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Effect of lesogaberan, a novel $GABA_B$-receptor agonist, on transient lower esophageal sphincter relaxations in male subjects

Authors: GUY E. BOECKXSTAENS[*,†], HANS RYDHOLM[‡], AALTJE LEI[*], JOHN ADLER[‡] & MAGNUS RUTH[‡]

[*]Academic Medical Center, Amsterdam, the Netherlands; [†]University Hospital Leuven, Catholic University of Leuven, Belgium; [‡]AstraZeneca R&D Mölndal, Sweden

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Correspondence to:

Professor Dr Guy E. Boeckxstaens

Department of Gastroenterology

University Hospital Leuven, Catholic University of Leuven

Herestraat 49

3000 Leuven

Belgium

Tel: +32 16 34 57 50

Fax: +32 16 33 02 38

E-mail: guy.boeckxstaens@med.kuleuven.be

SUMMARY

Background: Transient lower esophageal sphincter relaxations (TLESRs) are a major mechanism behind gastroesophageal reflux disease (GERD).

Aim: To assess the effect of lesogaberan (AZD3355) – a novel peripherally active $GABA_B$ receptor agonist – on TLESRs.

Methods: Twenty-four healthy men were enrolled in this single-blind, placebo-controlled, randomized, single-centre, three-period crossover phase 1 study. Subjects were randomized to receive single oral doses of lesogaberan (0.8 mg/kg), baclofen (40 mg) and placebo, separated by washout periods of ≤ 7 days. Subjects finished a meal 1 hour after the dose. Esophageal manometry and pH-metry measurements were taken during the 3 hours after the meal.

Results: Twenty-one subjects completed the study. Compared with placebo, lesogaberan 0.8 mg/kg significantly reduced the number of TLESRs by 36% (geometric mean ratio [GMR]: 0.64; 95% confidence interval [CI]: 0.51–0.82) and significantly reduced the number of acid reflux episodes (mean reduction: 1.6; 95% CI: 0.34–2.9). Lesogaberan also significantly increased lower esophageal sphincter (LES) pressure by 39% compared with placebo (GMR: 1.39; 95% CI: 1.18–1.64). Comparable results were observed with baclofen. Similar numbers of adverse events were reported by subjects taking lesogaberan and placebo.

Conclusions: Compared with placebo, lesogaberan significantly reduced TLESRs and acid reflux episodes, and increased LES pressure.

INTRODUCTION

Gastroesophageal reflux disease (GERD), characterized by troublesome heartburn and/or acid regurgitation, is a chronic condition that imposes a significant burden on patients.[1–3] Acid reflux is the major contributor to symptom generation in GERD[4] and acid suppression reduces associated symptoms and damage to the esophageal mucosa.[5,6] However, 20–30% of patients with GERD experience persistent reflux symptoms despite proton pump inhibitor (PPI) therapy.[7–10] Impedance monitoring in patients with GERD treated with a PPI revealed that symptoms can occur when the refluxate is only weakly acidic, and also when it is weakly alkaline.[11,12] There has therefore been growing interest in new therapeutic targets for GERD in addition to acid suppression, to help patients with a partial response to PPIs to achieve adequate symptom relief.

Targeting the lower esophageal sphincter (LES) to prevent reflux episodes is an attractive approach because it offers a new mode of action that could complement the acid-suppressive effects of a PPI by reducing all types of reflux. Much interest has been focused on transient lower esophageal sphincter relaxation (TLESR), the predominant mechanism underlying reflux in healthy individuals and in patients with GERD.[13,14] TLESRs are modulated by the neurotransmitter γ-aminobutyric acid (GABA) acting on GABA type B ($GABA_B$) receptors, which are located in the peripheral nervous system as well as in the brainstem.[15,16] Studies in healthy subjects and individuals with GERD have shown that the $GABA_B$-receptor agonist, baclofen, which is indicated for spasticity, reduces the number of TLESRs and reflux episodes, including weakly acidic and weakly alkaline reflux.[17–19] Furthermore, when added to existing PPI therapy, baclofen reduces reflux symptoms and the number of reflux episodes in patients with persistent GERD symptoms despite PPI treatment.[20] However, the adverse

effects of baclofen in the central nervous system (CNS) limit its clinical usefulness in the treatment of GERD, and therefore baclofen is not indicated for this disease.[18]

Lesogaberan (AZD3355) is a competitive, selective $GABA_B$-receptor agonist that dose-dependently inhibits TLESRs and reduces the number of reflux episodes and esophageal acid exposure in dogs.[21,22] Lesogaberan has been shown to reduce the activation of ferret gastric vagal mechanoreceptors,[23] indicating that it has a peripheral site of action. It has a high affinity for the GABA carrier, which results in low extracellular lesogaberan levels in the CNS, so there is relatively little potential for this agent to interact with central $GABA_B$ receptors.[23] These data support the concept that lesogaberan inhibits TLESRs through a peripheral site of action and has a lower propensity for CNS adverse effects than baclofen.

The current study is the first to assess the pharmacodynamic effects of the novel $GABA_B$-receptor agonist lesogaberan in humans. The primary objective was to assess the effect of oral lesogaberan on the number of TLESRs in healthy males. The study also aimed to measure the effect of lesogaberan on the number of acid reflux episodes and on LES pressure, and to assess tolerability. Although not indicated for GERD, baclofen was used as a positive control for measuring the effect of lesogaberan on TLESRs.

METHODS

Study participants

Male subjects aged 18–50 years, weighing 65–100 kg with a body mass index of 19–30 kg/m^2, and having no clinically abnormal physical findings or laboratory values at the time of the pre-entry visit, were included in the study. Subjects were excluded if they had experienced clinically significant illness in the 2 weeks before enrolment, had a history of

clinically significant comorbidity, were taking any prescribed medication in the 2 weeks before first administration of lesogaberan, were taking over-the-counter medication in the week before first administration of lesogaberan (with the exception of paracetamol or nasal spray), or had a previously noted LES pressure of < 5 mmHg. Smoking or other nicotine use was not permitted during each visit or in the preceding 24 hours.

This study was performed in accordance with the ethical principles of the Declaration of Helsinki, and the International Conference on Harmonisation Guidelines for Good Clinical Practice, and was approved by the Institutional Review Board of the study centre. All participants provided written informed consent before any study-related activities or procedures.

Study design and study drugs

This was a single-blind, placebo-controlled, randomized, single-centre, phase 1 crossover study. Subjects fasted overnight before each study visit; food after 22:00 h and fluid after 24:00 h on the preceding evening were not permitted.

Following initial screening to assess eligibility and a run-in period of up to 14 days, each subject received a single low dose of lesogaberan (0.4 mg/kg oral solution) followed by a safety evaluation, which included a follow-up visit 48 hours after administration of the drug. If no clinically significant adverse events occurred, the subject was randomized, after a washout period of at least 5 days, to a single-blind, three-period, crossover phase in which each subject received single doses of lesogaberan (0.8 mg/kg oral solution), baclofen (40 mg capsule) and placebo, each separated by a washout period of at least 7 days. Esophageal manometric and pH-metric data were collected in the 4 hours following the dose and subjects

received a standardized meal (minced beef, potatoes, butter, banana and a soft drink; 2929 kJ [30% fat]) 45 minutes after drug or placebo administration, to be consumed within 15 minutes (Figure 1).

Assignment and blinding

A dosing regimen allocation list was generated by AstraZeneca R&D Mölndal using a validated computer program. Dosing sequences according to a Latin square design balanced for carry-over effects were randomized to subject numbers (assigned sequentially as eligible subjects entered the study). The randomization was performed within blocks of consecutive subject numbers. Dose allocation was blinded for the subjects and for personnel evaluating the manometric/pH recordings but it remained open to other study personnel. Blinding was maintained using the double-dummy principle. To standardize the intake of fluids, all doses were diluted with sodium chloride solution 8 mg/mL to a volume of 50 mL.

Pharmacodynamic assessments

Manometric recordings from the pharynx, esophagus, LES and stomach were obtained using a perfused 10-channel silicone rubber assembly (Dentsleeve Pty Ltd, Adelaide, Australia). A sleeve with one side-hole for pharyngeal recordings and side-holes at 3 cm intervals for recordings in the proximal, middle and distal esophagus was used. A perfused sleeve with one side-hole on its proximal border and one intragastric side-hole (2 cm distal to the sleeve) was used to record LES pressure. Pressures were recorded with external pressure transducers (Baxter, Uden, the Netherlands). The assembly was perfused with degassed water at a rate of 0.3 mL/min (esophagus) and 0.6 mL/min (sleeve) using low compliance hydraulic flow restrictors (DentSleeve International Ltd, Mississauga, Ontario, Canada) and a portable water pump. The catheter was positioned with the proximal border of the sleeve 1 cm above the

LES. Esophageal pH was measured using a glass electrode with built-in reference (model LOT 440, Ingold A.G., Urdorf, Switzerland), positioned 5 cm above the proximal margin of the LES. The manometric and pH data signals were sampled at a frequency of 16 Hz. Subjects were in a sitting position during the manometric/pH recording.

The following variables were assessed for lesogaberan, baclofen and placebo based on manometric and pH tracings recorded from dosing to the end of the 3-hour postprandial period (excluding parts of the tracing recorded during consumption of the standardized meal).

- Number of TLESRs (defined according to previously described criteria[24]).
- Number of acid reflux episodes (defined as a period of more than 4 seconds during which intra-esophageal pH fell below 4 or fell by at least 1 unit if the pH was already below 4).
- Number of TLESRs temporally related to acid reflux episodes (defined as a TLESR during which there was a drop in esophageal pH).
- LES pressure (recorded every 15 minutes and expressed as the mean difference between the end-expiration LES pressure and the end-expiration intragastric pressure over 1 minute). Mean LES pressure during the 3-hour postprandial period was calculated from measurements taken from 15 minutes after the end of the meal and then every 15 minutes until 3 hours after the meal.
- Number of swallows (defined as a fast increase in pressure in the pharyngeal channel, clearly distinguishable from baseline activity).

Safety and tolerability assessments

Each subject underwent a physical examination in the 14 day period before the first study visit, including pulse and blood pressure measurements, together with full screening of

laboratory values and electrocardiogram (ECG) recording. These tests were repeated on the final follow-up visit 2–5 days after administration of the last drug/placebo. During each study visit, subjects were continuously monitored for safety for the first 4 hours after dose administration using a two-lead ECG system equipped with an alarm function. Pulse, and systolic and diastolic blood pressure were measured at all visits. Data on adverse events were collected from administration of first study drug until the final follow-up visit 2–5 days after administration of the last drug/placebo.

Pharmacokinetic assessments

Multiple blood samples (4 mL) were collected during the study visits during which lesogaberan and baclofen were administered for determination of area under the plasma concentration versus time curve (AUC_t), maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) for lesogaberan and baclofen. Plasma concentrations of lesogaberan and baclofen were determined by liquid chromatography and mass spectrometry. The limits of quantification of lesogaberan and baclofen in plasma were 0.030 µmol/L and 0.020 µmol/L, respectively. For each subject, one plasma sample taken during placebo dosing was analysed to confirm that these subjects had not been given lesogaberan or baclofen.

Statistical analysis

All subjects who received at least one dose of lesogaberan, baclofen or placebo were included in the safety analysis. The analysis of pharmacodynamic effects included all subjects who completed the study.

The analysis of AUC_t, C_{max}, number of TLESRs, number of acid reflux episodes and number of swallows was based on an analysis of variance (ANOVA) model, with dosing regimen, period and sequence as fixed effects and subject as a random effect. The difference in LES pressure was analysed using a paired *t*-test of the logarithm of the mean postprandial pressure. (This was not a planned analysis and was not presented in the clinical study report.) The point estimate and the limits of the confidence interval (CI) for the log transformed variables were transformed using the antilogarithm to give estimates of the ratio of geometric means and corresponding CIs.

The AUC_t, C_{max}, number of TLESRs and LES pressure were log-transformed in the analysis. CIs for the true mean were calculated in the logarithmic scale based on the mean square error obtained in the ANOVA. The limits were transformed back to the original scale to give a CI for the geometric mean for each dosing regimen or the ratio of geometric means between dosing regimens. Untransformed pharmacodynamic and pharmacokinetic variables, except t_{max}, were analysed in terms of arithmetic means and 95% CIs. Each CI was based on Student's *t*-distribution. The median, minimum, and maximum values are given for t_{max}.

No formal calculation of sample size was performed. However, based on general considerations, a sample size of 20 evaluable subjects was expected to be large enough to evaluate reductions in the number of TLESRs.

RESULTS

Participant flow and follow-up

The first subject enrolled in the study in September 2003 and the last subject completed the study in February 2004. In total, 27 healthy men were enrolled in the study. Two of these

subjects no longer met the inclusion criteria at the first visit and one withdrew consent, leaving 24 eligible subjects who received the low dose of lesogaberan (0.4 mg/kg). These 24 subjects were all subsequently randomized to receive lesogaberan 0.8 mg/kg, baclofen 40 mg or placebo. After randomization, one subject withdrew consent and two were discontinued because of low LES pressure. Twenty-one subjects therefore completed the study. All 24 randomized subjects received lesogaberan 0.4 mg/kg and were included in the pharmacokinetic and safety analyses. The 21 randomized subjects who completed the study were included in the pharmacodynamic analyses.

Subject demographics and clinical characteristics at baseline

All subjects were male and Caucasian. The mean age was 27 years (range: 18–50 years) and the mean body mass index was 23.7 kg/m^2 (range: 19.4–28.1 kg/m^2). At the time of enrolment, all subjects had normal blood pressure, pulse and ECG recordings, and all were found to be healthy on physical examination.

Analysis

Pharmacodynamic results

Figure 2 shows the number of TLESRs in individual subjects during the 3 hours following the standardized meal, which was ingested between 45 and 60 minutes after dosing. Compared with placebo, lesogaberan 0.8 mg/kg significantly reduced the geometric mean number of TLESRs by 36% (geometric mean ratio [GMR]: 0.64; 95% CI: 0.51–0.82; Table 1). Baclofen 40 mg, used as a positive control, significantly reduced the number of TLESRs by 47% compared with placebo (GMR: 0.53; 95% CI: 0.41–0.67; Table 1). The relative effects of both lesogaberan and baclofen compared with placebo were greatest during the first postprandial hour (Figure 3).

Table 1. Pharmacodynamic effects of lesogaberan 0.8 mg/kg and baclofen 40 mg compared with placebo during the 3 hours after the meal, which was completed 1 hour after dose administration (n = 21).

	Placebo	Lesogaberan 0.8 mg/kg	Baclofen 40 mg
Geometric mean number of TLESRs	13.0	8.3	6.8
Geometric mean LES pressure (mmHg)	7.2	10.0	10.4
Mean number of acid reflux episodes	3.6	2.0	1.4
Mean number of swallows	66.3	69.5	55.9

LES, lower esophageal sphincter; TLESR, transient lower esophageal sphincter relaxation.

The mean LES pressure after dosing with lesogaberan 0.8 mg/kg or placebo is shown in Figure 4. Over the 3 hours after the meal, the geometric mean LES pressure was significantly increased by 39% with lesogaberan 0.8 mg/kg compared with placebo (Table 1; GMR: 1.39; 95% CI: 1.18–1.64).

Lesogaberan 0.8 mg/kg significantly reduced the number of acid reflux episodes compared with placebo during the 3 hours after the meal, with an arithmetic mean reduction of 1.6 acid reflux episodes (95% CI: 0.34–2.9). The number of acid reflux episodes in individual subjects is presented in Figure 5 and mean values are given in Table 1. The reduction in acid reflux episodes was apparent by the first hour after the meal and was sustained until the end of the pharmacodynamic assessment period (Figure 6). Baclofen also reduced the number of acid reflux episodes compared with placebo, by a mean of 2.2 episodes (95% CI: 0.94–3.5).

The proportion of TLESRs temporally related to an acid reflux episode during the 3 hours after the meal were 18.9%, 18.7% and 23.9% with lesogaberan 0.8 mg/kg, baclofen 40 mg and placebo, respectively. For all three dosing regimens, the majority of acid reflux episodes were temporally related to a TLESR during the 3 hours after the meal (81.9% for lesogaberan 0.8 mg/kg, 91.4% for baclofen 40 mg and 82.6% for placebo).

There were similar numbers of swallows with lesogaberan 0.8 mg/kg and placebo (mean difference of 3.2 swallows; 95% CI: –5.5 to 11.8). Baclofen 40 mg reduced the number of swallows by a mean of 10.4 compared with placebo (95% CI: –1.8 to –19.0). Mean values are given in Table 1.

Safety results

A single dose of lesogaberan (0.4 mg/kg or 0.8 mg/kg) had no clinically significant effects on vital signs, ECG or laboratory values. Adverse events reported during the study are presented in Table 2. No serious adverse events were reported and no participants discontinued the study because of adverse events.

Table 2. Number of subjects reporting adverse events during active dosing (safety population).

	Lesogaberan 0.4 mg/kg (single dose) (n = 24)	**Lesogaberan 0.8 mg/kg (single dose) (n = 21)**	**Baclofen 40 mg (single dose) (n = 22)**	**Placebo (n = 22)**
Any adverse event	6	10	16	10
Serious adverse event	0	0	0	0
Discontinuation due to adverse event	0	0	0	0
Most frequently reported adverse events (reported by ≥ 2 subjects)				
Nervous system disorders	5	7	14	6
Paraesthesia	4	4	3	0
Headache	2	0	6	2
Somnolence	0	3	4	2
Dizziness	0	0	5	2
Burning sensation	0	1	1	0
Investigations	3	0	0	0
Urine output increased	2	0	0	0
Gastrointestinal disorders	0	2	2	3

	Lesogaberan 0.4 mg/kg (single dose) (n = 24)	Lesogaberan 0.8 mg/kg (single dose) (n = 21)	Baclofen 40 mg (single dose) (n = 22)	Placebo (n = 22)
Abdominal distension	0	0	0	2
Abdominal pain	0	2	0	0
Abdominal pain, upper	0	1	0	1
General disorders	0	1	2	2
Feeling hot	0	0	1	2
Fatigue	0	1	1	0

Overall, 22/24 subjects reported an adverse event; 16/22 with baclofen, 10/21 with lesogaberan 0.8 mg/kg and 10/22 with placebo. Of these adverse events, 15 for baclofen and 8 each for lesogaberan and placebo were considered to be attributable to the study drug Similar numbers of nervous system adverse events were reported after a single dose of lesogaberan 0.8 mg/kg (7/21) and placebo (6/22), but almost twice as many were reported after a single dose of baclofen 40 mg (14/22).

The most commonly reported adverse event during active dosing with lesogaberan 0.8 mg/kg was transient paraesthesia (reported by 4/21 subjects), which was mild or moderate in intensity. The onset of paraesthesia occurred 1–63 minutes after administration of lesogaberan 0.8 mg/kg and the symptoms quickly resolved, within 3–60 minutes. Three

subjects reported paraesthesia with baclofen 40 mg, occurring 13–165 minutes after dose administration, and symptoms resolved within 10–125 minutes.

Pharmacokinetic results

Lesogaberan 0.8 mg/kg was rapidly absorbed with a median t_{max} of 1.0 hour; geometric mean values for C_{max} and AUC_t were 1.60 µmol/L and 6.47 µmol·h/L, respectively. Baclofen was also rapidly absorbed with a median t_{max} of 1.5 hours; geometric mean values for C_{max} and AUC_t were 2.29 µmol/L and 9.61 µmol·h/L, respectively. Figure 7 shows the mean plasma concentrations of lesogaberan and baclofen in the 12 hours after dosing.

DISCUSSION

This randomized, single-blind, placebo-controlled, crossover study is the first to show that the novel $GABA_B$-receptor agonist lesogaberan reduces the number of TLESRs in the postprandial period in humans. These findings show that a single dose of lesogaberan is able to modulate the most important underlying mechanism of reflux in humans, as well as in animals.

TLESR is the predominant mechanism underlying reflux in GERD,[13,14] and use of pharmacological agents to reduce the number of TLESRs has been shown also to reduce the occurrence of reflux episodes in healthy subjects and patients with GERD.[25,26] In dogs, lesogaberan has been shown to inhibit TLESRs in a dose-dependent manner.[21] In the current study in healthy male subjects, a single oral dose of lesogaberan 0.8 mg/kg reduced the number of TLESRs by approximately 36% compared with placebo. As expected, lesogaberan had the greatest effect on TLESRs relative to placebo in the first postprandial hour, but the effect was demonstrated throughout the 4 hours after dosing. The effect of lesogaberan on the

number of TLESRs was similar to that of baclofen (reduction of 47%). This is comparable to findings from previous studies with baclofen in healthy subjects and patients with GERD.[17,18]

As expected in healthy subjects, the number of reflux episodes with all dosing regimens was low. Lesogaberan significantly reduced the number of acid reflux episodes to a similar extent to baclofen. Given that the majority of acid reflux episodes were temporally related to a TLESR, the reduction in the number of acid reflux episodes was probably largely due to the reduction in the number of TLESRs. Lesogaberan also increased LES pressure by approximately 39%, which may have contributed to the reduction in reflux episodes, but the exact importance of increased LES pressure remains unknown. The timing and magnitude of LES pressure increase is comparable to that of baclofen, with a maximal increase in the second and third postprandial hours. The increase in LES pressure observed with lesogaberan is likely to be provoked at a peripheral level,[23] although very little is known about the mechanisms that govern LES pressure.[27] Together, these data in healthy men support the future assessment of lesogaberan as a potential treatment for patients with GERD with persistent symptoms despite daily PPI therapy.

The clinical usefulness of the $GABA_B$-receptor agonist baclofen in the treatment of GERD is limited because of the common occurrence of adverse CNS effects.[26] Similarly, although a phase 1 study has demonstrated that the $GABA_B$-receptor agonist AZD9343 reduces the number of TLESRs, this compound was found to be associated with adverse events such as somnolence.[28] In contrast to baclofen, lesogaberan has a lower propensity to cause adverse CNS events because of its higher affinity for the GABA carrier.[23] This stronger binding to the GABA carrier results in low extracellular lesogaberan levels in the CNS and therefore a low potential for interaction with central $GABA_B$ receptors.[23] In the current study, nervous system

adverse events were reported by a similar number of subjects taking lesogaberan (7/21) to those taking placebo (6/22), but by approximately twice as many subjects (14/22) during dosing with baclofen. As expected, dizziness was one of the most commonly reported adverse events with baclofen; dizziness was not reported by any subjects during dosing with lesogaberan, but was reported by two subjects while on placebo. There was no clear difference between any of the dosing regimens in terms of the occurrence of somnolence (2/22 for placebo, 3/21 for lesogaberan and 4/22 with baclofen).

A decrease in the frequency of spontaneous swallowing may be a central effect,[29] and this was observed with baclofen but not lesogaberan, further suggesting a peripheral rather than a central action for lesogaberan. In line with this, transient paraesthesia was reported by four subjects taking lesogaberan. Paraesthesia was consistently mild to moderate and short in duration, as has been reported in other studies of lesogaberan.[30,31] The underlying cause of paraesthesia associated with the intake of lesogaberan is not known, but it may be speculated that the observed rapid onset of paraesthesia is a result of lesogaberan stimulating $GABA_B$ receptors located in peripheral cutaneous afferents, causing changes in membrane potential and an imbalance in the sensory input.[32,33] Interestingly, paraesthesia was also reported by three subjects taking baclofen in this study. According to other studies, occurrence of paraesthesia after baclofen administration is rare, possibly because baclofen has a lower selectivity and potency for $GABA_B$ receptors than lesogaberan, which results in a slower rate of binding to the receptors.[34] It is possible that the reports of paraesthesia in the subjects taking baclofen were a consequence of paraesthesia being described in the patient information leaflet for the study, although paraesthesia was not reported by any subject while on placebo. Transient paraesthesia is considered to be an uncomfortable rather than painful sensation, and did not cause any patients to withdraw from the current study. Moreover,

lesogaberan had no clinically significant effects on vital signs, ECG or laboratory values at any dose and no serious adverse events were reported during the study. Indeed, the total number of subjects experiencing an adverse event was very similar in the lesogaberan and placebo groups (10/21 and 10/22, respectively). Although the incidence of paraesthesia warrants further investigation, the collective data suggest a potential clinical advantage of lesogaberan over baclofen.

Acid suppression is an effective way to reduce the acidity of refluxate, and the clinical efficacy of PPIs is well established. The most promising treatment approach for the 20–30% of patients who experience persistent GERD symptoms despite PPI therapy appears to be an add-on therapy with a novel mode of action that could complement acid suppression. Reflux inhibition is attractive because it has the potential to prevent all types of reflux events, including weakly acidic and weakly alkaline reflux, which are known to generate symptoms in patients taking PPIs.[11,12]

In conclusion, the decreases in the number of TLESRs and reflux episodes in healthy men receiving lesogaberan, along with the increase in LES pressure, support further assessment of this novel $GABA_B$-receptor agonist as a potential add-on therapy in patients with GERD with persistent symptoms despite daily PPI therapy. Accordingly, several phase II clinical trials assessing lesogaberan in this patient group are currently at the recruitment or analysis stage (ClinicalTrials.gov Identifiers: NCT00743444, NCT01043185, NCT01005251 and NCT00394472).

FIGURE LEGENDS

Figure 1. Schedule of dosing, standardized meal and pharmacological assessments during each treatment period.

Figure 2. Number of TLESRs in individual subjects taking placebo, lesogaberan 0.8 mg/kg and baclofen 40 mg, during the 3 hours after a standardized meal, which was completed 1 hour after drug administration (n = 21).

TLESR, transient lower esophageal sphincter relaxation.

Figure 3. Mean number of TLESRs in subjects taking placebo, lesogaberan 0.8 mg/kg or baclofen 40 mg, during the pre-meal period (0–45 minutes after dose intake), and during the first, second and third hours after a standardized meal, which was completed 1 hour after dose intake (n = 21).

Bars indicate 95% confidence intervals.

TLESR, transient lower esophageal sphincter relaxation.

Figure 4. Mean LES pressure during the 4 hours following administration of placebo compared with (a) lesogaberan 0.8 mg/kg (n = 21) and (b) baclofen 40 mg (n = 21).

Bars show 95% confidence intervals.

LES, lower esophageal sphincter.

Figure 5. Number of acid reflux episodes in individual subjects taking placebo, lesogaberan 0.8 mg/kg and baclofen 40 mg, in the 3 hours after the standardized meal, which was completed 1 hour after dose administration (n = 21).

Figure 6. Mean number of acid reflux episodes in subjects taking placebo, lesogaberan 0.8 mg/kg and baclofen 40 mg, during the pre-meal period (0–45 minutes after dose intake) and the first, second and third hours after the standardized meal, which was completed 1 hour after dose intake (n = 21).

Bars show 95% confidence intervals.

Figure 7. Mean plasma concentration of lesogaberan and baclofen during the 12 hours after dosing with lesogaberan 0.8 mg/kg or baclofen 40 mg (n = 21).

1. Authors' declaration of personal interests:

(i) GEB has served as a speaker, a consultant or an advisory board member for AstraZeneca, GSK, Movetis, Norgine and Johnson & Johnson, and has received research funding from AstraZeneca.

(ii) HR, JA and MR are employees of AstraZeneca.

(iii) AL has no competing interests to disclose.

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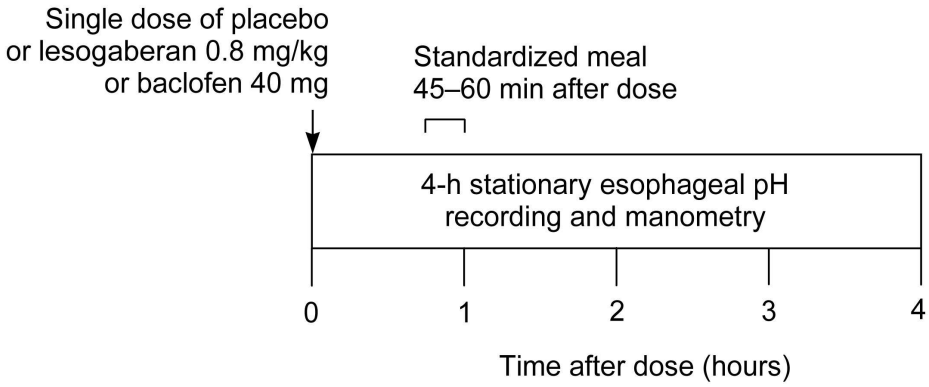

Figure 1. Schedule of dosing, standardized meal and pharmacological assessments during each treatment period.
98x38mm (600 x 600 DPI)

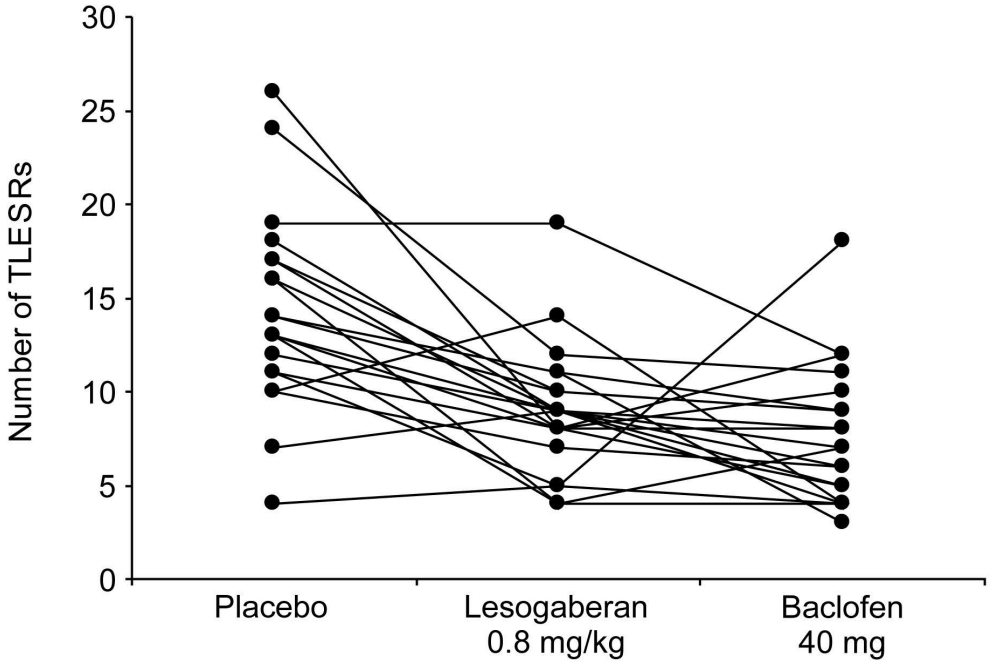

Figure 2. Number of TLESRs in individual subjects taking placebo, lesogaberan 0.8 mg/kg and baclofen 40 mg, during the 3 hours after a standardized meal, which was completed 1 hour after drug administration (n = 21). TLESR, transient lower esophageal sphincter relaxation.
78x52mm (600 x 600 DPI)

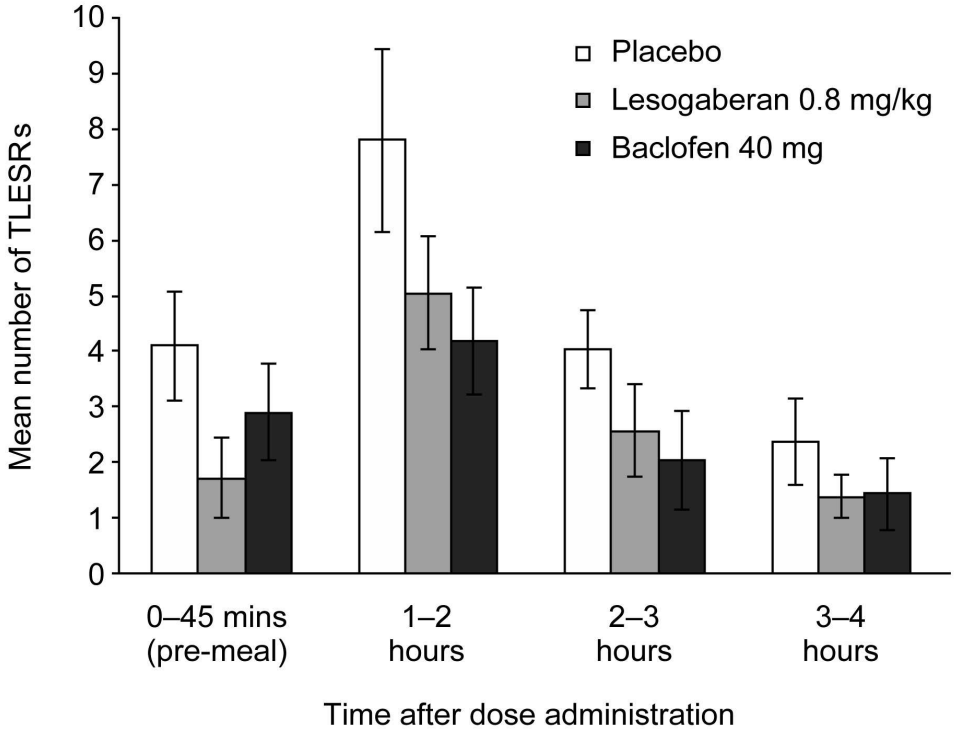

Figure 3. Mean number of TLESRs in subjects taking placebo, lesogaberan 0.8 mg/kg or baclofen 40 mg, during the pre-meal period (0–45 minutes after dose intake), and during the first, second and third hours after a standardized meal, which was completed 1 hour after dose intake (n = 21).
Bars indicate 95% confidence intervals.
TLESR, transient lower esophageal sphincter relaxation.
81x60mm (600 x 600 DPI)

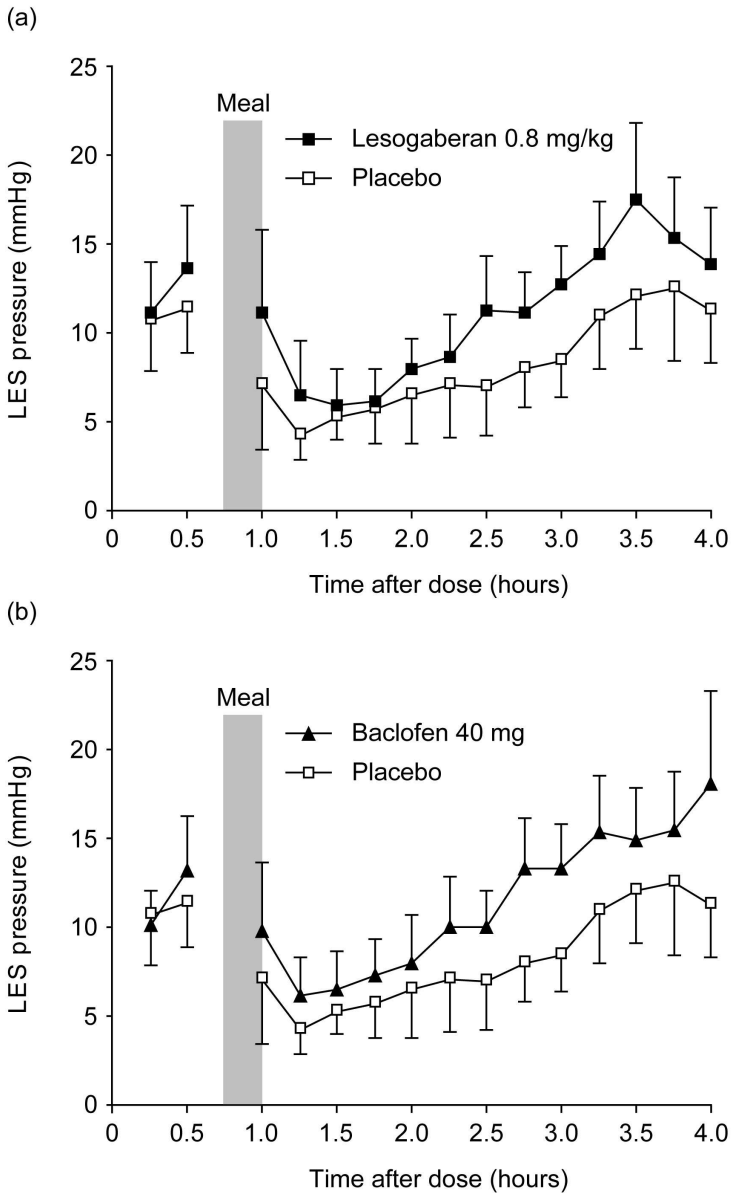

Figure 4. Mean LES pressure during the 4 hours following administration of placebo compared with (a) lesogaberan 0.8 mg/kg (n = 21) and (b) baclofen 40 mg (n = 21).
Bars show 95% confidence intervals.
LES, lower esophageal sphincter.
78x119mm (600 x 600 DPI)

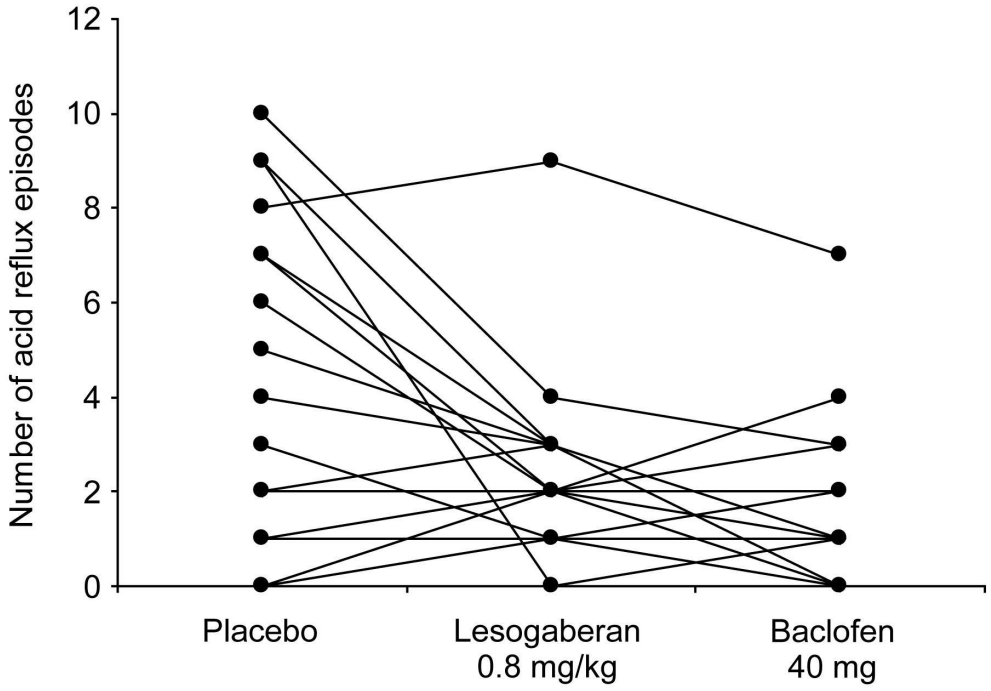

Figure 5. Number of acid reflux episodes in individual subjects taking placebo, lesogaberan 0.8 mg/kg and baclofen 40 mg, in the 3 hours after the standardized meal, which was completed 1 hour after dose administration (n = 21).
77x53mm (600 x 600 DPI)

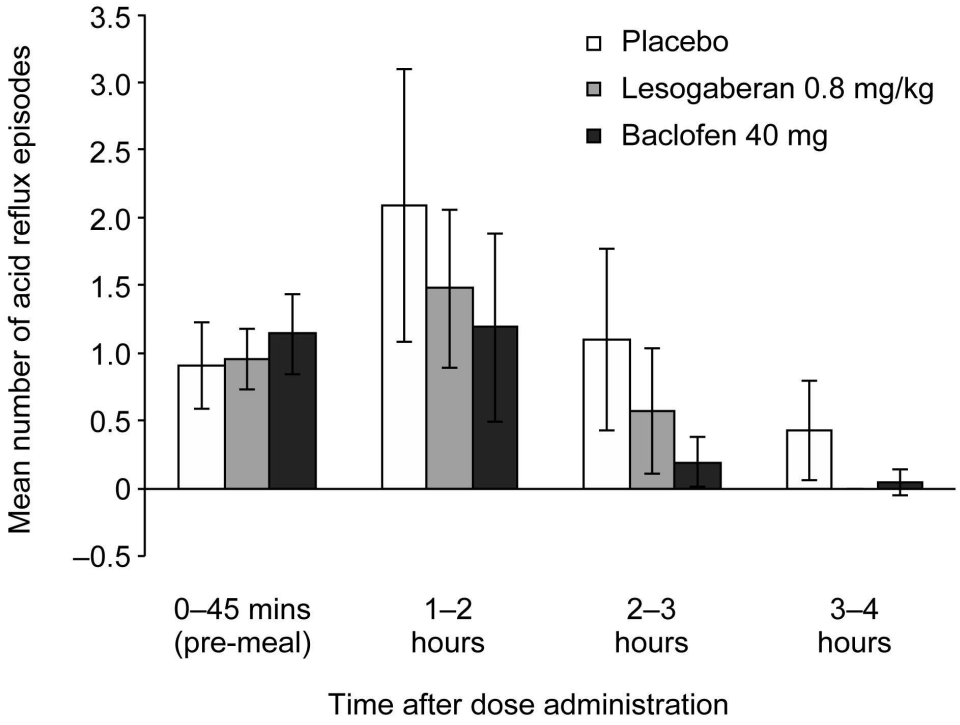

Figure 6. Mean number of acid reflux episodes in subjects taking placebo, lesogaberan 0.8 mg/kg and baclofen 40 mg, during the pre-meal period (0–45 minutes after dose intake) and the first, second and third hours after the standardized meal, which was completed 1 hour after dose intake (n = 21).
Bars show 95% confidence intervals.
83x62mm (600 x 600 DPI)

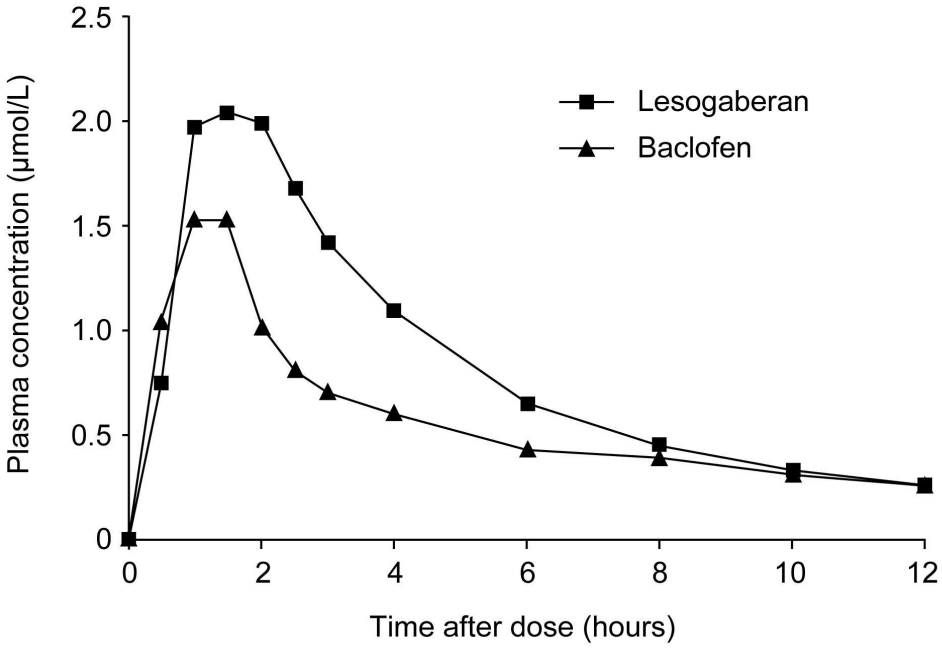

Figure 7. Mean plasma concentration of lesogaberan and baclofen during the 12 hours after dosing with lesogaberan 0.8 mg/kg or baclofen 40 mg (n = 21).
84x55mm (600 x 600 DPI)

CONSORT Statement 2001 Checklist

Items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	1 and 3
INTRODUCTION Background	2	Scientific background and explanation of rationale.	4 and 5
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	5 and 6
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	6 and 7
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	5, 8 and 9
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	10
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	7
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	7
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	7
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	7
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	9 and 10
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	10 and 11
Recruitment	14	Dates defining the periods of recruitment and follow-up.	10
Baseline data	15	Baseline demographic and clinical characteristics of each group.	11
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	11
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	11–16
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	10
Adverse events	19	All important adverse events or side effects in each intervention group.	13–15
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	16–18
Generalizability	21	Generalizability (external validity) of the trial findings.	16–18
Overall evidence	22	General interpretation of the results in the context of current evidence.	16–19

From Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357(9263):1191-1194.

The CONSORT Statement 2001 checklist is intended to be accompanied with the explanatory document that facilitates its use. For more information, visit www.consort-statement.org.