

CLINICAL TRIAL OPEN ACCESS

Clinical trial: The Effect on Intragastric pH and Pharmacokinetics of the PCAB Linaprazan Glurate in Healthy Subjects After Repeat-Dose Administration for up to 14 Days

Kajsa Larsson¹  | Kjell Andersson¹ | Gunilla Huledal¹ | Jouni Junnila²  | Kristofer Katkits Nilsson¹ | Elham Yektaei¹  | Matjaž Fležar^{3,4} | Peter Unge¹

¹Cinclus Pharma Holding AB (Publ), Stockholm, Sweden | ²EstiMates Oy, Turku, Finland | ³Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia | ⁴University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Correspondence: Kajsa Larsson (kajsa.larsson@cincluspharma.com)

Received: 15 April 2026 | **Revised:** 8 September 2026 | **Accepted:** 9 September 2026

Handling Editor: Colin Howden

ABSTRACT

Background: Linaprazan glurate (LG), a potassium-competitive acid blocker (PCAB), has shown up to 100% and 93% 4-week healing rates in a Phase 2 study in patients with LA grade A/B and C/D erosive oesophagitis, respectively.

Aim: To assess the Pharmacodynamic (PD) effect and Pharmacokinetics (PK) of multiple-dose administration of LG.

Methods: In the open, randomised, parallel-group, Phase 1 study, PD (intragastric pH) and PK were investigated after the first dose and 14 days of repeated administration of LG at dose levels 25, 50 and 75 mg q. d. and 25, 50 and 75 mg b.d.

Results: A total of 73 subjects were treated with LG during the study. After the first LG dose, pH > 4 was achieved within 60 and 10 min for the 50 mg b.d. and 75 mg b.d. dose groups, respectively. Dose-response was observed for HTRs at pH > 4, with > 90% for 50 mg b.d. and 75 mg b.d. on Day 1 and > 95% on Day 14. HTR was higher with 25 mg b.d. than with 50 mg q. d. both on Day 1 and Day 14. Mean AUC and mean C_{max} for linaprazan, the main LG metabolite, increased approximately in proportion to dose with no apparent accumulation.

Conclusions: LG provided a rapid increase in gastric pH after the first dose, with an HTR pH > 4 close to 100% for dose levels 50 mg b.d. and 75 mg b.d. Linaprazan AUC and C_{max} increased in proportion to LG dose. LG was safe and well tolerated at the studied dose levels.

1 | Introduction

Erosive oesophagitis (EE) is a common manifestation of GERD where acidic reflux causes mucosal erosions. While proton pump inhibitors (PPIs) are first-line treatment for healing EE, many patients, particularly those with severe LA grades C and D, respond only partially to PPIs [1]. Persistent EE carries risks of long-term complications, including peptic strictures and Barrett's oesophagus [2], necessitating more effective treatment options.

Gastric acid plays an important role in EE, and pharmacological reduction of acid secretion is the mainstay of treatment. Several studies show a correlation between the proportion of time with gastric pH > 4 and effective healing of EE [3–5] as well as a possible relationship with symptom control in patients with EE [6, 7]. Current guidelines suggest that clinicians may prescribe twice-daily PPIs in selected patients with documented acid-related reflux disease who fail therapy as well as in patients with more severe EE (LA grades C/D). Treatment with

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2026 Cinclus Pharma Holding AB. *Alimentary Pharmacology & Therapeutics* published by John Wiley & Sons Ltd.

Potassium-Competitive Acid Blockers (PCABs) is an alternative recommended for these patients [8].

PCABs belong to a class of molecules that inhibit gastric H^+ , K^+ -ATPase by K^+ -competitive binding, a unique mechanism that differentiates them from PPIs [9]. Thus, the effectiveness of PCABs depends on the actual concentrations of the respective PCAB at the binding site on the proton pump. A concentration above a certain level is likely needed to maintain an effective acid suppression over time.

PCABs have generally demonstrated a more rapid onset of acid suppression than PPIs [10]. Clinical pharmacology studies of marketed PCABs, including vonoprazan and tegoprazan, have demonstrated rapid, dose-dependent and sustained increases in intragastric pH following single and repeated administration [11–13]. These pharmacodynamic characteristics have translated into effective healing of EE, including in patients with more severe LA grade C/D disease [14, 15].

Linaprazan glurate (LG) is a PCAB under development and the glutaric acid prodrug of linaprazan, with improved pharmacokinetic (PK) properties compared with linaprazan. In the first-in-human study of LG, administration of LG resulted in lower linaprazan C_{max} compared with direct administration of linaprazan [16]. LG has been developed to provide clinically relevant efficacy in patients with all grades of acid-related EE, with a focus on patients with LA grades C or D, i.e., the hardest-to-treat population, representing the highest unmet medical need. In a Phase 2 study, the best-performing LG b.d. cohort receiving an LG base tablet demonstrated a per-protocol 4-week healing rate of 93% in EE patients with LA grades C/D and 100% in LA grade A/B, with a good safety profile. The incidence of treatment-emergent adverse events (TEAEs) was similar between all treatment groups, including the active comparator, and there was no dose-related increase seen in any adverse event [17].

In this article, we present the results of two studies. The first is a PD and PK study describing the intragastric pH and PK for 14 days of repeated q. d. and b.d. dosing of LG. The second is a relative bioavailability (BA) single-dose study comparing the LG HCl tablet also used in the PD and PK study with a previously developed tablet formulation including LG as the base and the effect of food intake on the BA of the LG HCl tablet.

2 | Material and Methods

2.1 | Study Designs

The PD and PK study and the relative BA study were conducted in Slovenia, from November 2022 to April 2023. Both studies were designed in accordance with ICH GCP E6 (R2), applicable local regulations and the 1996 Declaration of Helsinki. The studies were approved by an Independent Ethics Committee. All subjects gave their written informed consent. The studies are registered on clinicaltrials.gov (NCT05627518 and NCT05742984).

The PD and PK study was an open, randomised, parallel-group Phase 1 study in healthy subjects to investigate intragastric pH and PK after a single dose and 14 days of repeated

administration of LG HCl tablet. This study consisted of a screening visit (within 28 days prior to the start of treatment) followed by 6 visits and a follow-up visit via telephone 7 days (+/– 2 days) after the last dose (Visit 8). Visit 2 (Day –2 to 2), Visit 5 (Day 14 to 15), and Visit 7 (Day 16 to 17, 18 to 19, or 20 to 21) were residential stays at the clinical research unit (CRU), whereas subjects returned to the CRU for PK blood sampling on Visit 3 (Day 5), Visit 4 (Day 10), and Visit 6 (Day 16) (Figure 1a).

Eligible subjects were randomised into one of 6 dose groups to be administered for 14 days: 25 mg LG q. d., 50 mg LG q. d., 75 mg LG q. d., 25 mg LG b.d., 50 mg LG b.d. and 75 mg LG b.d. The first dose was administered on Day 1. In the once-daily dose groups, the first dose and subsequent doses were administered in the evening in a non-fasted state to optimise night-time pH control. In the twice-daily dose groups, the first dose and subsequent morning doses were administered following an overnight fast, and the second daily dose was administered in the evening in a non-fasted state. The intake of food was standardised on the days of intragastric pH measurements.

The subjects left the CRU on Day 2 and were instructed to continue taking LG according to their dosing schedules between Day 3 and Day 13. The subjects returned to the CRU on Day 14 for the last doses and remained at the CRU until Day 16 for PK sampling and removal of the pH catheter. After completion of the 14-day administration of LG, a period of 2, 4, or 6 days without drug dosing (i.e., drug holiday) followed, where 1/3 of the subjects in each dose group were randomised to each drug holiday period, followed by a re-challenge at the clinic with a single dose of LG on either Day 16, 18 or 20. All subjects were administered LG according to their dose group, followed by 24 h PK blood sampling and follow-up assessments prior to the subject leaving the clinic on Day 17, 19 or 21.

The relative BA study was a randomised, single-dose, crossover Phase 1 study in healthy subjects to investigate the relative bioavailability of linaprazan for the LG HCl tablet compared to the LG base tablet, and the effect of intake of a high-fat meal on the PK for the LG HCl tablet for a single dose of 100 mg LG. Subjects were screened within 28 days prior to the start of treatment, followed by 3 treatment visits separated by wash-out periods of a minimum of 5 days. Subjects remained in the clinic for at least 36 h after each dose, with a follow-up telephone contact 7 days (± 2 days) after the last dose (Figure 1b). Eligible subjects were randomised into one of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB and CBA), where A was 100 mg LG base in a fasting condition; B was 100 mg LG HCl in a fasting condition, and C was 100 mg LG HCl in a fed condition. Water was allowed *ad libitum* except for 1 h before dosing until 30 min after dosing. Fasting subjects were required to fast for at least 10 h pre-dose and 4 h post-dose. During the fed conditions, a high-fat, high-calorie breakfast was served 30 min prior to the dose.

2.2 | Participants

Healthy male and female subjects, 18–65 years of age (inclusive), with a body mass index (BMI) of 18.5–30.0 kg/m² (inclusive),

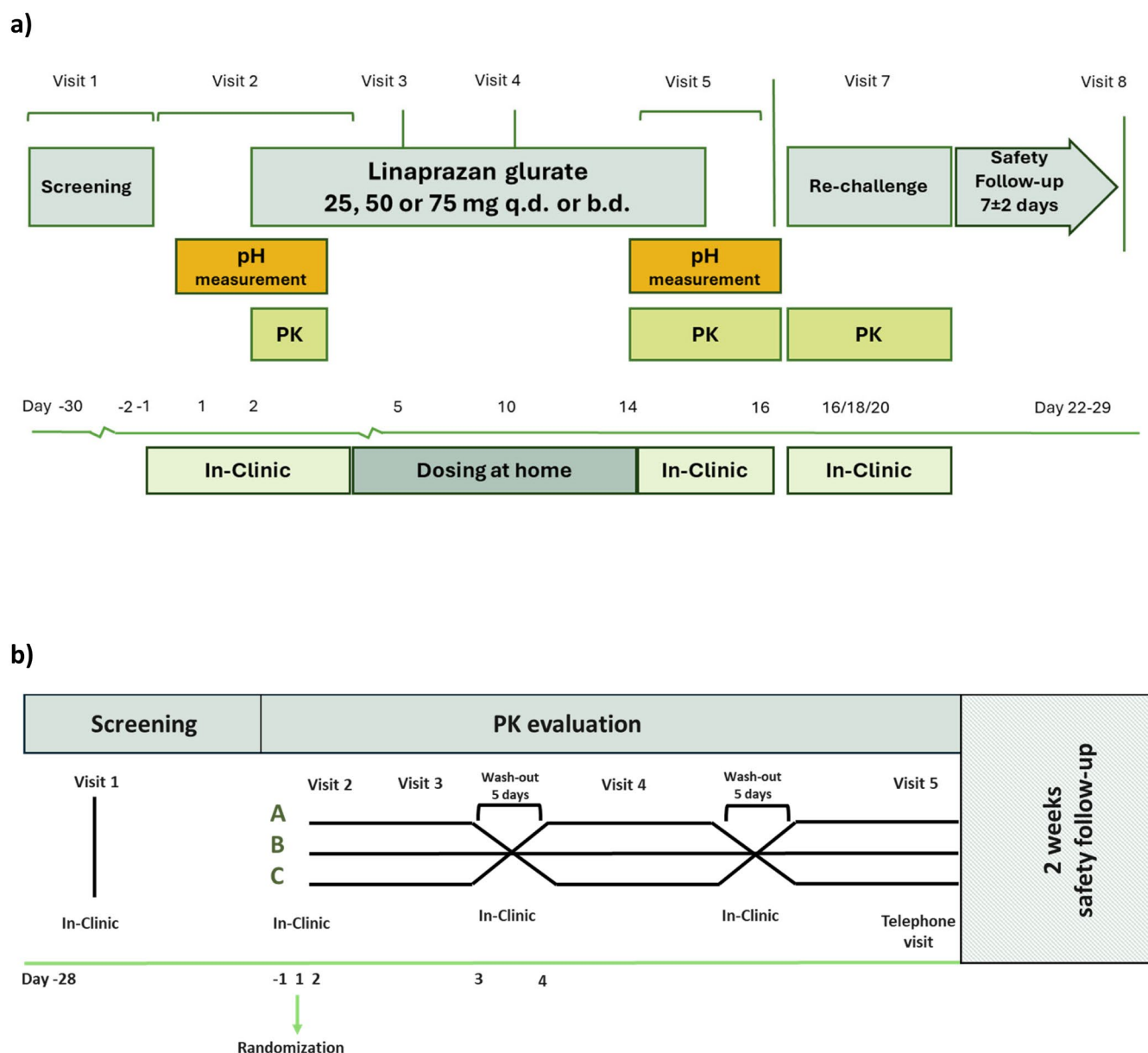


FIGURE 1 | Design of (a) PD and PK study and (b) Relative BA study. PK = Pharmacokinetics; q. d.: All doses were taken in the evening in a non-fasted state. b.d.: The 1st daily dose was taken fasted in the morning, and the 2nd daily dose was taken in the evening in a non-fasted state. The timeline is not to scale.

who were willing to comply with study procedures and who gave written informed consent were considered eligible for both studies. Subjects with a history or presence of any clinically significant disorders, or a history of GERD or clinically significant acid reflux, were to be excluded.

In the PD and PK study, subjects were also excluded if they had any of the following: Positive screening result for *Helicobacter pylori* (*H. pylori*); history of upper gastrointestinal or other surgery which may put the subject at risk, or influence the results or the subject's ability to participate in the study; sensitive gag reflex believed to interfere with pH-catheter application through the nose; or pain or other conditions interfering with pH-catheter application. Both male and female study subjects had to agree to use contraception with failure rates of less than 1% to prevent

pregnancy. No prescription or over-the-counter medications (including antacid medications) were permitted in the 14 days before the first study dose and until the end-of-study visit.

2.3 | Pharmacodynamic Measurements

Intragastric pH was assessed in the PD and PK study only. The measurements were performed for 48 h on two occasions, Day -1 to Day 2 and Day 14 to 16, with Day -1 providing the baseline data.

The electrode with two pH-measuring sensors, a distal and a proximal, was inserted via the nasogastric route, with the distal placed in the stomach and the proximal in the lower oesophagus.

The measurements were recorded using a Ditrigger pH-Z recorder from SynMed Medicinteknik AB, and the recordings were extracted using Reflux Software 6.1.1.11. Data points were collected every second.

2.4 | Pharmacokinetic Measurements

Venous blood samples were collected in heparinised tubes. Within 30 min of collection, blood samples were centrifuged at 1300 g for 10 min at room temperature and separated plasma samples were frozen in cryotubes at -70°C or lower until analysis.

Plasma samples for determination of plasma concentrations of LG and linaprazan were analysed by Lablytica Life Science AB, Uppsala, Sweden, by means of a validated liquid chromatography–tandem mass spectrometry (LC MS/MS) method. The lower limit of quantification (LLOQ) was 2 nmol/L for LG and 5 nmol/L for linaprazan.

In the PD and PK study, PK samples were collected pre-dose and 0.25, 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 14, 20 and 24 h after dose on Day 1, Day 14 and the day of completion of the drug holiday. PK samples were also collected 36 and 48 h after the Day 14 dose. In the b.d. dose groups, PK samples were also collected 12.25, 12.5, 13, 13.25, 13.5, 15, 16 and 18 h after the dose on Day 1, Day 14 and during the drug holiday. In addition, pre-dose samples were collected in the morning for b.d. dose groups and in the evening for q. d. dose groups on Day 5 and Day 10.

In the relative BA study, PK samples were collected for 72 h after dosing (pre-dose, 0.25, 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 14, 20, 24, 36, 48, 72 h).

PK parameters were calculated from the individual plasma concentration-time data of LG and linaprazan by non-compartmental analysis using the software Phoenix WinNonlin 8.3 or higher (Certara Inc., Princeton, NJ, United States). The area under the plasma concentration-time curves (AUCs) were calculated using the linear-log trapezoidal method with uniform weighting. Since LG is rapidly absorbed and converted to linaprazan, the main active metabolite, with high linaprazan plasma exposure rapidly reached after an oral LG dose, the PK data presented for the prodrug LG focus on PK parameters of linaprazan. Following the drug holiday, the accumulation ratio was calculated for the AUC within a dose interval (AUC_{tau}) as $\text{AUC}_{\text{tau}} \text{ last dose} / \text{AUC}_{\text{tau}} \text{ Day 1}$ and for C_{max} as $C_{\text{max}} \text{ last dose} / C_{\text{max}} \text{ Day 1}$.

2.5 | Safety Assessments

Subjects were monitored during visits, undergoing physical exams, vital sign checks, ECGs, and safety laboratory tests at specified timepoints. Adverse events (AEs) and concomitant medications were recorded from the first intake of study medication, with AEs coded using MedDRA Version 25.0. To oversee the safety of the subjects included in the PD study, bi-weekly internal safety review committee (iSRC) meetings, where all

aggregate safety data were reviewed, were added to the regularly scheduled safety assessments at site.

2.6 | Statistical Analysis

Safety analyses were based on the full analysis set (FAS), which consisted of all randomised subjects who received at least 1 dose of LG with at least 1 post-baseline assessment. PK analyses were based on the PK analysis set (PKAS), i.e., all subjects who received at least 1 dose of LG and provided an evaluable plasma concentration profile, with no AEs or protocol deviations judged to affect the PK analysis. The PD analyses in the PK and PD study were performed based on the PK/PD analysis set (PK/PDAS), which was a subset of the PKAS where subject data with major protocol deviations possibly impacting the pH data were excluded.

Holding Time Ratio (HTR), the percentage of time above a set pH value, was calculated based on 10-min pH medians. The primary evaluation was conducted for HTR pH > 4 on Day 1 and Days 14–15, supported by evaluations of HTR for pH > 5 and pH > 6. The intragastric pH data were presented as 10-min median values for comparability with other studies measuring pH. In both studies, continuous data were presented with common summary statistics by group. In addition, for the parameters AUC and C_{max} , the geometric mean and geometric coefficient of variation (CV%) were calculated. Categorical data were presented as counts and percentages.

The assessments of relative bioavailability were based upon 90% confidence intervals (CIs) for the ratios of the population geometric means (Treatment B [Test]/Treatment A [Reference]) for AUC_{inf} , AUC_{last} , and C_{max} , obtained from a Linear Fixed Effects model including sequence, treatment, treatment period and subject nested within sequence as fixed effects. The food effect evaluation was based upon similar ratios (Treatment C [Test, fed] / Treatment B [Test, fasted]) comparison obtained from the same model. The natural-log (ln) transformed values were used in the modelling and then back-transformed to the original scale (presented as geometric mean ratios and CIs).

The exposure-response relationship was explored by graphically exploring the association of HTR and $\text{AUC}_{0-24\text{h}}$ exposure using locally estimated scatterplot smoothing (LOESS) regression. Separate LOESS curves were fitted for the b.d. and q. d dosing groups, using the pooled data from Days 1 and 14.

All AEs (including SAEs, intensity, IMP relationship, and deaths) were summarised by subject and event counts for each SOC and PT. Safety ECGs, laboratory measurements, vital signs, and physical examination interpretations were reported descriptively by dose group and timepoint.

All descriptive summaries and statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC). Baseline was defined as the latest measurement prior to the first exposure to the IMP. No imputation of missing data was performed. Due to the nature of these Phase 1 studies, no multiplicity adjustments were used. The results of the conducted

statistical analyses were used as hypothesis-generating rather than confirmatory.

3 | Results

3.1 | Study Population

3.1.1 | PD and PK Study

A total of 75 subjects were randomised. Prior to dosing, one subject withdrew consent, and another withdrew due to an AE, resulting in 73 subjects receiving at least one dose of LG. During the dosing period, 2 subjects withdrew consent, and 2 subjects discontinued due to AEs, resulting in 69 subjects completing the study, reaching the prespecified target of between 54 and 72 participants evaluable for PK and PD. In total, 73 subjects were included in the FAS, and 72 in the PKAS. Since 5 of these were *H. pylori* positive, 67 subjects were included in the PK/PDAS. All subjects were White, and other baseline demographics were well-balanced in the different dose groups (Table 1).

3.1.2 | Relative BA Study

A total of 67 subjects were randomised and received at least one treatment, of which 49 completed the study, reaching the prespecified target of between 42 and 54 participants evaluable for PK. The main reasons for discontinuation were protocol violations, including 13 subjects who by mistake received 25 mg instead of 100 mg of the LG base tablet, adverse events ($n=3$), and withdrawal by subject ($n=3$). In total, 67 subjects were included in the FAS. In total, 54 subjects were included in the PKAS, which did not include subjects who received 25 mg LG. All subjects were White, with a mean age of 24.1 years and included 35 females and 32 males (Table 1).

3.2 | Pharmacodynamics

A gastric pH > 4 was reached at a median between 10 and 225 min after the first dose of LG Day 1, in a dose-dependent pattern (Table 2). The median time to pH > 4 for twice daily dosing (10 to 100 min post-dose), administered following an overnight fast, was shorter compared to the median time to pH > 4 (130 to 225 min post-dose) for the once daily doses, which were administered in the evening in a non-fasted state (Table 2).

A dose-response in the effect on gastric pH was also demonstrated in the full 24-h pH curves from Days 1 and 14 (Figure 2).

On the first day of dosing, the mean percentage of time with intragastric pH > 4 (pH > 4 HTR) ranged between 48.0% and 68.1% and the mean pH between 4.2 and 5.0 in the once daily dosing groups. The pH > 4 HTR was between 76.0% and 94.5%, and the mean pH was between 5.0 and 6.0 in the twice-daily dosing groups (Tables 2 and 3). On Day 14, the corresponding pH > 4 HTRs were 48.5% to 87.2% for once daily dosing and 76.9% to 99.0% for twice-daily dosing (Table 3). The pattern of higher HTR with increased dosing was also seen for HTR with pH > 5

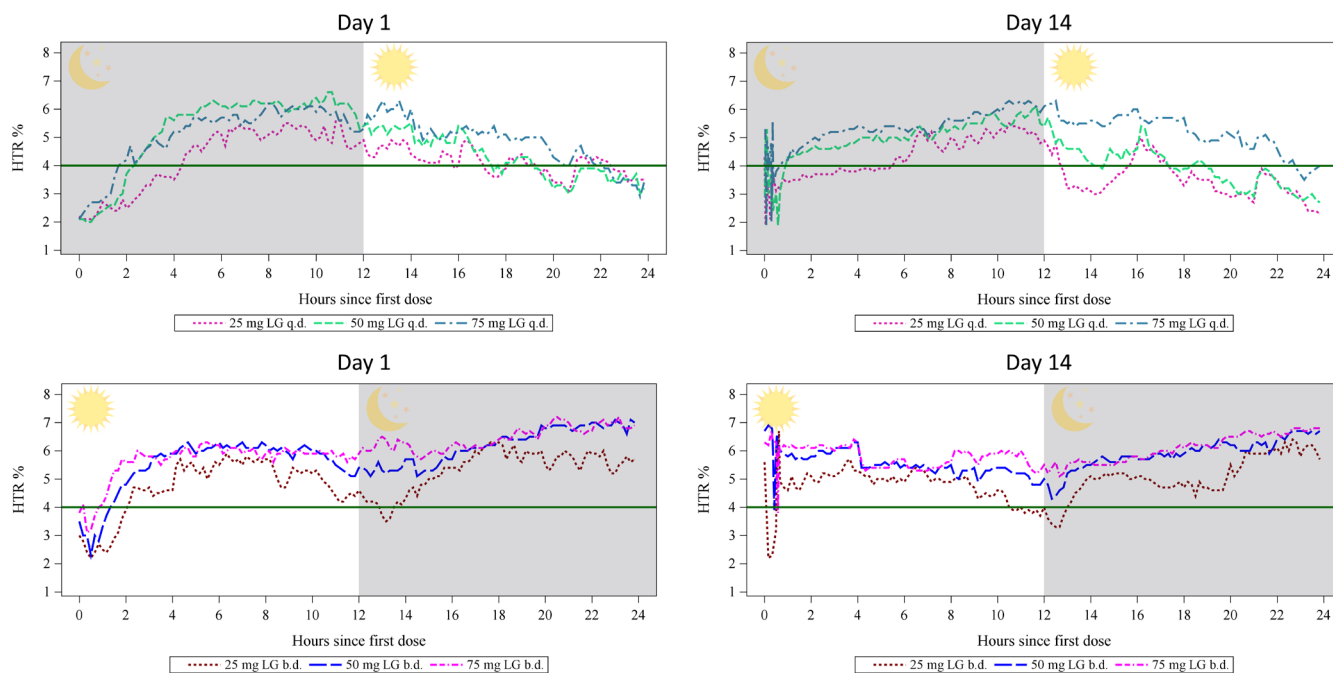
TABLE 1 | Baseline demographics in PD and PK study and Relative BA study by treatment group.

Category	Statistics	PD and PK Study						Relative BA Study	
		25 mg LG q.d. (N=12)	50 mg LG q.d. (N=13)	75 mg LG q.d. (N=13)	25 mg LG b.d. (N=12)	50 mg LG b.d. (N=11)	75 mg LG b.d. (N=12)	Total (N=73)	100 mg Single dose LG (N=67)
Age (years)	Mean (SD)	24.1 (8.26)	24.7 (8.35)	22.8 (2.45)	22.4 (1.88)	23.9 (3.48)	25.1 (8.25)	23.8 (6.05)	24.1 (6.07)
	Min, Max	19.0, 50.0	19.0, 51.0	18.0, 25.0	19.0, 25.0	19.0, 31.0	19.0, 49.0	18.0, 51.0	18.0, 48.0
Sex (F/M)	N	5/7	6/7	6/7	5/7	5/6	5/7	32/41	35/32
Weight (kg)	Mean (SD)	75.4 (12.27)	72.8 (8.82)	72.6 (11.41)	73.6 (9.33)	72.2 (14.97)	70.7 (8.15)	72.9 (10.69)	71.5 (11.22)
	Min, Max	54.1, 93.4	61.0, 91.5	54.0, 91.0	62.0, 90.0	54.0, 90.8	57.0, 82.6	54.0, 93.4	50.9, 102.1

TABLE 2 | Summary of Time to pH > 4 (minutes) and mean pH at Day 1 in PK and PD study.

Category	Statistics	25 mg LG q. d.	50 mg LG q. d.	75 mg LG q. d.	25 mg LG b.d.	50 mg LG b.d.	75 mg LG b.d.
Time to pH > 4 (min)	Median	225	135	130	100	60	10
	Min, Max	60, 650	70, 250	20, 980	10, 260	10, 210	10, 90
pH Day 1	Mean (SD)	4.2 (0.93)	4.8 (0.44)	5.0 (1.06)	5.0 (0.58)	5.8 (0.56)	6.0 (0.53)

Note: All doses were taken in the evening in a non-fasted state. The 1st daily dose was taken fasted in the morning, and the 2nd daily dose was taken in the evening in a non-fasted state.

**FIGURE 2** | Line plot of mean intragastric pH by treatment (LG 25 mg, 50 mg and 75 mg q. d. and LG 25 mg, 50 mg and 75 mg b.d.) on Day 1 and Day 14 in the PK and PD study. q. d.: All doses were taken in the evening in a non-fasted state. b.d.: The 1st daily dose was taken fasted in the morning, and the 2nd daily dose was taken in the evening in a non-fasted state.**TABLE 3** | HTR pH > 4 based on the mean of 10-minute medians of pH on Day 1 and Day 14.

Day	Statistics	LG 25 mg q. d. (N=12)	LG 50 mg q. d. (N=12)	LG 75 mg q. d. (N=13)	LG 25 mg b.d. (N=9)	LG 50 mg b.d. (N=11)	LG 75 mg b.d. (N=10)
pH > 4 HTR							
Day 1 (0-24h)	n	12	12	12	9	11	9
	Mean (SD)	48.0 (23.23)	64.6 (13.33)	68.1 (23.48)	76.0 (13.52)	87.4 (8.62)	94.5 (4.18)
Day 14 (0-24h)	n	12	12	11	9	11	8
	Mean (SD)	48.5 (30.62)	63.9 (20.09)	87.2 (11.44)	76.9 (20.13)	95.7 (5.55)	99.0 (1.54)

Note: All doses were taken in the evening in a non-fasted state.

Abbreviations: N = number of subjects; n = number of subjects with observations.

and pH > 6; however, with a higher pH cut-off, an increased benefit was seen with the highest dose group, 75 mg b.d., compared to the 50 mg b.d. dose group (data not shown).

When comparing the 50 mg daily dosage given either as 50 mg q. d. or 25 mg b.d., the b.d. dosing resulted in an approximately

10%–15% higher HTR with pH > 4 already from Day 1. Also, looking at individual pH data for all dosing groups on Day 14, 44% of subjects in the 25 mg b.d. had a pH > 4 for at least 80% of the 24h, with a corresponding value of 17% in the 50 mg q. d. group (Figure 3). All subjects in the 50 mg and 75 mg b.d. dose groups maintained a pH > 4 for at least 80% of the time on Day

14 (Figure 3); a higher variability between individuals was seen in the other dose groups.

Based on exploration of the relationship between HTR (%) and linaprazan exposure, an increase in linaprazan AUC_{0-24h} resulted in increased HTR (%) with a similar shape of the curves for linaprazan glurate q. d. and b.d. dosing (Figure 4). There was no clear relationship between C_{max} and HTR (%) (data not shown).

3.3 | Pharmacokinetics

3.3.1 | PD And PK Study

3.3.1.1 | Linaprazan. On Day 1, median linaprazan t_{max} was approximately 1.75h after the morning dose (fasted) in the b.d. dose groups and 3.00–5.00h after the evening dose (non-fasted) in the q. d. dose groups. Mean C_{max} and mean AUC were approximately 20% and 10% lower for the first daily dose for q. d. compared to b.d. dosing and approximately 30% and 15%

lower for the second daily b.d. dose as compared to the first daily b.d. dose (Figure 5 and Table 4).

Linaprazan C_{max} and AUC increased approximately in proportion to dose for both q. d. and b.d. dosing. There was no accumulation in linaprazan exposure upon 14 days of repeated administration for either q. d. or b.d. dosing, and steady-state plasma linaprazan concentrations were shown to be reached within 5 days based on similar mean pre-dose concentrations on Day 5 and Day 10 for all doses (Table 4). There was no apparent deviation from time-independent PK, even if exposure for the 75 mg q. d. and 75 mg b.d. dose groups on Day 14 was slightly lower (approximately 20%) than on Day 1 (Figure 5 and Table 4).

3.3.1.2 | Linaprazan Glurate. LG plasma exposure was substantially lower than linaprazan plasma exposure. LG C_{max} was rapidly reached, with a typical median t_{max} at 1 h; C_{max} was substantially lower than for linaprazan, and there was no accumulation of LG C_{max} upon repeated q. d. or b.d. administration (Table 4).

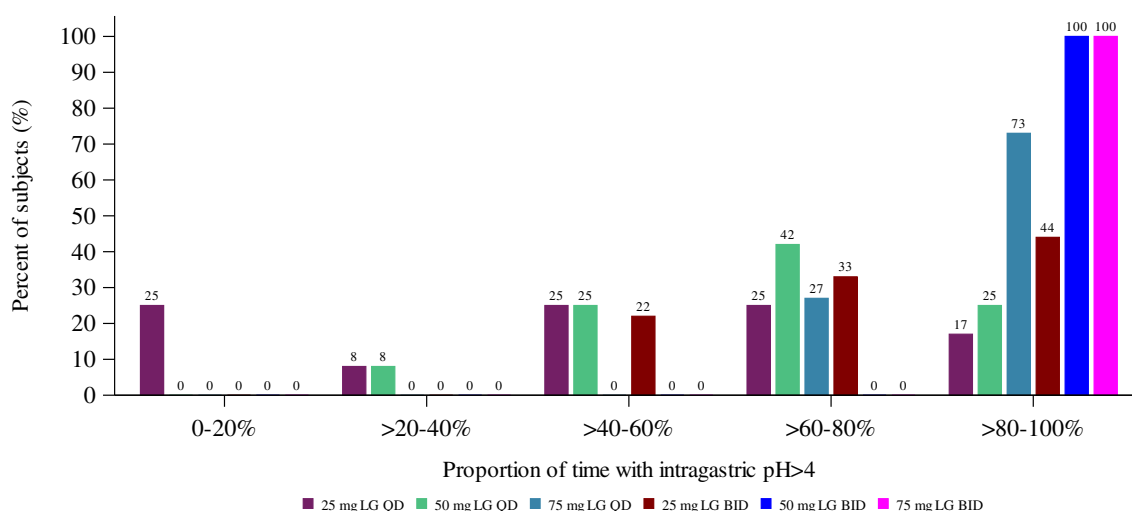


FIGURE 3 | Percent of subjects with proportion of time with intragastric pH > 4 on Day 14.

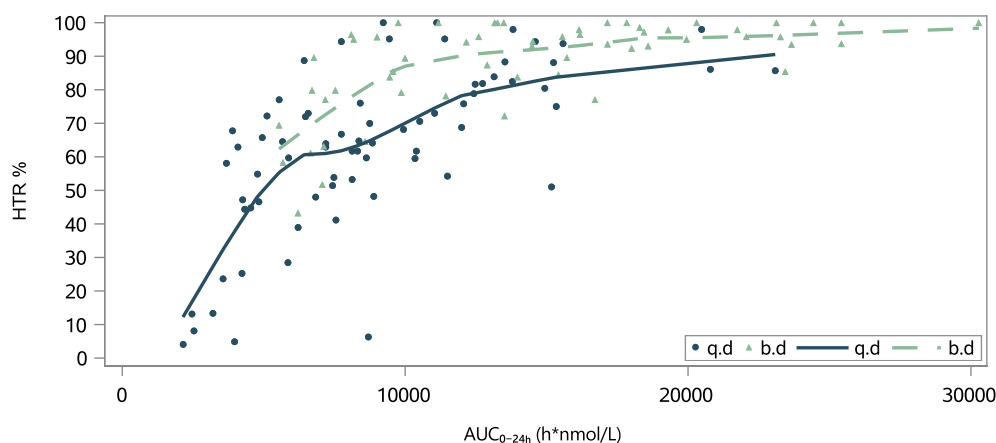


FIGURE 4 | HTR (%) versus linaprazan AUC_{0-24h} including locally estimated scatterplot smoothing (LOESS) regression curve based on Day 1 and Day 14 data.

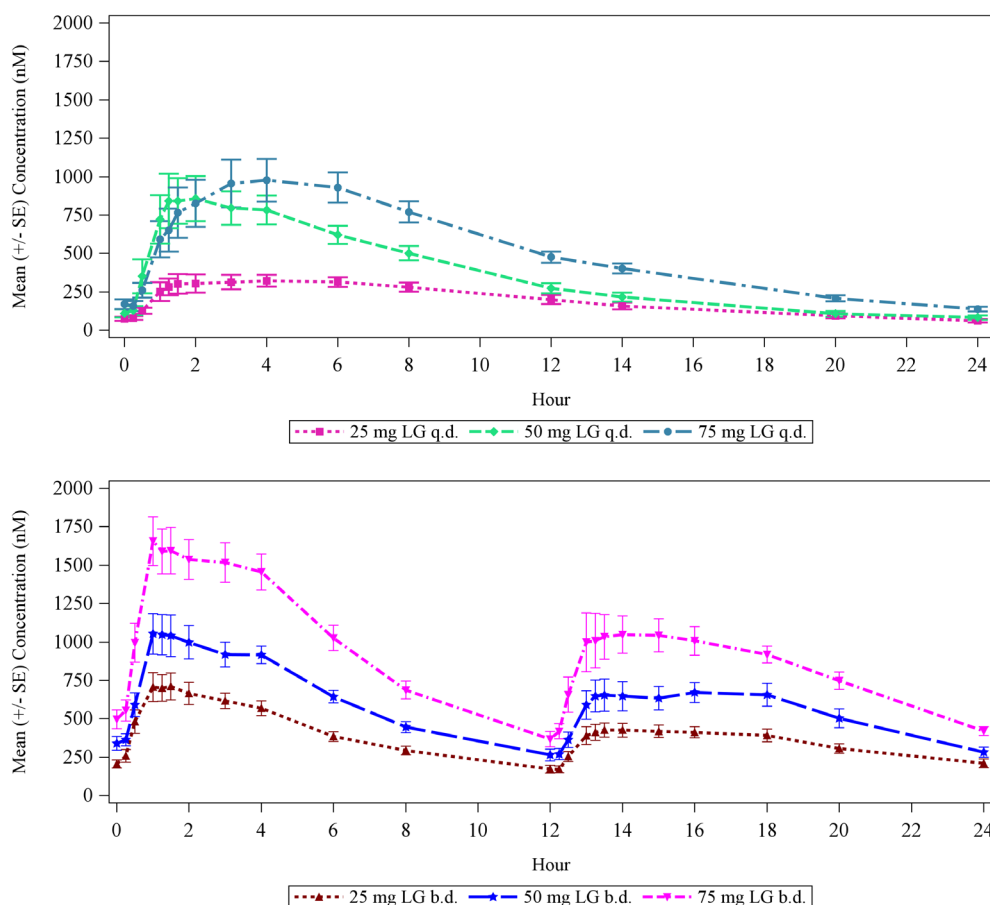


FIGURE 5 | Mean (+/-SE) linaprazan concentration over time in PD and PK study. q. d.: All doses were taken in the evening in a non-fasted state. b.d.: The 1st daily dose was taken fasted in the morning, and the 2nd daily dose was taken in the evening in a non-fasted state.

3.3.2 | Drug Holiday

Following the drug holiday, the median accumulation ratio versus Day 1 for linaprazan AUC and C_{max} and for LG AUC and C_{max} was close to one in most dose groups, with no apparent difference between 2-, 4- and 6-day drug holidays for administration of LG.

3.3.3 | Relative BA Study

The bioavailability of linaprazan from the LG HCl tablet was approximately 2-fold higher than from the LG base tablet based on the geometric LS mean ratio for AUC_{inf} , AUC_{last} and C_{max} (Suppl. Table 1 and Suppl. Figure 1). Median t_{max} for linaprazan was slightly later for the LG HCl tablet (3.00 h) compared to the LG base tablet (2.00 h). The bioavailability of LG from the LG HCl tablet was approximately 3-fold higher than from the LG base tablet based on the LS mean ratio for AUC_{inf} , AUC_{last} and C_{max} , with similar t_{max} for both formulations (Suppl. Table 1).

A high-fat, high-calorie meal reduced linaprazan mean AUC_{inf} and mean C_{max} by 24% and 55%, respectively, compared to fasted intake of the LG HCl tablet based on the geometric LS mean ratio (Suppl. Table 1 and Suppl. Figure 1). Linaprazan median t_{max} occurred later following intake of the LG HCl tablet in a

fed state (6.00 h) than in a fasting state (3.00 h). When taken in a fed state, LG mean AUC and mean LG C_{max} were approximately 50% and 75% lower compared to fasted intake of the LG HCl tablet (Suppl. Table 1).

3.4 | Safety

Both studies were performed in healthy subjects, where LG was safe and well tolerated in single and repeat dosing up to 14 days. There were no dose- or exposure-related increases seen in any adverse event. No significant changes in vitals, ECG, or mean lab results were observed in the studies (Table 5).

3.4.1 | PD And PK Study

During the study, 39 subjects (53.4%) experienced 87 TEAEs, mostly mild (54 events) or moderate (32 events). Eight subjects (11.0%) had 12 gastrointestinal TEAEs possibly related to treatment, including four moderate cases. One SAE (concussion from syncope) occurred before dosing, and four subjects (5.5%) discontinued due to TEAEs. Nervous system disorders were the most common TEAEs (27 events), mainly headaches, and all were assessed as unlikely to be related to treatment.

TABLE 4 | Summary of linaprazan and linaprazan glurate PK parameters in the PD and PK study.

	C_{max} (nmol/L) Mean (SD)		t_{max} (h) Median (min-max)		AUC (nmol/L*h) Mean (SD)		C_{pre-dose} (nmol/L) Mean (SD)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 5	Day 10
Linaprazan								
LG 25 mg q. d.	527.2 (184.93)	404.8 (174.07)	5.00 (2.00–14.00)	4.00 (1.25–12.00)	5089 (1607.1)	4640 (1657.4)	81.1 (66.26)	75.4 (44.06)
LG 50 mg q. d.	1066.2 (209.97)	1002.0 (538.57)	3.00 (1.00–6.00)	3.03 (1.23–6.00)	9342 (2462.3)	8626 (3571.9)	104.2 (69.32)	109.4 (94.07)
LG 75 mg q. d.	1594.4 (585.52)	1044.9 (478.10)	3.50 (1.25–12.00)	3.99 (1.25–13.97)	14,614 (4601.9)	11,697 (4053.3)	192.3 (144.58)	170.1 (102.21)
LG 25 mg b.d.								
Dose 1	658.4 (212.10)	782.9 (264.00)	1.75 (1.25–6.00)	1.50 (1.00–8.03)	4081 (1351.9)	8898 (2247.9)	210.4 (118.56)	205.3 (91.58)
Dose 2	520.9 (126.38)	520.8 (144.57)	4.00 (2.00–2.47)	4.99 (1.00–6.00)	3947 (939.8)			
LG 50 mg b.d.								
Dose 1	1380.2 (303.28)	1148.6 (415.25)	1.50 (1.25–4.00)	1.50 (1.00–4.00)	8084 (1400.5)	13,852 (3174.1)	374.2 (251.95)	339.8 (149.25)
Dose 2	997.1 (363.66)	842.4 (270.40)	2.00 (1.25–11.92)	4.00 (1.00–8.00)	7107 (1917.8)			
LG 75 mg b.d.								
Dose 1	1942.0 (667.28)	1740.6 (468.20)	1.75 (0.98–6.00)	1.25 (0.85–4.00)	11,814 (3181.8)	21,366 (4323.8)	559.2 (322.49)	496.8 (192.06)
Dose 2	1283.9 (435.40)	1285.5 (443.70)	4.00 (1.50–8.08)	1.78 (0.98–8.02)	9532 (2118.1)			
Linaprazan glurate								
LG 25 mg q. d.	27.5 (21.28)	18.4 (18.78)	1.25 (0.50–3.00)	1.13 (0.50–4.00)				
LG 50 mg q. d.	62.2 (53.65)	126.3 (168.83)	1.5 (1.00–2.05)	1.00 (0.25–3.00)				
LG 75 mg q. d.	100.4 (64.58)	107.1 (292.90)	1.25 (0.50–2.00)	1.00 (0.50–12.35)				
LG 25 mg b.d.								
Dose 1	32.5 (19.70)	47.6 (46.28)	0.50 (0.50–1.27)	0.50 (0.25–2.98)				
Dose 2	14.7 (10.29)	22.3 (13.41)	1.25 (0.50–6.02)	1.16 (0.50–4.00)				
LG 50 mg b.d.								
Dose 1	101.3 (49.18)	61.1 (43.23)	1.00 (0.50–1.25)	0.50 (0.50–1.00)				
Dose 2	46.6 (40.04)	41.5 (38.11)	1.00 (0.50–7.97)	1.00 (0.25–1.50)				

(Continues)

TABLE 4 | (Continued)

	$C_{\max}$ (nmol/L) Mean (SD)		$t_{\max}$ (h) Median (min-max)		AUC (nmol/L*h) Mean (SD)		$C_{\text{pre-dose}}$ (nmol/L) Mean (SD)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 5	Day 10
LG 75 mg b.d.								
Dose 1	148.2 (80.80)	151.7 (145.53)	0.50 (0.25–1.00)	0.50 (0.50–1.00)				
Dose 2	40.4 (32.42)	94.4 (140.22)	0.50 (0.50–4.05)	0.75 (0.25–2.05)				

Note: AUC Day 1: AUC_{inf} for q. d. and AUC_{0–12h} and AUC_{12–24h} for b.d. AUC Day 14: AUC_{0–24h} for q. d. and b.d.

3.4.2 | Relative BA Study

A total of 35 subjects (52.2%) experienced 55 TEAEs, mostly mild. Six moderate events occurred, including headaches, sciatica, Wolff-Parkinson-White syndrome, and a skin infection (also an SAE), all considered unlikely related to treatment, and three subjects withdrew due to TEAEs. The most common adverse events were infections (nasopharyngitis, rhinitis, skin infection).

4 | Discussion

This paper reports on PD (intra-gastric pH) and PK properties of LG, a new PCAB in development, together with its short-term safety outcomes following multiple-dose administration for 14 days in healthy subjects. The PK of the LG tablet (LG as an HCl salt) used in this PD and PK study was compared to the initial LG tablet (LG as base), and the effect of food intake on the PK of the LG HCl tablet was also evaluated.

PCABs inhibit gastric acid secretion through reversible, potassium-competitive inhibition of the gastric H⁺, K⁺-ATPase. Unlike PPIs, their pharmacological activity does not depend on acid-mediated activation of the drug, and members of this class have generally demonstrated rapid onset and sustained suppression of gastric acid secretion [9, 10]. These pharmacological characteristics have been demonstrated particularly for vonoprazan and tegoprazan, for which substantial increases in intra-gastric pH have been observed from the first day of treatment in healthy-subject studies [11–13].

This study was not designed to compare LG with other PCABs; however, the gastric acid suppression observed with LG was consistent with these general pharmacodynamic characteristics of other PCABs.

LG produced a rapid and dose-related increase in pH > 4 HTR, reaching almost 90% in steady state for the highest q. d. dosing group and close to 100% in the highest b.d. dosing cohort, with a higher HTR at higher dose levels. Although these data are mostly descriptive, they indicate that there may be a maximum effect for the 25 mg q. d. and b.d. as well as the 50 mg q. d. dose groups already on Day 1, as there is no increase in pH > 4 HTR on Day 14. The difference in variability for the PD effect between individuals may contribute, as well as the increased time to reach pH > 4 in the once daily dosing groups, likely due to the subjects not having a full night-time fasting period

before the first dose. Notably, already on the first day of dosing, the HTR for pH > 4 reached approximately 90% and in steady state, > 95% in the two highest dosing groups (50 mg and 75 mg b.d.). Also, every individual in the 50 mg and 75 mg b.d. dosing cohorts had a pH > 4 for > 80–100% of the time during Day 14 and thus, the lowest responders still demonstrated gastric acid control in these dosing cohorts. Consistent with the exposure-dependent pharmacology of PCABs, pH > 4 HTR was related to linaprazan exposure (AUC_{0–24h}), without a clear difference in the exposure–response relationship between q. d. and b.d. administration.

Exposure-dependent increases in acid suppression have also been reported for other PCABs, for which increasing dose or systemic exposure is associated with greater and more sustained elevation of intra-gastric pH [11, 13].

The rapid onset and sustained acid suppression observed with LG are broadly consistent with findings reported for other PCABs. For example, multiple-dose studies of vonoprazan in healthy subjects have demonstrated dose-dependent acid suppression and 24-h pH > 4 HTRs approaching 90% or higher at the upper investigated doses, while tegoprazan has also demonstrated rapid increases in intra-gastric pH and sustained acid suppression following single and repeated administration [11–13]. These observations provide useful pharmacological context for the present findings; however, no conclusions regarding the relative potency or clinical efficacy of LG compared with vonoprazan, tegoprazan, or other PCABs can be drawn from these data. The LG HCl tablet provided an approximately 2-fold higher bioavailability with respect to linaprazan AUC and $C_{\max}$ compared to the LG base tablet for a single dose of 100 mg. Linaprazan exposure ($C_{\max}$ and AUC) increased in proportion to dose without any apparent accumulation upon once- and twice-daily dosing of 25 mg to 75 mg LG HCl tablet, with similar linaprazan exposure on Day 1 and Day 14. Based on these data, the LG HCl tablet will be used in future clinical studies. There was only a limited effect of intake of a high-fat meal on the PK with the LG HCl tablet with respect to linaprazan AUC (24% reduction), whereas $t_{\max}$ occurred later when taken in a fed condition (6 h compared to 3 h post-dose) and the effect on $C_{\max}$ was larger (55% reduction). The effect of food intake on linaprazan exposure was also reflected in the PK and PD study, where $C_{\max}$ was approximately 20%–30% lower when LG was administered in a non-fasted state in the evening compared to intake following an overnight fast.

TABLE 5 | Type of TEAEs in the PD and PK study and in the Relative BA study.

Summary of Adverse Events in PD and PK study (Full Analysis Set)									
Type of TEAE	25 mg LG q. d. (N = 12) n (%); f	50 mg LG q. d. (N = 13) n (%); f	75 mg LG q. d. (N = 13) n (%); f	25 mg LG b.d. (N = 12) n (%); f	50 mg LG b.d. (N = 11) n (%); f	75 mg LG b.d. (N = 12) n (%); f	Total (N = 73) n (%); f		
Total Number of TEAEs	6 (50.0); 12	8 (61.5); 21	6 (46.2); 10	7 (58.3); 13	6 (54.5); 11	6 (50.0); 20	39 (53.4); 87		
Any Drug-Related TEAEs	0; 0	3 (23.1); 6	1 (7.7); 2	1 (8.3); 1	2 (18.2); 2	1 (8.3); 1	8 (11.0); 12		
Severe TEAEs	0; 0	0; 0	0; 0	0; 0	0; 0	1 (8.3); 1	1 (1.4); 1		
Serious TEAEs	0; 0	0; 0	0; 0	0; 0	0; 0	1 (8.3); 1	1 (1.4); 1		
TEAEs leading to early termination	0; 0	1 (7.7); 1	1 (7.7); 2	0; 0	0; 0	2 (16.7); 2	4 (5.5); 5		

Summary of Adverse Events in Relative BA study (Full Analysis Set)									
Type of TEAE	1 × 25 mg LG base fasted (N = 13) n (%); f	4 × 25 mg LG base fasted (N = 51) n (%); f	1 × 100 mg LG HCl fasted (N = 53) n (%); f	1 × 100 mg LG HCl fed (N = 50) n (%); f	Total (N = 67) n (%); f				
Total Number of TEAEs	4 (30.8); 4	17 (33.3); 21	12 (22.6); 15	14 (28.0); 15	35 (52.2); 55				
Any Drug-Related TEAEs	0; 0	1 (2.0); 1	2 (3.8); 2	0; 0	3 (4.5); 3				
Severe (or worse) TEAEs	0; 0	0; 0	0; 0	0; 0	0; 0				
Serious TEAEs	0; 0	0; 0	1 (1.9); 1	0; 0	1 (1.5); 1				
TEAEs leading to early termination	1 (7.7); 1	0; 0	2 (3.8); 3	0; 0	3 (4.5); 4				

Limitations in the study design include administration of the evening doses of LG in a non-fasted state in the PD and PK study, resulting in slightly lower linaprazan exposure. However, the reduction in gastric acidity was still in line with the effect following morning doses of LG given in a fasted state, which indicates that food intake has minimal impact on the effect of LG on intragastric pH in healthy subjects. Recommendation on how LG should be given in relation to meals for optimal clinical outcome will, however, be based on future patient studies. Also, due to the limited number of individuals at each dose level and the descriptive nature of the study, exposure-response relationships need to be interpreted with caution.

In conclusion, in healthy subjects, LG provided a rapid onset of pH control in all dose groups and resulted in a gastric pH > 4 for close to 100% of the time at the highest dose groups. LG was safe and well tolerated for up to 14 days of dosing, and the PK was linear with no apparent accumulation of linaprazan exposure. The efficacy and safety of LG will be evaluated further in Phase 3 studies in patients with erosive oesophagitis.

Author Contributions

Kajsa Larsson: supervision, writing – review and editing, writing – original draft, validation. **Kjell Andersson:** writing – original draft, writing – review and editing. **Gunilla Huledal:** writing – original draft, writing – review and editing, validation, methodology, formal analysis. **Jouni Junnila:** formal analysis, writing – review and editing, methodology, data curation, visualization. **Kristofer Katkits Nilsson:** writing – review and editing, project administration. **Elham Yektaei:** writing – original draft, writing – review and editing, visualization, project administration. **Matjaž Fležar:** investigation, writing – review and editing. **Peter Unge:** conceptualization, writing – original draft, writing – review and editing.

Acknowledgements

We thank Andrej Kravos, CRS Klinične raziskave in storitve Ljubljana, Slovenia for being the Principal Investigator in the Relative bioavailability study, Alojz Šmid (University of Ljubljana, Ljubljana, Slovenia) for being the initial Principal Investigator in the PK and PD study and David Pekar (Lablytica Life Science, Sweden) for the bioanalytical analysis.

Funding

The authors have nothing to report.

Data Availability Statement

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

References

1. P. O. Katz, K. B. Dunbar, F. H. Schnoll-Sussman, K. B. Greer, R. Yadlapati, and S. J. Spechler, “ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease,” *American Journal of Gastroenterology* 117, no. 1 (2022): 27–56.
2. N. Vakil, S. V. van Zanten, P. Kahrilas, J. Dent, R. Jones, and the Global Consensus Group, “The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus,” *American Journal of Gastroenterology* 101, no. 8 (2006): 1900–1920.
3. N. J. Bell, D. Burget, C. W. Howden, J. Wilkinson, and R. H. Hunt, “Appropriate Acid Suppression for the Management of Gastro-Oesophageal Reflux Disease,” *Digestion* 51, no. Suppl 1 (1992): 59–67.

4. R. H. Hunt, “Importance of pH Control in the Management of GERD,” *Archives of Internal Medicine* 159, no. 7 (1999): 649–657, <https://doi.org/10.1001/archinte.159.7.649>.

5. C. W. Howden, C. Scarpignato, E. Leifke, et al., “Mathematical Model of the Relationship Between pH Holding Time and Erosive Esophagitis Healing Rates,” *CPT: Pharmacometrics & Systems Pharmacology* 14, no. 1 (2025): 28–41.

6. J. G. Hatlebakk, “Review Article: Gastric Acidity-Comparison of Esomeprazole With Other Proton Pump Inhibitors,” *Alimentary Pharmacology & Therapeutics* 17, no. Suppl 1 (2003): 10–15.

7. A. Gasiorowska, “The Role of pH in Symptomatic Relief and Effective Treatment of Gastroesophageal Reflux Disease,” *Przegląd Gastroenterologiczny* 12, no. 4 (2017): 244–249.

8. A. Patel, L. Laine, P. Moayyedi, and J. Wu, “AGA Clinical Practice Update on Integrating Potassium-Competitive Acid Blockers Into Clinical Practice: Expert Review,” *Gastroenterology* 167, no. 6 (2024): 1228–1238.

9. K. Andersson and E. Carlsson, “Potassium-Competitive Acid Blockade: A New Therapeutic Strategy in Acid-Related Diseases,” *Pharmacology & Therapeutics* 108, no. 3 (2005): 294–307.

10. C. Scarpignato and R. H. Hunt, “Potassium-Competitive Acid Blockers: Current Clinical Use and Future Developments,” *Current Gastroenterology Reports* 26, no. 11 (2024): 273–293.

11. H. Jenkins, Y. Sakurai, A. Nishimura, et al., “Randomised Clinical Trial: Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Repeated Doses of TAK-438 (Vonoprazan), a Novel Potassium-Competitive Acid Blocker, in Healthy Male Subjects,” *Alimentary Pharmacology & Therapeutics* 41, no. 7 (2015): 636–648.

12. L. Laine, P. Sharma, D. J. Mulford, et al., “Pharmacodynamics and Pharmacokinetics of the Potassium-Competitive Acid Blocker Vonoprazan and the Proton Pump Inhibitor Lansoprazole in US Subjects,” *American Journal of Gastroenterology* 117, no. 7 (2022): 1158–1161.

13. S. Han, H. Y. Choi, Y. H. Kim, et al., “Randomised Clinical Trial: Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Oral Doses of Tegoprazan (CJ-12420), a Novel Potassium-Competitive Acid Blocker, in Healthy Male Subjects,” *Alimentary Pharmacology & Therapeutics* 50, no. 7 (2019): 751–759.

14. L. Laine, K. DeVault, P. Katz, et al., “Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial,” *Gastroenterology* 164, no. 1 (2023): 61–71.

15. K. J. Lee, B. K. Son, G. H. Kim, et al., “Randomised Phase 3 Trial: Tegoprazan, a Novel Potassium-Competitive Acid Blocker, vs. Esomeprazole in Patients With Erosive Oesophagitis,” *Alimentary Pharmacology & Therapeutics* 49, no. 7 (2019): 864–872.

16. P. Unge and K. Andersson, “A First-In-Human, Open-Label, Healthy Volunteer Study of the New P-Cab X842 Demonstrating 24H Acid Control for Treatment of Acid Related Diseases,” *Gastroenterology* 154 (2018): 238.

17. P. Sharma, M. Vaezi, P. Unge, et al., “Clinical Trial: Dose-Finding Study of Linaprazan Glurate, A Novel Potassium-Competitive Acid Blocker, Versus Lansoprazole for the Treatment of Erosive Oesophagitis,” *Alimentary Pharmacology & Therapeutics* 61, no. 10 (2025): 1590–1602.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Table 1 Linear fixed effects model for AUC_{inf} , AUC_{last} and C_{max} (Linaprazan) in Relative BA Study. Suppl. Figure 1 Mean (+/-SE) linaprazan concentration over time in Relative BA Study.