guidelines suggest that clinicians may use P-CABs in selected patients with documented acid-related reflux who fail therapy with twice-daily PPIs and also in patients with more severe EE (LA grade C/D) [10].

P-CABs function by reversibly binding to the proton pump [10]. Thus, the effectiveness of these drugs depends on the relative concentrations at the binding site of the proton pump; to maintain effective acid suppression, continuous exposure is required. To ensure high enough concentrations of the P-CAB at the binding site at all times during treatment, a twice daily (b.d.) dosing of P-CABs could lead to an improved acid control resulting in faster healing, especially in patients with more severe EE.

Linaprazan glurate (LG), is a glutaric acid prodrug of the active P-CAB linaprazan that showed non-inferiority to esomeprazole in two large phase II studies [12, 13]. Linaprazan glurate, a next generation P-CAB, shows improved pharmacokinetic properties compared to linaprazan, with a lower C_{max} and a longer residence time in plasma after oral administration, as demonstrated in the first-in-human study of LG [14].

A tablet formulation of linaprazan glurate has been developed for clinical study purposes. In the current study the tablet was dosed twice daily to ensure effective acid control over the entire 24-h period.

This was a phase 2, randomised, double-blind, active comparator-controlled, 5-arm parallel group, dose-finding study of LG (25, 50, 75 or 100 mg twice daily [b.d.]), with the approved dose of lansoprazole (30 mg once daily [q.d.]) for comparison of safety outcome, on 4-week endoscopic healing of erosive oesophagitis (EO). The study was powered for dose finding, in particular for achieving a sufficiently narrow confidence interval for the prediction of a dose giving 85% response. All statistical comparisons between treatment groups presented in this paper are descriptive in nature. They serve as an initial evaluation of efficacy, which will be confirmed in phase 3 studies. Week 4 was selected as the time point for evaluation of healing, since a shorter healing time, as compared to current standard regimen of 4–8 weeks, is expected from P-CABs and is considered more beneficial for patients.

2 | Methods

2.1 | Patients and Study Design

This was a multicentre, randomised, double-blind, active comparator-controlled, five-arm parallel group (planned 1:1:1:1:1), dose-finding study of LG, with lansoprazole for comparison of safety outcome, on four-week endoscopic healing of EE, with safety and tolerability as secondary endpoints (Figure 1). The study was conducted at 36 sites in the European Union and the United States in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guideline for Good Clinical Practice, and applicable local regulatory requirements. The study was approved by the ethics committee of each study site. Written informed consent was obtained from all patients before the initiation of any study procedure. The study was registered at ClinicalTrials.gov (NCT05055128), and at EudraCT (2020-003319-91).

The study consisted of a screening period in which upper endoscopy was performed, with eligible patients being randomised to a double-blind treatment period of 4 weeks, after which upper endoscopy was planned to assess the primary endpoint, followed by a subsequent open-label lansoprazole treatment period for all patients to ensure a standardised 4 week safety follow-up after the primary endpoint assessment. Endoscopic findings in the

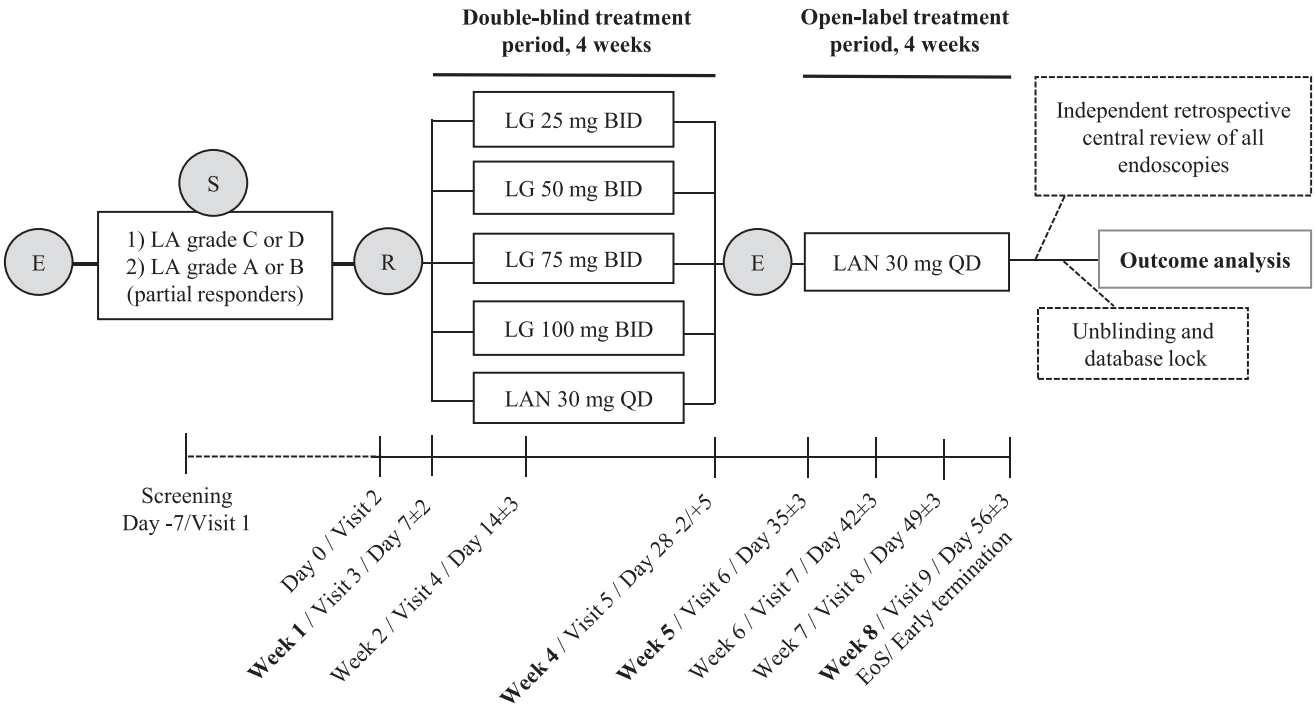

FIGURE 1 | Study design. b.d., twice daily; E, endoscopy; EoS, end of study; LA grade, Los Angeles classification system grade; LAN, lansoprazole; LG, linaprazan glurate; q.d., once daily; R, randomisation; S, screening.

distal oesophagus were reported as LA grade A to D at baseline and as LA grade A to D or healed at follow up and documented as video recordings or still images. The patients were stratified by baseline LA grades A/B or C/D.

During the screening period, information on demographics, medical/surgical history, prior/concomitant medications, drugs of abuse, vital signs, safety laboratory and symptom assessment by the investigator were collected for all patients. In addition, complete physical examination, 12-lead electrocardiogram (ECG) evaluation, serology testing for HIV, hepatitis B and C and *Helicobacter pylori*, pregnancy testing, adverse event (AE) reporting and upper endoscopy were performed in all patients. Many of these assessments, including all safety related information, were repeated at regular intervals throughout the study.

From visit 2 (randomisation) patients were to record their heartburn symptoms by completing the modified Reflux Symptom Questionnaire-electronic Diary (mRESQ-eD) [15] at home. Two items in the mRESQ-eD queries patients about the severity of heartburn, 'A burning feeling behind breastbone/in upper stomach' and 'Pain behind breastbone/in upper stomach'. Response options are on a 6-point ordinal scale (0—did not have; 5—severe). In this study, we used the recall period developed in the original RESQ-eD [16], so during the first 4 weeks, patients reported morning and evening heartburn, giving four data points (two items twice daily) and the highest of these was derived as the daily heartburn score.

Blood sampling was performed for pharmacokinetic analysis in all patients at Weeks 1, 2 and 4 for determination of linaprazan glurate and the active metabolite linaprazan in plasma. Samples were analysed by Lablytica Life Science AB, Uppsala, Sweden, by means of validated liquid chromatography–tandem mass spectrometry (LC MS/MS) method, with lower level of quantification 2 nmol/L for linaprazan glurate and 5 nmol/L for linaprazan.

2.2 | Central Review

In agreement with regulatory bodies, a change in study assessments was implemented after the study had been started, through an amendment to the protocol and the statistical analysis plan (SAP) that included a central review of all endoscopy data and interpretations, including the LA grades used to determine study eligibility and efficacy endpoint assessments. Thus, the baseline endoscopic LA classification for oesophagitis status as well as ultimate healing grades of oesophagitis (the primary endpoint of this study) were adjudicated by an independent panel. Endoscopic images/videos were reviewed by two independent experts, who were blinded with regards to patient, site and treatment timepoint in study (i.e., if the endoscopy was a screening or treatment evaluation at 4 weeks), with a third independent endoscopy expert performing a separate review for any case in which the two initial experts reported different LA grades. If the third expert's adjudicated grade agreed with one of the initial grades, this was recorded as the final adjudicated grade; for any case where all three independent endoscopy experts had differing opinions, an adjudication meeting was held to reach consensus and in all cases consensus was reached. In cases where imaging quality was missing (screening only) or quality did not allow for central review at screening or at Week 4, the investigators'

evaluations (local readings) replaced the missing central reading (see Data S1). The primary analyses were based on central review with imputations of local readings.

2.3 | Inclusion and Exclusion Criteria

Patients aged 18–75 years, and body mass index ≥ 18 and ≤ 40 kg/m^2 at screening, with endoscopically confirmed EE with either (i) LA grade C or D, or (ii) LA grade A or B together with a documented history of ≥ 8 weeks of PPI therapy plus at least partial symptom response, were eligible for inclusion.

The full inclusion and exclusion criteria can be found in 'Data S1'.

2.4 | Dose Rationale and Treatment

The lowest dose, 25 mg LG b.d., was chosen to achieve pH control comparable to or lower than that observed with lansoprazole 30 mg q.d. at steady state (data not shown). The highest dose, 100 mg LG b.d., was selected to maintain intragastric pH control for 85% of the time.

The patients were enrolled by the participating sites and randomised to receive LG 25, 50, 75 or 100 mg (b.d.), or lansoprazole 30 mg (q.d.), administered orally for 4 weeks (i.e., double-blind treatment period), followed by 4 weeks of subsequent treatment with lansoprazole 30 mg (q.d.) only (i.e., open-label treatment period). To blind treatment, each patient received two tablets (containing LG or placebo) and one capsule (containing lansoprazole or placebo) in the morning, and 2 tablets (containing LG or placebo) in the evening. Study treatments were taken with 100 mL of noncarbonated water at least 30 min before food intake.

2.5 | Efficacy Assessments

The primary efficacy endpoint was endoscopic healing of EE after 4 weeks of double-blind treatment, with the objective of supporting dose selection. Endoscopic healing was defined as the absence of endoscopically confirmed mucosal breaks based on the central review. Patients with a missing endoscopy at Week 4 were imputed as non-healed in the primary analysis. The secondary efficacy objective was evaluation of the reflux related symptom pattern (e.g., heartburn), reported daily in the patient's diary during weeks 1–8. Pre-dose plasma concentrations of LG and linaprazan were measured just before the first and second dose administration at days 7, 14 and 28.

2.6 | Safety Assessments

Safety and tolerability assessments were based on AEs, recorded at each study visit using standard medical terminology and terms in the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0, clinical laboratory evaluation (including serum gastrin), vital sign measurement, resting 12-lead ECG and physical examination.

2.7 | Sample Size and Statistical Analysis

2.7.1 | Determination of Sample Size

The sample size calculations targeted dose finding, in particular to achieve a sufficiently narrow confidence interval for the prediction of a dose giving 85% response, based on the estimated healing proportions of the four LG dose levels. Simulations showed that 20 patients were needed in each LG treatment dose group, for the prediction to get a sufficiently narrow confidence interval. (more in-depth description available in Data S1). In order to enable dose prediction separately for patients with LA grades C/D, and those with endoscopically unhealed (LA grades A/B) after 8 weeks' history of standard PPI therapy, 40 patients per LG treatment group, each balanced between the two LA groups, were needed. Allowing a dropout rate of 16%, it was calculated that at least 240 patients should be enrolled to yield 200 evaluable patients (i.e., 160 patients randomised to LG—40 to each of the 4 LG doses—and 40 patients randomised to lansoprazole).

2.7.2 | Randomisation and Blinding

The randomisation schedule was balanced between treatment groups (1:1:1:1:1) and all patients were centrally randomised using an interactive voice response system (IVRS), in which each patient was assigned a unique number (randomisation number) encoding the patient's assignment to one of the five treatment groups. This was a double-blind study, and the allocation of treatments was not disclosed until the file had been declared clean and the database locked. All study medication was provided in blister packs according to the randomisation list through the IVRS.

The study was conducted at several sites, and the randomisation was not initially stratified by site. After 128 patients were randomised, a new randomisation scheme with stratification by site was put in place to ease the treatment supply on site. Randomisation was set as approximately 50% of patients with LA grade A or B and approximately 50% of patients with LA grade C or D.

2.7.3 | Statistical and Analytical Plans

All patients who were randomised and received at least one dose of study treatment were included in the safety analysis set. The ITT analysis set was defined as all patients that were classified as erosive GERD at screening by central review or by imputed local reading if missing. The per protocol set (PPS) was defined as all patients who were randomised and completed the study without a major protocol deviation.

The proportion (95% CI) of patients with healing at Week 4 (primary endpoint) was summarised descriptively for ITT and PPS by treatment group and in total, and stratified by baseline LA grade, including 95% Clopper Pearson CIs. Five parametric models—the E_{max}, Sigmoidal E_{max}, Logistic, Exponential and Linear models—were applied, and the best fitting significant model(s) was then selected for estimation of the 85% healing dose.

A post hoc statistical analysis was performed to assess superiority of LG healing rates in LA grade C/D patients compared to lansoprazole. Each LG dose was compared to lansoprazole using Fisher's exact test. *p* values were then combined into a harmonic mean, to give an overall comparison between the healing rates for LG and lansoprazole.

The treatment emergent adverse events (TEAEs) reported were coded in accordance with the MedDRA, system organ class (SOC) and descriptively summarised. The occurrence of individual TEAEs was summarised in accordance with SOC and preferred term (PT) by treatment group. TEAEs were also summarised by severity and relationship with the study treatment. TEAEs occurring in 2% or more of the total study population, or in two or more patients in any treatment group were summarised by SOC and PT. In addition, TEAEs leading to discontinuation of study treatment, and serious TEAEs, were summarised by treatment group.

3 | Results

3.1 | Patient Population

From August 2021 to July 2022, 248 patients were randomised to the double-blind treatment period, receiving at least one dose of either LG or lansoprazole (Week 1–4), and 231 patients continued to the open-label treatment period (Week 5–8) with lansoprazole (LAN) only (Figure 2). The last patient completed the study in September 2022.

Eleven of 248 patients (4.4%) had one visit each, that was affected by the COVID-19 pandemic. All visits but one were performed, six as telephone visits, three out of the stated visit window and one listed as otherwise affected, not specified. In one of these 11 patients, COVID-19 lead to termination of treatment and study participation at study day 10.

The retrospective central review of the screening endoscopies resulted in reclassification from EE to non-erosive GERD in 66 of the 248 randomised patients (26.6%); these were excluded from the primary efficacy endpoint evaluation, leaving 182 evaluable patients with confirmed EE for the intention-to-treat (ITT) analysis (Figure 3). The retrospective central review also resulted in patients being reclassified from the investigator assessed LA grade at baseline, changing the intended 50/50 proportion of LA grade A/B versus C/D to 64/36 in the ITT population. The reclassification of severity grade also resulted in 46 of the 115 patients with LA grade A/B included in the ITT analysis did not fulfil the inclusion criterion of being partial responders and were thus excluded from the PPS (Figure 4). In order to present data that reflects the intended partial responder group, the data presented for the LA grade A/B subgroup is based on the PPS analysis.

In the ITT, there were no notable differences in baseline demographic characteristics across the treatment groups, apart from a higher median age in the LG 100 mg treatment group, as well as an imbalance in the distribution of baseline LA grades (Table 1).

For PPS, the baseline demographic characteristics were consistent with those of the ITT group, except for a different distribution with regards to baseline LA grades across the treatment groups.

3.2 | Efficacy Analysis

3.2.1 | Healing at Week 4

Overall, in the ITT, 71.1% of patients receiving LG reached the primary endpoint of healing at Week 4 with healing rates of 73.7%, 75.7%, 78.0% and 54.5% in the LG25, LG50, LG75 and LG100 groups, respectively. The corresponding figure for healing rate of lansoprazole were 60.6%. (Table 2). Among the patients with LA grade C/D (66 patients; 36.3%), the proportions of healed patients at Week 4 were 58.3%, 72.7%, 85.0%, 50.0% and 33.3%, respectively (Figure 5a).

Post hoc statistical analysis showed higher healing rates for LA grade C/D EE in LG-treated compared to lansoprazole-treated patients ($p = 0.0373$). This analysis was not predefined and the result should be interpreted as exploratory. As indicated by the overlapping confidence intervals in Figure 5, the healing rates were not significantly different between single treatment groups.

In PPS, the proportions of patients who demonstrated healing at Week 4 were 81.0%, 77.8%, 90.5%, 75.0% and 59.1% in the LG25, LG50, LG75, LG100 and lansoprazole treatment groups, respectively (Table 2). For patients with LA grade C/D (53 patients; 47.7%), the proportions of healed patients at Week 4 were 70.0%, 80.0%, 93.3%, 50.0% and 37.5%, respectively (Figure 5b). For patients with LA grade A/B (58 patients; 52.3%), the corresponding proportions were 90.9%, 76.5%, 83.3%, 100.0% and 71.4%, respectively (Figure 5c).

Due to a higher healing rate than expected in the lower dose groups and lower healing rate in the highest dose group, additional exploratory analyses were performed to evaluate any influence from different demographic factors, including age, sex, smoking habits, *H. pylori* status, country and site. The demographic variations across dosing groups did not seem to have any major impact on the efficacy results or explain the lower-than-expected healing rate in the 100 mg dosing cohort (data not shown). As a consequence of these unexpected healing rates, the dose–response prediction models were not possible to fit according to plan and alternative post hoc investigations were pursued as follows.

3.2.2 | Improvement to LA Grade A or Better

This endpoint was only evaluated in the subset of patients with LA grade B, C or D at baseline. All PPS patients improved to at least LA grade A in cohorts receiving twice daily LG doses of 75 and 100 mg. Figure 6 shows the proportions of LG and LAN treated patients in the PPS who improved to at least LA Grade A.

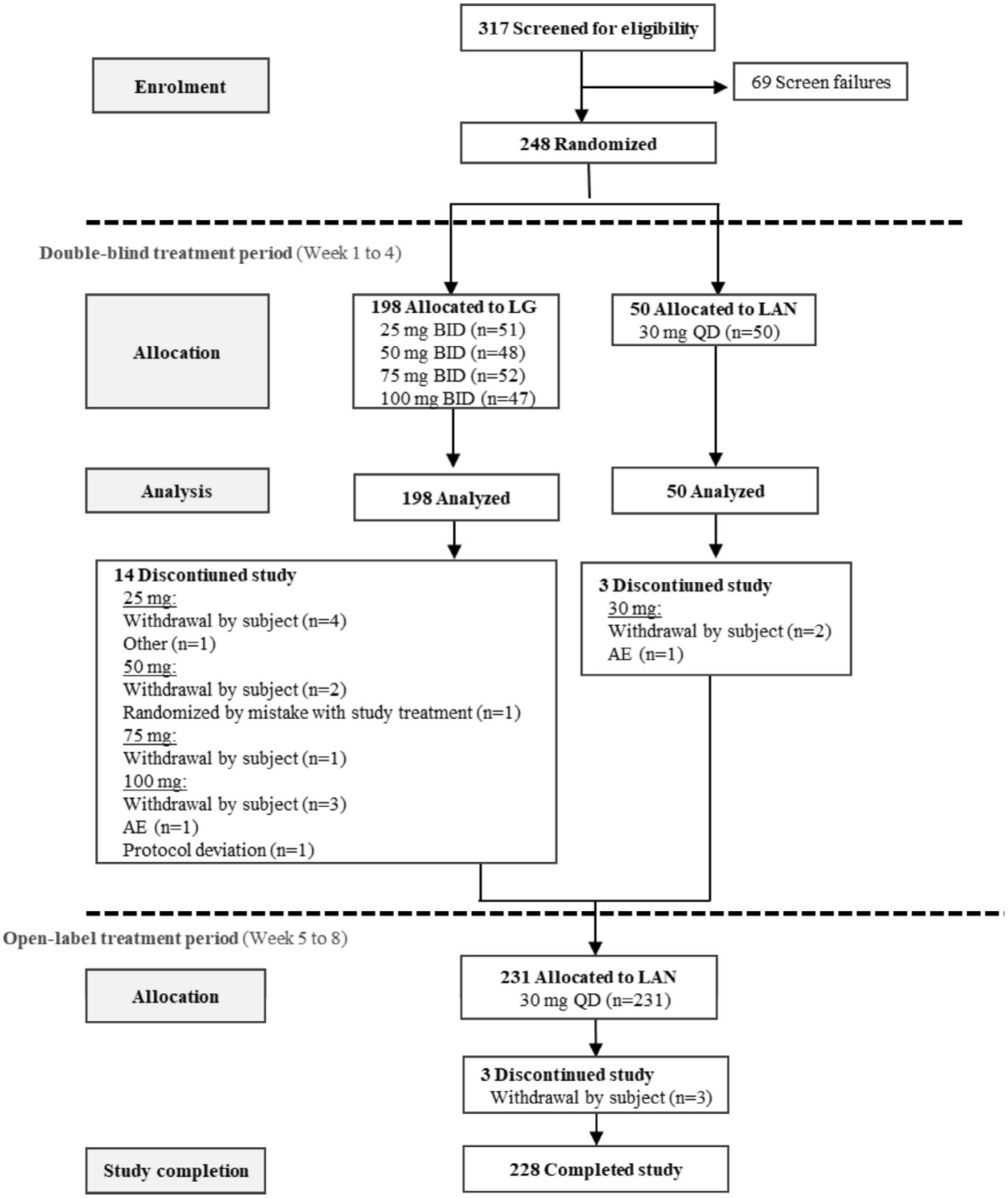

FIGURE 2 | Flow diagram showing progression of patients through the study. AE, adverse event; LAN, lansoprazole; LG, linaprazan glurate; *n*, number.

3.2.3 | Improvement to Lower Grade

LA grade improvement at 4 weeks was assessed for patients with LA grades C/D. A patient with LA grade D at baseline could have a maximum step improvement count of 4 (healed mucosa) and a minimum of 0 (continued grade D oesophagitis). A patient with LA grade C at baseline could have a maximum step improvement count of 3 (healed mucosa) and if the patient got worse the step improvement count would be −1. Mean step improvement counts, with 95% CIs based on the

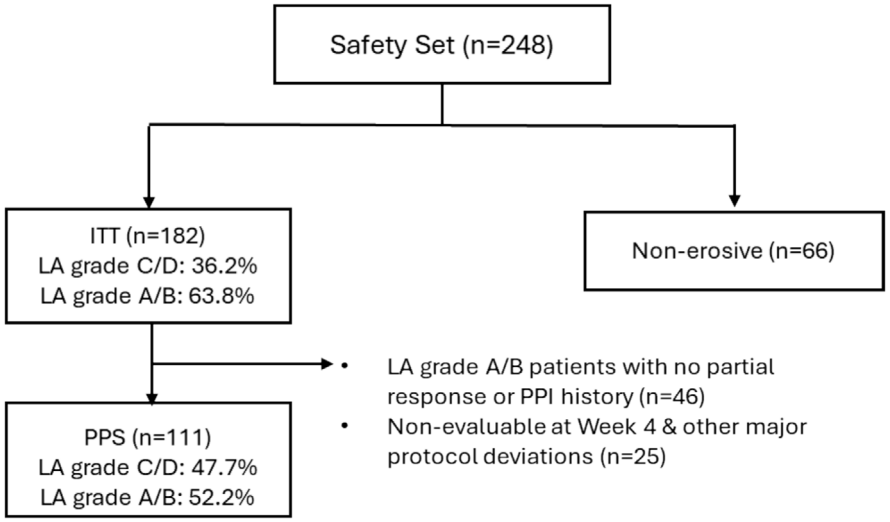

FIGURE 3 | Disposition of patients in the study. ITT, intention-to-treat; LA grade, Los Angeles classification system grade; *n*, Number; PPI, proton-pump inhibitor; PPS, per protocol set.

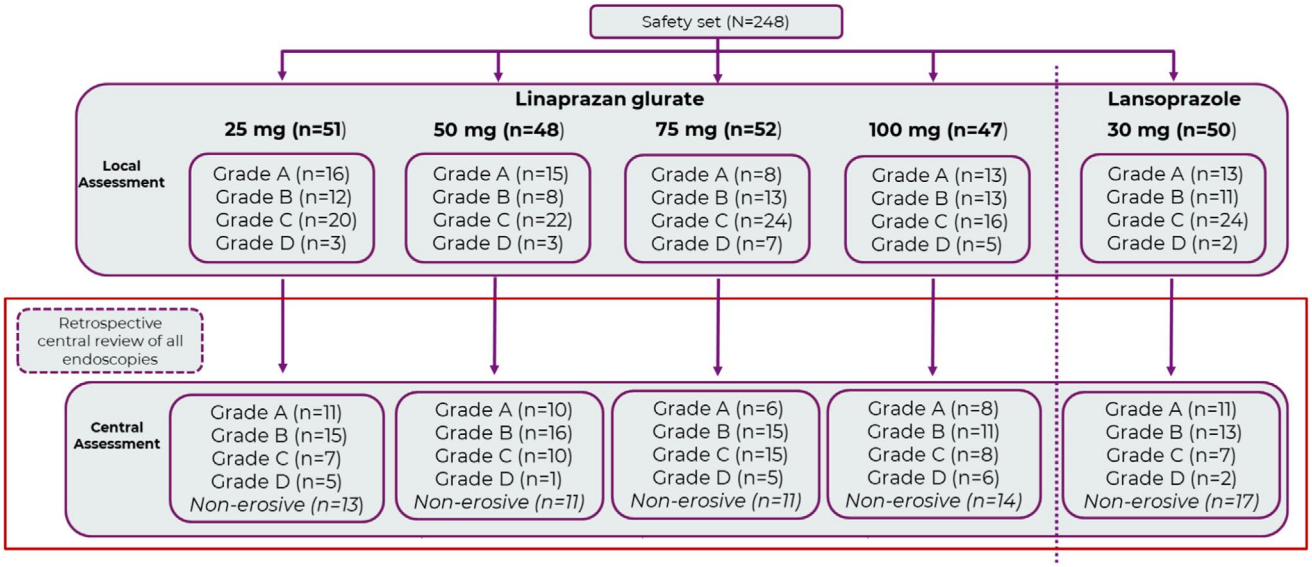

FIGURE 4 | Reclassification of LA grades as the outcome of the retrospective central review of screening endoscopies.

t-distribution, are shown in Figure 6 for LG- and lansoprazole-treated patients in PPS.

3.2.4 | Patient-Reported Heartburn

Mean severity of heartburn over the first week of treatment was mild, at most 1.75 on a scale from 0 (absent) to 5 (very severe). Both for morning and evening, patients receiving LG 75 mg reported the lowest severity grade and patients receiving lansoprazole reported the highest severity grade.

Irrespective of treatment, patients reported 30% heartburn-free days during the first week. From Week 2, descriptive data showed that the LG treatment groups reported less severe heartburn and more heartburn-free days (also when including mild symptoms), as compared to lansoprazole. The LG 75 mg dosing group reported the highest percentage of heartburn-free days at Week 2 (57.2%) and Week 3 (62.6%), while at Week 4, the LG 100 mg dosing group reported the highest percentage of heartburn-free days (65.2%).

Since data collection started at randomisation (i.e., the first day of treatment) symptom improvement compared to the pre-treatment period could not be evaluated.

3.2.5 | Linaprazan C_{trough} Levels Upon LG Treatment

From Week 1 and onward, steady state was reached for each treatment group, as indicated by stable C_{trough} levels of linaprazan. Mean C_{trough} linaprazan levels were approximately twofold higher upon a fourfold increase in LG dose with large variability in data (data not shown).

TABLE 1 | Demographic and other baseline characteristics (Safety Set).

	LG 25 mg	LG 50 mg	LG 75 mg	LG 100 mg	LAN 30 mg	Total
Number of patients	51	48	52	47	50	248
Age (years)	51.0 (20.0, 76.0)	40.0 (24.0, 74.0)	49.0 (19.0, 73.0)	59.0 (32.0, 75.0)	49.0 (25.0, 75.0)	49.0 (19.0, 76.0)
Gender						
Female	18 (35.3)	19 (39.6)	22 (42.3)	17 (36.2)	20 (40.0)	96 (38.7)
Male	33 (64.7)	29 (60.4)	30 (57.7)	30 (63.8)	30 (60.0)	152 (61.3)
Height (cm)	173.0 (155.0, 195.0)	171.5 (155.0, 195.0)	170.0 (153.0, 192.0)	174.0 (153.0, 192.0)	171.5 (152.0, 195.0)	172.0 (152.0, 195.0)
Weight (kg)	81.0 (48.0, 114.0)	86.0 (52.0, 140.0)	80.7 (47.0, 117.0)	86.5 (48.0, 136.0)	80.7 (50.0, 132.0)	82.9 (47.0, 140.0)
LA grade (retrospective central review)						
Non-erosive	13 (25.5)	11 (22.9)	11 (21.2)	14 (29.8)	17 (34.0)	66 (26.6)
Grade A	11 (21.6)	10 (20.8)	6 (11.5)	8 (17.0)	11 (22.0)	46 (18.5)
Grade B	15 (29.4)	16 (33.3)	15 (28.8)	11 (23.4)	13 (26.0)	70 (28.2)
Grade C	7 (13.7)	10 (20.8)	15 (28.8)	8 (17.0)	7 (14.0)	47 (19.0)
Grade D	5 (9.8)	1 (2.1)	5 (9.6)	6 (12.8)	2 (4.0)	19 (7.7)
Helicobacter pylori status						
Positive	16 (31.4)	26 (54.2)	24 (46.2)	20 (42.6)	13 (26.0)	99 (39.9)
Negative	35 (68.6)	22 (45.8)	26 (50.0)	26 (55.3)	34 (68.0)	143 (57.7)
Current smoker	9 (20.0)	10 (25.0)	10 (22.2)	8 (21.6)	8 (18.6)	45 (21.4)

Note: Data are presented as the number of patients with percentages in parentheses or median (min, max) unless stated otherwise. Baseline LA grades are presented as per retrospective central review.
Abbreviations: LA grade, Los Angeles classification system grade; LAN, lansoprazole; LG, linaprazan glurate.

TABLE 2 | Proportions of patients with oesophageal mucosal healing at Week 4, assessed by central review (ITT and PPS).

	LG 25 mg	LG 50 mg	LG 75 mg	LG 100 mg	LAN 30 mg
ITT	28/38 (73.7)	28/37 (75.7)	32/41 (78.0)	18/33 (54.5)	20/33 (60.6)
95% CI	56.9–86.6	58.8–88.2	62.4–89.4	36.4–71.9	42.1–77.1
PPS	17/21 (81.0)	21/27 (77.8)	19/21 (90.5)	15/20 (75.0)	13/22 (59.1)
95% CI	58.1–94.6	57.7–91.4	69.6–98.8	50.9–91.3	36.4–79.3

Note: Healing data are presented as number of patients with percentages in parentheses. The investigator reading was imputed as central review if the central review was missing. Clopper Pearson CI was used. If LA grading of GERD was neither A, B, C or D at Week 4, the patient was considered as having oesophageal mucosa healing. If Week 4 assessment was completely missing, the patent was considered as not healed (ITT specific).
Abbreviations: CI, confidence interval; GERD, gastrooesophageal reflux disease; ITT, intention-to-treat; LA grade, Los Angeles classification system grade; LAN, lansoprazole; LG, linaprazan glurate; PPS, per protocol set.

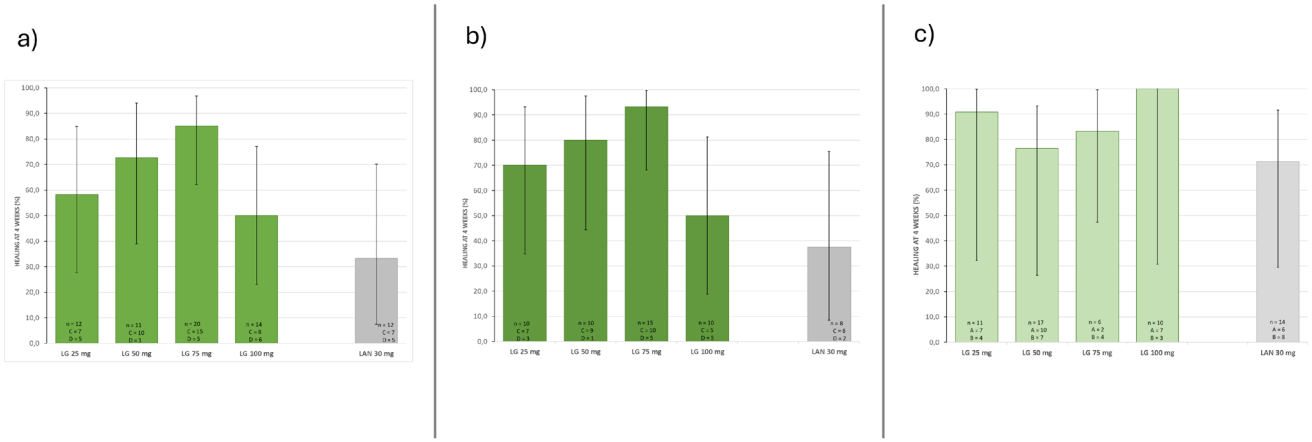

FIGURE 5 | Proportion of patients with healing at Week 4 by Baseline LA grade, as shown by endoscopy assessed by central review in (a) ITT LA grade C/D, (b) PPS LA grade C/D and (c) PPS LA grade A/B. The investigator reading was imputed as central review if the central review was missing. Clopper Pearson CI was used. If LA grading of GERD was neither A, B, C or D at Week 4, the patient was considered as having oesophageal mucosa healing. If Week 4 assessment was completely missing, the patient was considered as Not healed (ITT specific). Error bars represent 95% CI. CI, confidence interval; ITT, intention-to-treat; LA grade, Los Angeles classification system grade; LAN, lansoprazole; LG, linaprazan glurate; *n*, number; PPS, per protocol set.

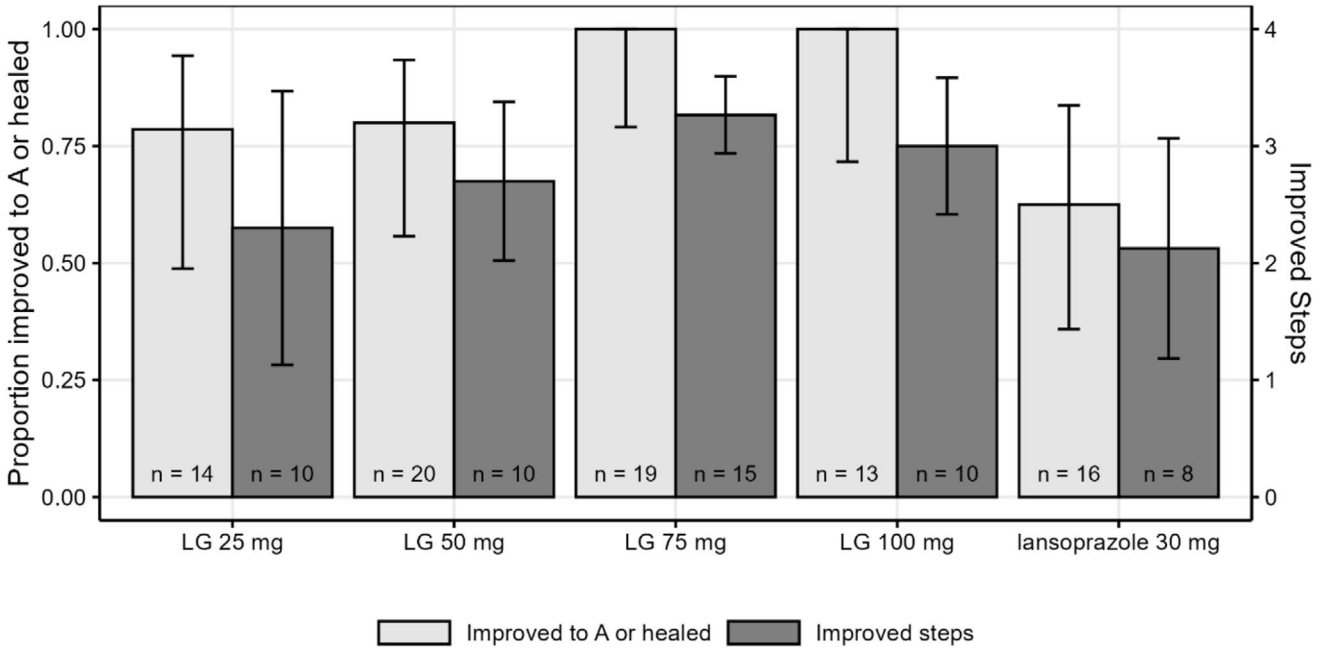

FIGURE 6 | Proportion improved to A or healed based on LA grades B–D PPS patients (95% Clopper Pearson CIs) and Improvement counts based on LA grades C and D PPS patients (95% CIs based on t-distribution). LG, linaprazan glurate; *n*, number.

3.2.6 | Dose Response Analysis

The response to the lowest dose level was higher than expected, hence the planned estimation strategy of a single therapeutic dose providing 85% healing was not possible to pursue, as none of the models supported an increasing dose response pattern over a flat horizontal noise line (none of the fitted models were statistically significant).

3.3 | Safety Analysis

Of the 248 treated patients, 57 (23.0%) experienced at least one TEAE (Table 3) during the full study period, including open label lansoprazole treatment in all dosing groups. Of these, 10 patients (4.0%) experienced 27 TEAEs (16 moderate and 9 mild events) that were considered by the investigator to be related to study treatment. TEAEs leading to study discontinuation were reported by two patients (0.8%). The incidence of TEAEs was similar among the treatment groups, with no dose-related increase in any event; the most common TEAEs were COVID-19 (4.0%) and headache (2.8%).

In the double-blind treatment period, eight patients (3.2%) experienced at least one TEAE that was considered by the investigator to be related to study treatment; TEAEs were reported for six patients who received LG (14 moderate and 5 mild events) and two who received lansoprazole (1 moderate and 2 mild events). There were no dose-related differences in the occurrence of any TEAE.

Serious TEAEs were reported in two patients (0.8%); one severe cholecystitis in the 25 mg LG dosing group and one moderate laryngospasm in the 75 mg LG dosing group. Both events were reported during the double-blind treatment period and were considered by the investigator as unlikely to be related to study treatment. No deaths or clinically significant liver function test abnormalities were reported during the study.

There was an increase in serum gastrin levels from Baseline to Week 4 following administration of LG or lansoprazole (Table 4). A similar pattern for gastrin levels was seen when subdividing by LA grade (data not shown).

No notable differences between the treatment groups were observed in clinical laboratory evaluation, vital signs, physical findings or other safety observations.

4 | Discussion

In patients with severe oesophagitis (LA grade C/D), high healing rates after 4–8 weeks of treatment have been difficult to achieve with PPIs [10]. A 4-week healing endpoint was selected with the purpose of maximising the dose-related differences in healing rates for the four different LG doses. The expectation was that lower doses would produce healing rates similar to the active comparator, lansoprazole 30 mg q.d.

The b.d. dosing regimen of LG for 4 weeks was chosen to demonstrate the optimal effectiveness in healing of EE. While

TABLE 3 | Summary of treatment-emergent adverse events during the full study period, including 4 weeks open label treatment with lansoprazole in all dose groups (safety analysis set).

	LG				LAN 30 mg	
	25 mg ($n=51$)	50 mg ($n=48$)	75 mg ($n=52$)	100 mg ($n=47$)	($n=50$)	Total ($n=248$)
Any TEAE	14 (27.5)	10 (20.8)	12 (23.1)	11 (23.4)	10 (20.0)	57 (23.0)
Treatment-related TEAEs	4 (7.8)	2 (4.2)	0	2 (4.3)	2 (4.0)	10 (4.0)
TEAEs leading to study discontinuation	1 (2.0)	0	0	1 (2.1)	0	2 (0.8)
Serious TEAEs	1 (2.0)	0	1 (1.9)	0	0	2 (0.8)
TEAEs reported by ≥2% of full safety set ($n=248$) or by ≥2 patients in any treatment group						
COVID-19	1 (2.0)	2 (4.2)	1 (1.9)	4 (8.5)	2 (4.0)	10 (4.0)
Headache	1 (2.0)	3 (6.3)	1 (1.9)	1 (2.1)	1 (2.0)	7 (2.8)
Constipation	2 (3.9)	1 (2.1)	2 (3.8)	0	0	5 (2.0)
Nausea	1 (2.0)	0	0	0	4 (8.0)	5 (2.0)
Regurgitation	0	2 (4.2)	0	2 (4.3)	0	4 (1.6)
Nasopharyngitis	1 (2.0)	2 (4.2)	0	1 (2.1)	0	4 (1.6)
Diarrhoea	2 (3.9)	0	1 (1.9)	0	0	3 (1.2)
Eructation	0	0	0	2 (4.3)	0	2 (0.8)

Note: Data are presented as number of patients with percentages in parenthesis, followed by number of events.
Abbreviations: COVID-19, Coronavirus disease 2019; LAN, lansoprazole; LG, linaprazan glurate; *n*, number; TEAE, treatment-emergent adverse event.

TABLE 4 | Serum gastrin concentrations at baseline and at Week 4 (safety analysis set).

	LG 25 mg (*N* = 51)	LG 50 mg (*N* = 48)	LG 75 mg (*N* = 52)	LG 100 mg (*N* = 47)	LAN 30 mg (*N* = 50)	Total (*N* = 248)
Baseline						
n	50	48	50	46	50	244
Median (Q1:Q3)	16.5 (11.0; 43.0)	17.0 (13.0; 33.0)	22.5 (14.0; 45.0)	33.0 (19.0; 53.0)	19.5 (14.0; 64.0)	21.0 (13.0; 45.0)
Visit 5						
n	45	45	51	41	45	227
Median (Q1:Q3)	78.0 (35.0; 195.0)	62.0 (36.0; 116.0)	100.0 (54.0; 164.0)	126.0 (80.0; 210.0)	58.0 (33.0; 85.0)	77.0 (41.0; 145.0)

Abbreviations: LAN, lansoprazole; LG, linaprazan glurate.

a q.d. dose of LG may provide sufficient pH control for a large subset of patients, the b.d. regimen is anticipated to result in faster and more consistent healing across an even broader spectrum of patients. The sustained and near-continuous acid suppression achieved with b.d. dosing is expected to create a more consistent and optimal environment for oesophageal healing, potentially leading to faster resolution of erosive lesions. In this study, promising 4-week healing rates were also observed in patients with more severe disease. The b.d. dosing in this study did not raise any compliance concerns. In the ITT population, overall study treatment compliance was reported at 96.9% during the initial 4 weeks treatment period. The b.d. concept used for this study needs to be evaluated in further clinical studies; in the current study this dosing strategy may however have contributed to higher-than-expected healing rates seen in the lower dosing groups. It is also not clear if this concept adds any value in longer term treatment, once healing has been achieved.

The mean healing rate for all patients treated with LG in the four dosing groups was 71% (ITT) and 81% (PPS). Due to the impact from the retrospective central review process, healing rates in the patients with LA grade A/B with partial response to PPI could only be evaluated in the PPS and the results from this analysis are also affected by removal of patients with major protocol deviations during the study. In this set however, the LG treated patients had a mean healing rate of 86.4% compared to lansoprazole 71.4% (PPS), with the best performing LG dose achieving 100% healing. These 4-week healing results from LG are promising, with a 28% difference in healing rates between the best performing LG dosing group and lansoprazole.

The corresponding mean healing rate in the more severe LA grade C/D patients were 68% (ITT) and 76% (PPS), with the best performing dose having a healing rate of 85% (ITT) and 93% (PPS). In comparison, in the LA grade C/D patients, treatment with lansoprazole resulted in 33.3% (ITT) and 37.5% (PPS) healing; a difference in absolute healing rates of more than 50% compared to the best performing LG dosing group. The sample size for LA grade C/D patients who received lansoprazole in this study was very small. Although, lansoprazole healing rates seen in our study was slightly lower, they were over all consistent with a meta-analysis showing a 4-week lansoprazole healing rate of 43% in patients with LA grade C/D [17].

The healing rates for LG did not translate into a statistically significant dose–response relationship, explained by the unexpected high healing rates in the two lowest doses of LG together with the lower healing rate in the 100 mg LG treatment group seen in the LA grade C/D patients. Additional post hoc analyses, including multiple subgroup evaluations, did not provide a definitive explanation for the poor healing response observed in the 100 mg LG dose group compared to other dose cohorts. However, the healing rates in the 100 mg LG cohort for the LA grade A/B partial responder patients was very high, so the efficacy results of the 100 mg dose are mixed. Also, the s-gastrin levels after 4 weeks of LG dosing does not indicate any lower acid controlling properties of this dose level compared to the other cohorts. Thus, it is hard to draw any firm conclusions on the results of the LG 100 mg dose group from these data.

While healing is the ultimate evaluation of treatment success, smaller levels of improvement are also relevant for the selection of an optimal dose for Phase 3 studies. Since the healing endpoint was binary, all non-healed patients were classified as treatment failures irrespective of how much they improved from treatment; however, a more granular analysis of the LA grade data to assess improvement from baseline [18], was also employed post hoc in this study. The degree of improvement for the LA grade C/D patients (PPS) in the present study indicated the best efficacy being reached in the LG 75 mg cohort.

The use of outcome measures such as symptom severity or symptom-free days has increased during the years with the purpose of assessing improvements in quality of life. The design of this study was not powered for formal statistical testing of symptoms, and any results should be interpreted with caution, however descriptive data from patients in the LG 75 and 100 mg cohorts showed the best symptom improvement, though the absolute differences between the dosing groups were small.

There was a limited pharmacokinetic difference between the dosing groups with only a minor tendency toward increased mean C_{trough} levels of linaprazan with increasing doses of LG, and a large variability of data, that might have contributed to the limited separation in healing and symptom control between doses. This was likely due to the tablet formulation used in this trial. A new improved formulation has been developed for future trials.

Overall, LG was shown to be safe and well-tolerated throughout the study period at all doses studied, with no dose-related increase in TEAEs, and the safety profile was similar to that of lansoprazole. The majority of reported TEAEs were mild to moderate in severity and unlikely to have been related to study treatment. The two serious TEAEs reported during the double-blind period were one occurrence of cholecystitis in the LG 25 mg treatment group and one occurrence of laryngospasm in the LG 75 mg treatment group; these were considered by the investigator and sponsor as unlikely to be related to study treatment. There were no deaths or significant changes in any clinical laboratory tests reported.

The strengths of this study lie in the centralised review of endoscopies performed at screening and at 4 weeks by a group of independent endoscopy experts. To determine the endoscopic outcome, at least two experts had to agree on the patient's LA grading.

The limitations of the study relate to the sample size and symptom registration strategy as well as the retrospective central review of the screening endoscopy results. (i) Unexpected high healing rate in the 25 mg LG dose group and low healing rates for LA grade C/D patients in the 100 mg LG dose group, made the dose response analysis challenging. Additionally, the retrospective nature of the central review led to (ii) a number of patients being reclassified from erosive oesophagitis to non-erosive GERD at study start, which decreased the number of patients in the analysis sets, (iii) a number of patients being reclassified to an LA severity grade other than the initial investigator's documentation, and (iv) an imbalance between treatment groups. Furthermore, (v) the lack of baseline data on patient-reported symptoms limited the possibility of analysing symptom data.

5 | Conclusions

High healing rates in erosive oesophagitis were seen after 4 weeks of twice-daily LG treatment, with a 28% difference between the best performing LG dosing group compared to lansoprazole in patients with EE of LA grade A or B with partial response to PPI and correspondingly more than 50% difference in patients with more severe EE of LA grade C or D. LG was safe and well-tolerated with no dose-related increase in TEAEs. The safety profile was similar to that of lansoprazole. Although the results should be interpreted with caution due to the small sample size and corresponding wide confidence intervals, the high 4-week healing rates support further development of LG for the treatment of EE.

Author Contributions

Prateek Sharma: investigation, writing – review and editing. **Michael Vaezi:** investigation, writing – review and editing. **Peter Unge:** methodology, conceptualization, investigation, writing – original draft, writing – review and editing, supervision. **Kjell Andersson:** conceptualization, writing – original draft, methodology, writing – review and editing. **Kajsa Larsson:** writing – original draft, writing – review and editing, investigation, supervision. **Ivan Popadiyn:** investigation, writing – review and editing. **Maria Rosenholm:** supervision, writing – review and editing, project administration, resources. **Andras Rosztóczy:** investigation, writing – review and editing. **Elham Yektaei:** writing – original draft, writing – review and editing. **David Armstrong:** investigation, writing – review and editing.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship

Guarantor of the article: Kajsa Larsson.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.