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ORIGINAL ARTICLE

Short-Term Effects of Relamorelin on Descending Colon Motility in Chronic Constipation: A Randomized, Controlled Trial

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Abstract
Background The pentapeptide ghrelin agonist, relamorelin, accelerates colonic transit in patients with chronic constipation (CC). In a murine model, relamorelin decreased excitability of colonic circular smooth muscle cells and colonic intraluminal pressure.
Aim To determine short-term effects of relamorelin on colonic motility measured by barostat and multilumen manometry in CC.
Methods In a placebo-controlled, single-dose, double-blind, randomized study in patients with CC, we investigated the motor effects of relamorelin, 100 μg, SQ (12 patients) compared to placebo SQ (six patients). A motility-barostat balloon assembly was used to measure colonic compliance; tone and phasic pressure activity were measured before and after a 1000-kcal milkshake meal (administered ~60 min post-medication). Overall "background" phasic pressure activity was assessed by: average amplitude and motility index (MI = ln[sum amplitudes × #contractions + 1]) over defined periods. High-amplitude propagating contractions (HAPCs) were characterized by amplitude >75 mmHg and propagating contractions >50 mmHg; both were propagated over at least 10 cm. Postprandial HAPCs were the primary end point. The study sample had 80 % power to detect an increase of 3.3 HAPCs in the hour post-meal.
Results Relamorelin, 100 μg, significantly induced more pre-meal propagated contractions [PCs of either >50 or >75 mmHg] compared to placebo ($p < 0.05$). Relamorelin also induced more post-meal PCs >50 or >75 mmHg than placebo. Relamorelin did not significantly alter colonic compliance, fasting or postprandial phasic pressure activity (20 min pre-meal fasting MI) or tone, and 60 min post-prandial phasic pressure amplitude or MI, or tone.
Conclusions Relamorelin stimulates propagated colonic contractions without alteration of background irregular contractions in CC.
ClinicalTrial.Gov registration number: NCT 01781104.

Keywords Colonic transit · Constipation · Ghrelin agonist

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Introduction

Ghrelin is a 28-amino residue peptide which was first isolated from rat stomach. Ghrelin is the natural ligand for the GHS-1a receptor and a potential target for treatment of clinical conditions associated with impaired gastric motility and energy balance [1]. Administration of ghrelin has been shown to promote gastric motility in mice, rats, dogs, and humans [2–4]. However, the short half-life and plasma instability of native ghrelin limit its utility as a potential

treatment for gastrointestinal motility disorders. Synthetic ghrelin agonists, predominantly small molecules, are being developed as prokinetic agents that may prove useful in the treatment of gastrointestinal motility disorders such as gastroparesis [5]. Actions and therapeutic pathways of ghrelin for gastrointestinal disorders have been reviewed elsewhere [6].

Relamorelin (RM-131) is a pentapeptide synthetic ghrelin analog that binds to the growth hormone secretagogue (GHS)-1a receptor with approximately threefold greater affinity than natural ghrelin. The ability of relamorelin to stimulate growth hormone (GH) release is comparable to that of native ghrelin. The potential for relamorelin as a treatment for gastrointestinal motility disorders has been reviewed elsewhere [7]. Relamorelin significantly improved bowel functions, with an increased number of spontaneous bowel movements (BMs), accelerated time to first BM after first dosing, and accelerated colonic transit in patients with chronic constipation during a 14-day treatment trial [8]. As expected from the known prokinetic effects in stomach, relamorelin also significantly accelerated gastric emptying of solids in patients with CC. The motor repertoire associated with the acceleration of colonic transit with relamorelin treatment is unknown. One of the most important motor mechanisms associated with colonic propulsion that is absent or present in decreased frequency when assessed in prolonged studies in patients with severe constipation is the high-amplitude propagated contraction (HAPC) [9, 10].

Some subtypes of ghrelin receptors are identified throughout the gastrointestinal tract, including the colon [11]; the expression of ghrelin receptors in rodent intestine is actually higher in small intestine and large intestine than in the stomach. Relamorelin hyperpolarized resting membrane potential of human colon circular smooth muscle cells in vitro [12], suggesting that it influences colonic motility. In an in vivo model in conscious mice with a miniaturized pressure transducer catheter introduced into the colon $\sim$ 2.5 cm proximal to the anus, intraperitoneal relamorelin reduced phasic contractile activity in the colon. Others have also shown that intrathecal ghrelin induces strong propulsive contractions in the distal colon. These effects are thought to be mainly mediated by activating the defecation center in the L1–S3 lumbosacral region of the spinal cord [13, 14]. The site of stimulation of colonic transit appears to be outside the central nervous system; Shimizu et al. showed that acyl-ghrelin stimulated rat colonic contractility when given intravenously or intrathecally, but not when given into the fourth ventricle. Additionally, intraventricular acyl-ghrelin did not affect small bowel motility, suggesting there is no vagal stimulation in the brain stem. They concluded that ghrelin activates pelvic nerves at the sacral defecation center, innervating the enteric neurons in the distal colon [14].

However, the effects of ghrelin on colonic motor functions (phasic motility, tone, and compliance) in humans are not known. In this study, we aimed to determine the short-term effects of a ghrelin agonist, relamorelin (RM-131), on colonic motility measured by colonic barostat and multilumen manometry in patients with chronic constipation. Our study did not address the frequency of the colonic contractions such as HAPCs over a prolonged (e.g., 24-h) period after chronic stable administration of the medication. We were interested in the acute effects on contractile patterns that have been shown to be induced within a few minutes to 3 h after the administration of parenteral neostigmine [15], intraluminal bisacodyl [16], or fatty acids such as oleic acid [17, 18].

Methods

Study Design

In a placebo-controlled, single-dose, double-blind, randomized study performed in patients with chronic constipation, we investigated the motor effects in cleansed colon of relamorelin, 100 μg, SQ (12 patients) compared to placebo SQ (six patients). Subjects attended the Mayo Clinic Clinical Research Unit (CRU) for a single study day. Colonic motor and sensory functions were assessed using the barostat technique as described previously [19–25] and detailed below.

The study was approved by Mayo Clinic Institutional Review Board (IRB #14-002145) on April 25, 2014. Participants provided written informed consent before participation.

Participants

Participants with chronic constipation were recruited from the group that participated in a previous randomized, controlled trial to study the effect of relamorelin on colonic transit in patients with chronic constipation and by public advertisement. Each subject completed a screening validated bowel disease questionnaire [26] to ensure symptoms fulfilled functional constipation by Rome III criteria [27]; in addition, there was no evidence of a rectal evacuation disorder as assessed by physical (digital rectal) examination [28] conducted by the study investigators, or evidence of a rectal evacuation disorder appraised by anorectal manometry in their medical records. All participants met eligibility criteria, including age 18–65 years, body mass index (BMI) of 18–40 kg/m^2, off other medications for constipation, and had a negative qualitative urine pregnancy

test at screening. The study enrolled 18 patients who had previously participated in a placebo run-in phase, randomized, controlled, parallel-group study of relamorelin compared to placebo [8]. Information garnered during the 2-week run-in phase was used to characterize the baseline bowel function and colonic transit using scintigraphy.

Study Medication

The study drug was supplied by Rhythm Pharmaceuticals (Boston, MA). Relamorelin is formulated as an isotonic solution in 5 % mannitol. Relamorelin (100 μg) and placebo (5 % mannitol for injection) were delivered with a consistent 300 μL volume in a pre-filled syringe. Relamorelin or placebo was administered as subcutaneous doses by injection into the abdomen during the colonic motility study. The dose level of 100 μg was chosen based upon the safety, tolerability, and the pharmacokinetics/pharmacodynamics profile established in the phase 1 healthy volunteer ascending single- and multiple-dose studies (Rhythm Pharmaceuticals, Boston, MA). This dose was also previously shown to stimulate gastric emptying in symptomatic people with type 1 or 2 diabetes [29–31] and to increase colonic motility (measured by wireless motility capsule) in healthy volunteers [32]. The preclinical and current clinical perspectives of relamorelin were recently published [7, 33]. The timing of the intra-colonic measurements was selected to coincide with the period when the medication would achieve maximum concentration and a significant area under the plasma concentration curve would be expected, based on prior pharmacokinetic studies. In humans, across all dosing groups studied and after single or multiple administrations for 10 days, the median time to peak plasma concentration (T_{max}) was 0.74 h (minimum and maximum 0.27 and 1.02 h, respectively). In addition, across all dose groups, the average relamorelin half-life was ~4.5 h in the single-ascending dose study. Therefore, the drug levels were likely to be appropriate to appraise the pharmacodynamic effects of relamorelin on colonic motility over the 3-h duration of the study in this protocol.

Endoscopy and Colonic Tube Placement

Patients ingested standard colonic bowel lavage preparation (polyethylene glycol-electrolyte solution) during the prior 24 h, and fasted overnight (at least 8 h). Trained endoscopists (MC assisted by AA) performed unsedated flexible sigmoidoscopy, during which a guidewire was placed in the colon in order to facilitate positioning the combined barostat–manometry catheter in the descending colon. The six manometric sensors recorded pressure through water-perfused catheters.

Tube Placement and Procedure for Colonic Sensation and Motility

The combined catheter was inserted into the colon along a Teflon® guidewire so that the barostat balloon was located in the descending colon. The methods for measurements of colonic compliance (with stepwise distensions increasing by 4 mmHg at each step, lasting 1 min, and recording balloon volume during the second 30 s of each minute), tone, phasic pressures, and sensation [thresholds during stepwise distension (ascending method of limits) and ratings in response to random order phasic distensions at predefined levels] are described in the literature [19–25]. The manometric sensors were spaced 5 cm apart.

Colonic Barostat–Manometry Procedure

After placement of the tube into the descending colon, the subject was brought to the testing room and the placebo or study medication was administered SQ at time 0 min, and a rest period of 20 min followed. After the rest period, there was a conditioning distention of the barostat balloon to 20 mmHg, lasting for 2 min, followed by an equilibration period at zero pressure for 8 min. Thirty minutes after placebo or study medication was administered, colonic compliance was assessed as the volume response to 4 mmHg stepwise increments in intra-balloon pressures from 0 to 60 mmHg. During assessment of compliance, participants were asked to report first sensation and first perception of gas and pain. Once the pain threshold was reached, the inflation stopped. After the compliance measurement, the operating pressure (OP) was set at 2 mmHg above the minimum distending pressure (the pressure at which respiratory excursions during deep inspiration were accompanied by a noticeable deflection in the balloon volume). Then, fasting resting colonic tone and motility were assessed at the OP for 20 min. At 60–75 min after the placebo or study medication was given, the standard 1000-kcal meal (750 mL milkshake containing 53 % fat, 35 % carbohydrate, and 12 % protein) was ingested, and postprandial colonic motility and tone were assessed during 60 min after ingestion of the meal (Fig. 1).

Colonic Motility Analysis

Colonic High-Amplitude Propagating Contractions (HAPCs)

Colonic HAPCs were defined by rapidly propagated (>0.5 cm/s), high-amplitude (>75 mmHg) contractions occurring over at least 10 cm (that is, at least three manometric sensors), consistent with recommendations on propagation distance by Bassotti et al. [34] and amplitude

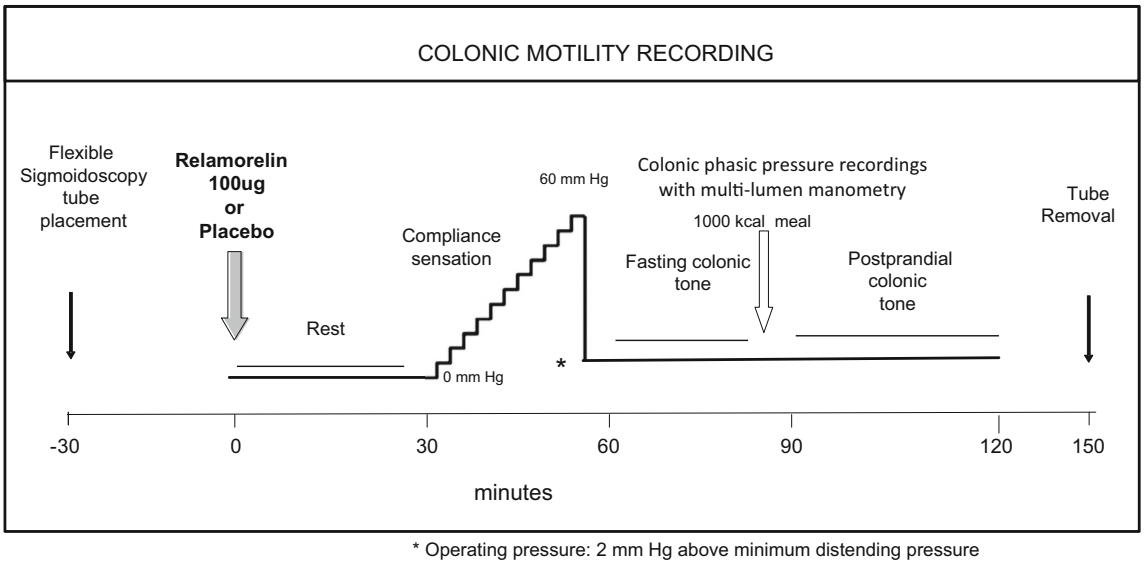

Fig. 1 Colonic motor function assessment protocol

based on the average reported by Bassotti et al. using water-perfused manometry and Hagger et al. [35] using solid-state transducers. HAPCs were characterized by amplitude >75 mmHg and propagating contractions >50 mmHg; both were propagated over at least 10 cm. We also estimated the combined number of propagated contractions (PCs), that is, all contractions >75 or >50 mmHg. The data (e.g., number of HAPCs) were analyzed for two epochs: 20-min fasting and 60 min postprandially.

Phasic Pressure Activity

Phasic pressure activity was assessed by a computerized program that assesses all phasic pressure activity >10 mmHg and provides an automated readout of average amplitude and motility index (MI = ln[sum amplitudes × #contractions + 1]) over defined periods.

Colonic Tone and Compliance

Colonic tone, reflected in the intra-balloon volume at the operating pressure, was calculated by averaging the colonic volume throughout the periods of assessment, as in previous studies [22, 23]. Postprandial change in tone was calculated as the difference or proportionate change between postprandial and fasting colonic balloon volumes (averaged for the 20-min fasting and 1-h postprandial periods).

Compliance was summarized by the pressure corresponding to 50 % of maximum volume (P_{half}) using the linear interpolation method [36].

Colonic Sensation Thresholds

Data for colonic sensation thresholds were collected during the stepwise increases in barostat balloon pressure.

Statistical Analysis

End Points for Analysis

The primary end point for this study was postprandial high-amplitude propagated contractions (HAPC) per hour, upon which the study was powered. The secondary end points were analyzed to preliminarily appraise potential effects of relamorelin and determine variation to be used in planning future studies: colonic compliance; fasting colonic tone; postprandial colonic tone; postprandial phasic pressure motility index; and thresholds for first sensation, gas and pain sensations.

Statistical Analysis

An intention-to-treat (ITT) analysis was used, including all subjects randomized. An analysis of covariance (ANCOVA) was used to assess treatment effects in the primary and secondary end points, with the corresponding baseline end point response used as a covariate. A rank transformation was used to accommodate non-Gaussian distributions of the residuals in the ANCOVA models. Participants, technicians, investigators, and statistician were blinded during the study until the blinded analyzed data were locked by the study statistician.

Sample Size Assessment

The sample size was based on the results of primary end points in our laboratory (Table 1, data show mean ± SD). Estimated effect sizes were based on a two-sample *t* test at an alpha level of 0.05. The expected difference in mean postprandial HAPCs per hour was 2 for relamorelin compared to placebo. The standard deviation was calculated from the observed number of HAPCs in patients with normal transit constipation in the absence of any treatment: 1.27 ± −0.63 (SEM) [37]. The detectable effect size (with 80 % power) was the difference in mean number of HAPCs per hour. Similarly for the other end points, the detectable difference was in the corresponding units of the response. It was anticipated that the ANCOVA analyses would provide similar power for somewhat smaller effect sizes by incorporating relevant covariates.

The sample size of 12 patients receiving relamorelin had sufficient power to detect a drug-associated difference in the number of postprandial HAPCs per hour of 3.33 and a difference in postprandial colonic tone of 67 mL. The group difference in number of postprandial HAPCs per hour of 2 was considered clinically relevant, as seen in prior studies [38, 39].

Results

Participants, Demographics, and Baseline Parameters

Twenty-four participants were invited to participate; 21 were screened. One was excluded due to positive pregnancy test, another withdrew consent after tube placement, and one participant signed consent but did not perform the study. The qualified participants were all females, predominantly Caucasian (88 %), with mean (±SEM) age of 43.4 ± 1.8 years and mean BMI of 26.3 ± 0.7 kg/m^2 (Table 2). Demographics and baseline bowel functions, as well as baseline colonic transit measurement, were similar in the two treatment groups (Table 2). The colonic transit measurements at 24 h (GC24 1.49 to 2.37) suggested that the patients had normal transit constipation (colonic transit GC24 >1.3).

Table 2 Patient demographics and bowel diary data during baseline (mean ± SEM) two-week period during which participants received placebo in a parallel study (Ref. [8])

	Placebo $n = 6$	Relamorelin $n = 12$
Age (years)	40.7 ± 3.3	44.8 ± 2.3
Gender (F)	6	12
BMI, kg/m^2	25.9 ± 1.2	26.4 ± 0.9
Race (Caucasian %)	83	92
Number of SBMs/week	1.7 ± 0.25	1.8 ± 0.32
Stool consistency (Bristol scale)	1.3 ± 0.2	1.5 ± 0.3
Colonic transit GC24 h[#]	2.08 ± 0.30	1.91 ± 0.13

[#] Colonic transit data available for nine of the 18 patients; none of the patients had GC24 <1.3; the range of GC 24 was 1.49–2.37

Normal colonic transit, geometric center at 24 h based on 319 healthy participants, 1.3–4.4 (5th and 95th percentiles) (Ref. [47])

BMI body mass index, *SBMs* spontaneous bowel movements

Colonic Motor Function

Propagated Pressure Activity

There were no significant differences in the numbers of HAPCs (>75 mmHg) between the two treatment groups. However, there were more patients with recorded HAPCs during fasting and postprandially in the relamorelin treatment group (Table 3).

Relamorelin, 100 μg, induced significantly more pre-meal PCs (>50 or >75 mmHg, $p < 0.05$) and numerically (but not significantly) more post-meal PCs >50 or >75 mmHg compared to placebo. Relamorelin also numerically increased the number of patients with such PCs. Examples of these types of contractions are shown in Fig. 2. In the placebo group, none of the propagated contractions observed in the fasting or postprandial period exceeded 116 mmHg; in contrast, in the relamorelin-treated group, there was one propagated contraction in the fasting period and three contractions in the postprandial period that exceeded 116 mmHg. Figure 3 shows a postprandial tracing in a patient who received relamorelin in whom several propagated contractions were observed, one reaching >116 mmHg at one level in the colon.

Table 1 Sample size analysis and power calculation

Response	Mean	SD	Effect size detectable, $n = 12$ versus 6
# Postprandial HAPC/hour*	1.27	2.18	3.33
Colonic compliance (Pr½) mmHg**	17.8	4	6.2
Colonic postprandial tone mL (avg. of 0–30 min)**	34.7	43.5	67

Data obtained from * (Ref. [37]) and ** (Ref. [46])

HAPC high-amplitude propagated contractions

Table 3 Effects of relamorelin on colonic motor functions in chronic constipation

Group	Placebo ($n = 6$)	Relamorelin 100 μg ($n = 12$)
Propagated contractions		
High-amplitude propagated contractions (HAPCs)		
Average # HAPCs pre-meal	0	0.4 ± 0.3
Average # HAPCs post-meal	0.5 ± 0.3	1.7 ± 0.8
# patients with HAPCs (>75 mmHg), pre-meal	0	2
# patients with HAPCs (>75 mmHg), post-meal	2	5
All propagated contractions (PCs)		
Average # PCs (>50 or >75 mmHg), post-meal	1.2 ± 1.0	2.6 ± 1.0
# patients with PCs (>50 or >75 mmHg), pre-meal*	0	6
# patients with PCs (>50 or >75 mmHg), post-meal	3	10
Effect of meal on phasic pressure activity		
Pre-meal 20 min motility index	9.7 ± 0.6	10.0 ± 0.4
Pre-meal 20 min average amplitude, mmHg	23.3 ± 1.9	24.1 ± 1.4
Post-meal 20 min motility index	11.4 ± 0.3	11.0 ± 0.2
Post-meal 20 min average amplitude, mmHg	26.0 ± 2.5	26.7 ± 1.8
Compliance		
Compliance $Pr_{½}$, mmHg	17.5 ± 1.1	18.6 ± 0.8
Sensation thresholds		
First sensation, ml [#]	7.3 ± 5.9	21.3 ± 4.2
Gas, ml[##]	18.7 ± 7.7	32.7 ± 5.5
Pain, ml	52.7 ± 6.2	53.0 ± 4.4
Colonic tone		
20-min fasting tone	133.4 ± 4.7	134.9 ± 6.7
Effect of meal on colonic tone		
Post-meal 60 min tone, ml	116.3 ± 9	121.7 ± 6.4
Change in tone (post–pre), ml (− = increased tone)	−23.9 ± 6	−17.2 ± 4.3

Data presented as mean ± SE, * $p \leq 0.05$; [#] $p = 0.10$; [##] $p = 0.16$

Compliance and Overall Phasic Pressure Activity

Relamorelin did not significantly alter colonic compliance, fasting phasic pressure activity (20-min pre-meal fasting MI) or tone, and 60 min postprandial phasic pressure amplitude or MI, or tone (Table 3).

Sensation Thresholds

There were no differences in sensation thresholds for first sensation, gas and pain in the two treatment groups.

Discussion

In this single-center, randomized, double-blinded, placebo-controlled study in patients with chronic constipation, the ghrelin receptor agonist, relamorelin, stimulated colonic motor activity in the form of propagated contractions; these findings are consistent with the previously reported acceleration of colonic transit [8] with relamorelin. Relamorelin, 100 μg, induced significantly more pre-meal PCs and there were numerically more post-meal PCs compared to placebo. Relamorelin also numerically increased the numbers of patients with such PCs and HAPCs compared to placebo treatment.

Our findings are consistent with the hypothesis that relamorelin improves bowel functions and accelerates colonic transit by inducing propagated contractions in the colon. Additionally, the lack of effect on background phasic contractions estimated by the calculated MI suggests that there is no generalized upregulation of the irregular or mixing contractions that may actually retard colonic transit or aggravate constipation, as shown by Connell et al. [40]. The lack of background increase in irregular contractility also confirms the decreased colonic intraluminal pressure observed in effects of relamorelin in mouse model which was associated with facilitated colonic transit [12].

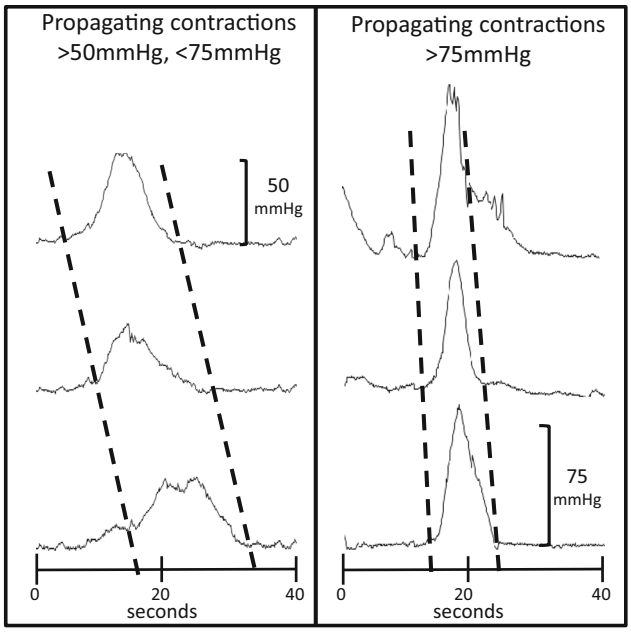

Fig. 2 Examples of manometric patterns observed in patients with chronic constipation administered relamorelin to illustrate the different colonic motor patterns assessed. The interrupted line is drawn to help identification of propagated pressure activity. Manometric sensors in the descending and sigmoid colon were 5 cm apart; the second sensor was located just below the distended barostatically controlled balloon, resulting in reduced sensitivity of the sensor to accurately record pressure amplitude

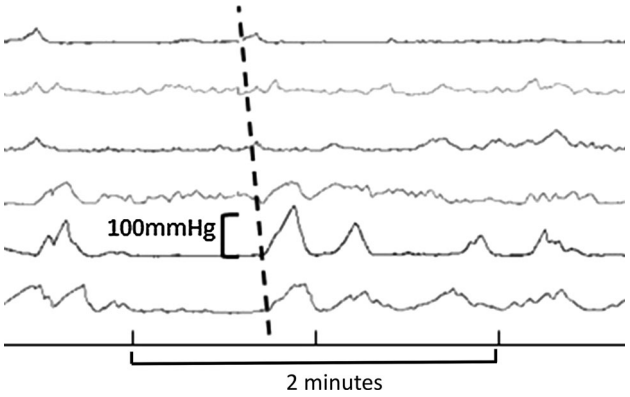

Fig. 3 Postprandial recording from a patient who received relamorelin; note several propagated contractions were observed, one of which was >116 mmHg at one level in the colon. Manometric sensors in the descending and sigmoid colon were 5 cm apart. The interrupted line coincides with the onset of each phasic pressure activity, illustrating the propagation through the *left colon*

The current study is the second clinical investigation to demonstrate that a ghrelin agonist, compared to placebo, significantly improves colonic motor function in humans after our prior report on the effects of relamorelin on colonic transit and bowel function [8]. Relamorelin increased the frequency of propagating contractions similar to other colonic prokinetics, such as the 5-HT_4 receptor agonist, prucalopride [39], bisacodyl [41], chenodeoxycholic acid [42], and neostigmine [43]. Additionally, relamorelin's effect on the colon mimics the ghrelin effect seen in upper gastrointestinal motility where relamorelin induces migrating motor complexes [4] and accelerates gastric emptying [29, 30]. It is conceivable that the prokinetic effect of ghrelin and its agonists is mediated through two different pathways, a vagal pathway and lumbosacral stimulation. This hypothesis is supported by studies in rodents which showed that ghrelin stimulated colonic contractility when given intravenously or intrathecally, but not when administered centrally into the fourth ventricle. This suggests a non-central effect of ghrelin in the stimulation of colonic motility, specifically activation of pelvic nerves from the sacral defecation center, innervating the enteric neurons in the distal colon [14]. This stimulation may lead to relamorelin's acceleration of the time to first bowel movement in patients with chronic constipation [8].

In colonic motility studies, the amplitude criteria for HAPCs in the literature vary from 50 to 116 mmHg [44]. To be conservative and consistent with previous studies [34, 37, 38] that measured amplitude using water-perfused manometric sensors, we defined HAPCs as >75 mmHg contractions propagating over at least 10 cm (that is, at least three manometric sensors) and PCs as >50 mmHg contractions propagating over at least 10 cm.

We were careful to exclude rectal evacuation disorder among our study cohort; the variability in responses observed may stem from the inclusion of patients with IBS-C; the literature documents the significant overlap and symptom phenotype transitions between IBS-C and functional constipation [45]. We attempted to avoid this confounder by excluding patients who at the time of study had predominant pain; however, we cannot completely exclude the possibility that the study group may have been heterogeneous.

A limitation of our study is that we did not simultaneously measure colonic transit and, therefore, the relationship of the numerical increases in HAPCs or PCs and the statistically significant increase in fasting PCs remain unproven and would require simultaneous manometry and transit measurements, preferably in an unprepared colon. Nevertheless, our data support the observation that the ghrelin agonist, relamorelin, stimulates colonic transit. In addition, our study appraised the effect of relamorelin over a 1-h postprandial period, and we did not address the frequency of the colonic contractions such as HAPCs over a prolonged (e.g., 24-h) period after chronic stable administration of the medication, which could be the focus of future studies, especially as we have demonstrated medium-term efficacy of relamorelin in the acceleration of

colonic transit and improvement of bowel function in patients with chronic constipation [8].

In conclusion, relamorelin may stimulate colonic motor activity in the form of propagated contractions, in addition to the previously reported acceleration of colonic transit in chronic constipation.

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Author contributions Andres Acosta is a fellow co-investigator and co-author and contributed toward screening of patients. Michael Camilleri is the principal investigator, helped with endoscopy and placement of colonic device, and author of manuscript. Amy Boldingh is the study coordinator and recruited participants. Irene Busciglio is the colonic motility technician and analyzed data. Alfred D. Nelson is a fellow co-investigator and co-author and contributed toward screening of patients. Duane Burton is the laboratory supervisor and analyzed data.

Compliance with ethical standards

Conflict of interest Dr. Camilleri serves on the advisory board of Rhythm Pharmaceuticals with payment for his services to his employer, Mayo Clinic. The other authors have no conflicts of interest.

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