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Study ID: RLM-MD-02

Title: A 12-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Protocol Amendment 3 Date: 05Mar2019

Title Page

Protocol Title: A 12-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Brief Protocol Title: Diabetic Gastroparesis Study 2

Protocol Number: RLM-MD-02

Amendment Number: 3

Product: Relamorelin

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND: [redacted]

EudraCT: 2017-002177-20

Emergency Telephone Number: Refer to study contacts list

Serious Adverse Event Reporting Email/Fax Number:
Email: [redacted]
Fax Number: [redacted]

Allergan Medical Safety Physician: Refer to study contacts list

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Protocol Amendment 3 Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	25 Mar 2018
Amendment 1	17 Jan 2018
Original Protocol	03 Oct 2017

Amendment 3 (05 Mar 2019)

Overall Rationale for Amendment 3:

This summary includes changes made to Protocol RLM-MD-02 from Protocol Amendment 2 (Dated 25 Mar 2018; details provided in Section 12.18). The purpose of Protocol Amendment 3 is to communicate changes made in response to recommendation from health authorities. These changes will not impact safety assessment of relamorelin or alter the risk-benefit ratio for study participants.

The following is a summary of content-oriented changes that were made. Strikethrough text denotes text removed and bolded text denotes added text. Additional administrative edits were also made, but not specifically noted (eg, corrected spelling, punctuation, grammar, abbreviation, and style errors) including global edits required for consistency.

Section Number	Description of Change	Rationale
Section 1 Synopsis and Section 4 Objectives and Endpoints	Modified definition of primary endpoints, added more details, and replaced definition for Responder with definition for Baseline.	For a more appropriate, clearly defined endpoint.
Section 1 Synopsis, Section 5.1 Overall Design, Section 12.9/Appendix 9 Study Tabular Design	Increased duration of study from 16 weeks to 18 weeks and increased Screening Period from 2 weeks to up to 4 weeks.	To align with change in the length of the Screening Period as described below.
Section 1 Synopsis and Section 5.1 Overall Design	Removed references to a BMI requirement	To align with the removal of the BMI inclusion criteria
Section 1 Synopsis Figure 1 Section 2 SOA**,** and Section 5.1 Overall Design Figure 2	Start of Screening Period revised form Day -28 to Day -42.	To allow more time for completion of endoscopy or upper GI series with contrast and for washout of prohibited medications.
Section 1 Synopsis and Section 5.1 Overall Design	Added requirement for study population at screening to have had a history of at least 2 vomiting episodes and to have had at least 1 vomiting episode during the Run-in Period.	To clarify that history of vomiting episodes and GEBT should be noted in the Run-in Period and not the Screening Period
Synopsis, Section 5.2 Participant and Study Completion, Section 12.9/ Appendix 9 Study Tabular Summary	Increased the number of sites from approximately 200 to approximately 350. Increased the number of screened participants from approximately 2000 to approximately 2500.	To allow for additional sites.

Section Number	Description of Change	Rationale
Section 2 SOA	Changed number of days for Screening Period from up to 14 days to up to 28 days. Added footnote "a" to specify when results from assessments at Visit 1 should be obtained; adjusted numbering of all footnotes that followed. Added ECG assessment at Visit 4. Modified footnote referencing urine drug screen (ie, footnote "j"), to specify that opioids are not drugs for which the investigator may choose not to consider exclusionary. Added footnote "k" to fasting blood glucose: Serum for all visits except for Visits 4 and 6 (plasma).	To align with the change in the start of in the Screening Period from Day -28 to Day -42. To provide details regarding additional requirements with the increase length of the Screening Period To meet recommendations made by MHRA and ANSM in its review of the protocol. To align with changes made to Exclusion Criteria #12 For clarification.
Section 2 SOA, Section 9.4.6 Self-monitoring of Blood Glucose, Section 12.2 Table 12-1 Protocol-Required Safety Laboratory Assessments	Removed assessment of glycated albumin from SOA and all related text in Section 9.4.6 and Section 12.2 Table 12-1	Preliminary results do not show that assessment of glycated albumin is useful for the adjustment of glycemic control.
Section 4.1 Clinical Hypotheses	Reformat section heading as level 2 per CPT. Updated and clarified both hypotheses.	To align with change in primary endpoint

Section Number	Description of Change	Rationale
Section 6.1 Inclusion Criteria	Amended Inclusion Criterion #6 to allow for a GI series with contrast as an assessment tool for documenting absence of an obstructing lesion and adjust timing of assessments from some time before screening (Visit 1) to sometime before the Run-in Period (Visit 2). Removed BMI criterion #9. Inclusion Criteria #10: added a reference to Appendix 3	To clarify what an acceptable alternative to upper endoscopy is for exclusion of an obstructing lesion (upper GI series with contrast) and to allow the procedure to be done during the Screening Period if not done previously. BMI not relevant for treatment of gastroparesis. To clearly comply with country-specific guidelines in CPT.
Section 6.2 Exclusion Criteria	Amended Exclusion Criterion #3 to specify that participants with active eating disorders at the time of screening are to be excluded, as opposed to those with a history of eating disorders. Exclusion Criterion #11: Added 5HT agonists as exclusionary drug. Amended Exclusion Criteria #12 to allow a participant with a positive urine drug screen at Screening to continue in the study while confirmatory testing is done on an aliquot of the original sample; specified that opioids are not drugs for which the investigator may choose not to consider exclusionary. Added exclusion criteria for hypersensitivity to the study treatments and their excipients (Exclusion Criterion #25) and for specific corrected ECG results (Exclusion Criterion #26).	For clarification Added because 5HT agonists are still approved in some countries To verify that positive urine drug screen results are not false-positive before excluding a participant from continuing in screening and clarify that use of opioids is exclusionary. To meet recommendation made by MHRA in its review of the protocols
Section 6.4 Screen Failures	Added option for the sponsor to permit a participant with a positive urine drug screen at Screening to continue in the Screening Period while confirmatory urine drug screen testing by a more specific method is carried on an aliquot of the original sample.	To verify that positive urine drug screen results are not false-positive before excluding a participant from continuing in screening, and to clarify that the use of barbiturates, benzodiazepines and amphetamines are allowable if prescribed for continuous use for a clinically appropriate indication

Section Number	Description of Change	Rationale
Section 7.1 Treatments Administered	Clarified that the first dose of study treatment is to be administered within ***approximately*** 30 minutes ***before*** the morning meal and the second daily dose is to be administered ***approximately*** 30 ***before*** the evening meal. Deleted option for investigator to contact sponsor if the participant could not inject study treatment into abdomen.	To clarify the timing of dosing and to be consistent with the wording in the ICF. Option to contact the sponsor removed as the sponsor does not currently have any information to support injection into alternative sites.
Section 7.1.1 Run-in Medications and Administrations	Replaced "breakfast" and "dinner" with "morning" and "evening" meals, respectively. Clarified that placebo should be administered **approximately** 30 minutes before each meal.	To be consistent with dosing of study treatment.
Section 7.4 Blinding	Unblinding procedures modified; requirement of investigator to notify sponsor prior to unblinding modified to encouraging the investigator to notify the sponsor prior to unblinding, but requiring notification within 24 hours after breaking the blind.	To meet recommendation made by MHRA in its review of the protocols, but applicable globally
Section 7.7.1 Prohibited Treatments	SLGT-1 added as an exception to prohibited drugs along with SLGT-2; specified that SGLT-1 and SGLT-2 inhibitors are prohibited for 3 days prior to the GEBT performed at the start of the Run-in Period for all participants and for a subset of participants at Visit 7 or Early Termination Visit at a subset of sites. Table 7-2: Corresponding changes as per above; rearranged rows by washout period; specified 3 consecutive weeks or more to clarify that once weekly requirements of anti-emetics for this amount of time is prohibitory; added row for 5HT4 agonists; added tramadol as an example of an opioid; amended washout period for opioids from "10 days prior to the start of the Run-in Period" to Not applicable since the use of opioids is not allowed and referenced exclusion criteria #12 and #13 accordingly.	To clarify that the SGLT-1 or SGLT-2 inhibitors are prohibited only 3 days prior to GEBT as they may affect interpretation of the test, but are otherwise allowed. In response to FDA request for more definitive direction to investigators regarding contacting the sponsor to discuss the advisability of continued participation in the study by a patient needing frequent anti-emetic treatment; Tramadol added as an example; 5H4T agonists added since they are still approved in some countries; aligned with exclusion criteria.
Section 7.7.3 Rescue Medicine	Clarifications made to text; Removed antihistamines as an example of an anti-emetic drug	Requested by FDA as described above; there is no clear evidence that antihistamines have anti-emetic benefits in the context of vomiting and nausea associated with DG

Section Number	Description of Change	Rationale
Section 8 Discontinuation/Withdrawal Criteria; Section 12.8 Appendix 8: Standard Discontinuation Criteria	Removed: "non-compliance with study treatment"	Non-compliance minimum criterion is not defined for this protocol
Section 8.1.1 Temporary Discontinuation	Added requirement for the investigator to contact the sponsor under specific conditions.	In response to FDA request to include standardized criteria for restarting study treatment, including proposed dose adjustments
Section 9.1 Efficacy Assessments	Defined zero and 10 scores of the DG assessments.	To align with the change in the primary endpoint and updates made to the SAP in response to FDA request
Section 9.1.1.1 Primary Efficacy Assessments	Specified time period (ie, from baseline to Week 12) for which the change in DGSSS will be assessed; deleted definition and details of numerical rating scale scores; deleted definition for a DGSSS Responder	To align with the change in the primary endpoint and updates made to the SAP in response to FDA request
[redacted]		
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Specified that medical occurrences that begin before the start of study treatment but after obtaining IC will be recorded in the AE section of the eCRF instead of the Medical History/Current Medical Conditions section of the eCRF as previously stated.	To reflect current practices.

Section Number	Description of Change	Rationale
Section 9.2.4 Regulatory Reporting Requirements for SAEs	Details added to second bullet for clarity.	To clearly comply with country-specific guidelines in CPT
Section 9.2.7.1 Hy's Law	Editorial changes for clarity.	For clarification and to align with changes made in Appendix 4
Section 9.2.7.2 Inadequate Control of Diabetes: Hyperglycemia and Hypoglycemia	Added the phrase "Inadequate Control of Diabetes" to section title.	For consistency with MSMP language
Section 9.2.8 Medication Error	Specified 10 µg BID or 20 µg/day as the maximum recommended dose. Deleted statement referencing a dose of greater than 150 µg BID to be considered an overdose.	For clarity and accuracy.
Section 10.1 Sample Size Determination	Revised and clarified sample size determination	To align with updated SAP: sample size calculations based on the CFB to Week 12
Section 10.2 Populations for Analyses	Table 10-1, Analysis Populations – specified "double-blind" treatment for Safety Population	To align with SAP.
Section 10.3.1 Key Statistical Methodology, Table 10-2 Statistical Methodology	Added row to describe CFB.	For clarification and to align with updated endpoints
Section 10.3.2 Efficacy Analysis, Table 10-3 Primary and Secondary Endpoints	Updated primary endpoint and its description.	To align with change in primary endpoint
Section 10.3.2.2 Multiple Comparisons Procedure	Clarifications made to Family 1/Hypothesis H1; reference made to SAP for other efficacy analyses.	To align with change in primary endpoint
Section 10.3.2.3 Missing Data	Updated how missing data will be handled.	To align with updated SAP
Section 10.3.4 Other Analyses	Replaced language about specific analyses and how they will be described in SAP with general language that analyses for additional endpoints will be specified in the SAP	Correction and clarification
Section 10.3.5 Interim Analyses	Added a requirement for a DSMB to review interim safety data at defined intervals throughout the study.	As requested by health authorities including FDA and National Agency for the Safety of Medicine and Health Products (ANSM)

Section Number	Description of Change	Rationale
Appendix 1 Abbreviations	Abbreviations added and deleted throughout as appropriate for those abbreviations being used or not used throughout this document	Clarity and corrections
Section 12.2 Appendix 2 Clinical Laboratory Tests, Table 12-1 Protocol-Required Safety Laboratory Assessments	Added footnote for fasting blood glucose specifying that serum will be assessed for all visits except Visits 4 and 6, when plasma will be assessed.	For clarification
Section 12.3 Appendix 3 Study Governance Considerations	Made un-numbered subsections level 3 headings Reorganized subsections to align with revised CPT	To align with revised CPT
Section 12.3.3 Appendix 3 Informed Consent Process	Additional criteria added for IC process for written documentation to be obtained in accordance with relevant country and local privacy requirements.	To align with revised CPT
Section 12.3.5 Appendix 3 Data Quality Assurance	Replaced requirement for records and documents to be retained for 15 years after study completion to requirement for them to be retained as per the clinical trial agreement.	To align with revised CPT
Section 12.3.9 Publication Policy	Section added	To align with revised CPT
Section 12.4 Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Made un-numbered subsections level 3 headings	To align with revised CPT
Section 12.4.1 Appendix 4, Definition of AE	Revised procedures for reporting AESIs. Identified specific AESIs (ie, Hy's law cases, inadequate control of diabetes: hyperglycaemia and hypoglycaemia, and MACE).	To comply with Allergan's current practices. As required per current CPT.

Section Number	Description of Change	Rationale
Section 12.5 Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information	Female Participants Who Become Pregnant – deleted text that an elective termination is an AE or SAE; provided examples and details for abnormal pregnancy outcomes, including genetic abnormalities. Deleted footnote "b" regarding hormonal contraception's susceptible interactions with study intervention. Pregnancy Testing – specified that pregnancy test should be performed as per SOA, instead of "at the end of relevant systemic exposure" as previously stated. Specified "unless required by local regulations" when stating that pregnancy testing is not required during the treatment period or after the last dose of study treatment.	To align with revised CPT Correction, as the information in footnote b is not relevant to this study intervention. For clarity

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1. Synopsis

Protocol Title: A 12-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Brief Title: Diabetic Gastroparesis Study 2

Study Phase: 3

Study Rationale:

Previous non-clinical and Phase 1 studies have shown relamorelin to have a potent prokinetic effect on the stomach, accelerating gastric emptying (GE) in both healthy volunteers and patients with diabetic gastroparesis (DG).

Gastroparesis (GP) is a disorder characterized by signs and symptoms of nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety along with delayed GE, such that movement of food from the stomach to the small intestine takes longer than normal and occurs with unpredictable timing. Diabetes mellitus, either type 1 or 2 (T1DM or T2DM), is considered to be the most common identifiable cause of GP. This complication is a result of chronically elevated blood glucose levels, which are known to damage nerve structure and function. DG complicates management of blood glucose for both T1DM and T2DM patients due to carbohydrates being delivered to and therefore absorbed from the small intestine at variable times after ingestion. As a result, diabetic patients with DG often have poorly controlled diabetes, frequently with alternating hypo- and hyperglycemia, especially if treated with insulin.

In Phase 2 studies, the pharmacodynamic effect of relamorelin was confirmed in larger numbers of participants with DG, and in addition, beneficial effects on the symptoms of DG were observed. Safety and tolerability were shown at therapeutic doses, including the 10 µg twice daily (BID) dose to be studied in Phase 3 studies, supporting the decision to obtain confirmatory evidence of safety and efficacy of relamorelin in Phase 3, and specifically in Study RLM-MD-02.

A significant unmet medical need exists for a safe and effective treatment of patients with DG whose quality of life is impacted by their disease and for whom the current standard of care is suboptimal; therefore, the sponsor is performing this study to further the development of relamorelin for the treatment of DG.

Objectives and Endpoints:

Objectives	Endpoints
Primary	

• To compare the efficacy of relamorelin with placebo in participants with DG with respect to a composite of the following core signs and symptoms of DG:
  • Nausea
  • Abdominal pain
  • Postprandial fullness
  • Bloating
	• Change from Baseline to Week 12 in the weekly DGSSS. Baseline is defined as the average of the 2 weekly DGSSS from the 2-week placebo Run-in Period.

• To compare the efficacy of relamorelin with placebo in participants with DG with respect to vomiting frequency	• Vomiting Responder, defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the 12-week Treatment Period
Secondary	Secondary

• To compare the efficacy of relamorelin with placebo in participants with DG with respect to the following individual symptoms of the DGSSS:
  • Nausea
  • Abdominal Pain
  • Postprandial fullness
  • Bloating
	• Individual Symptom (ie, nausea, abdominal pain, postprandial fullness, and bloating) Responder, defined as a participant with at least a 2-point decrease in the change from baseline on the weekly average of the symptom severity (at its worst) during each of the last 6 weeks of the 12-week Treatment Period

• To compare the safety of relamorelin with placebo in participants with DG	• AEs, clinical laboratory values, vital signs, ECGs, HbA1c, and anti-relamorelin antibodies

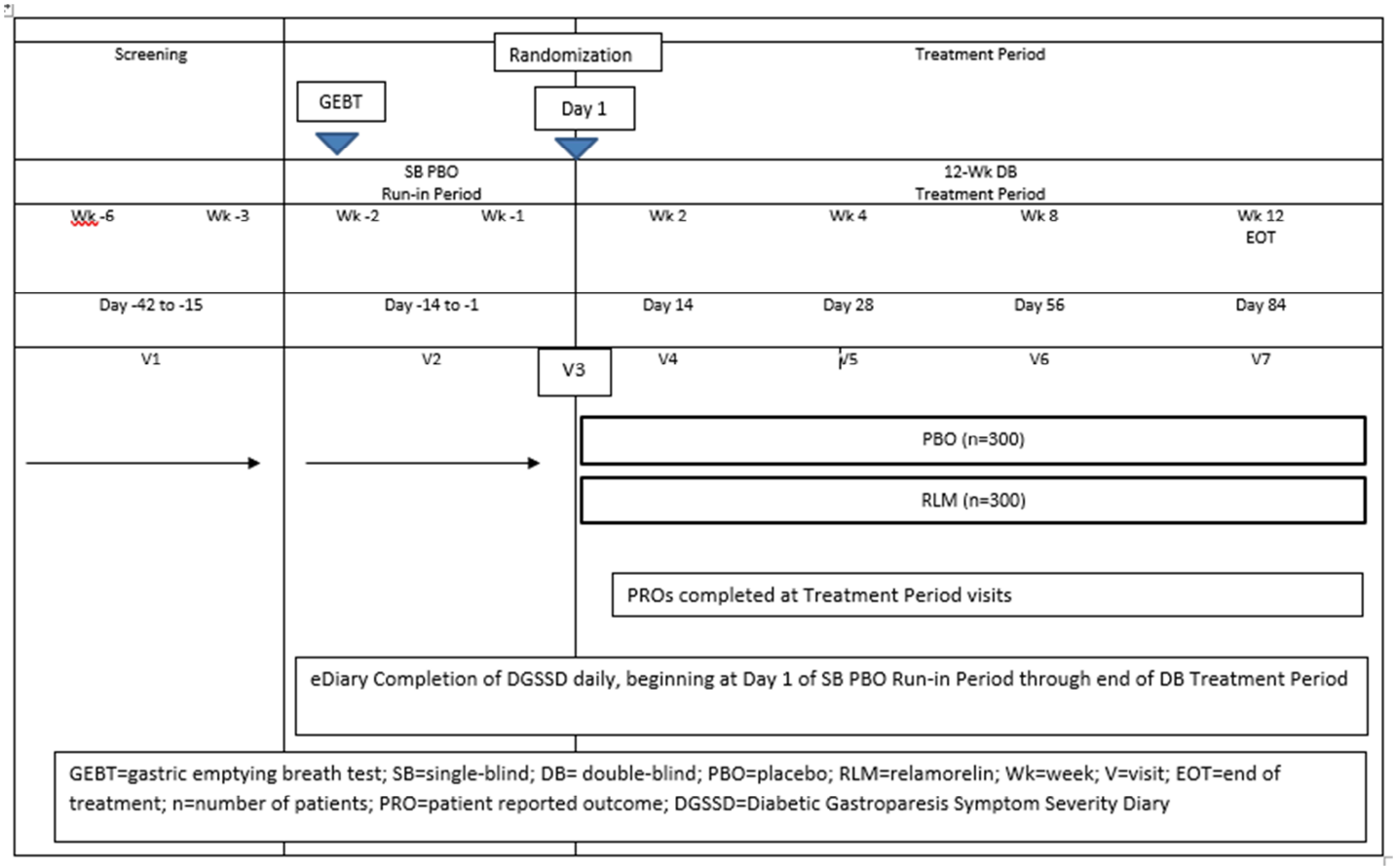
Overall Study Design:

- Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group
- Treatment Groups: Relamorelin 10 µg or placebo subcutaneously (SC) twice daily (BID),
- Study Duration: Up to 18 weeks, including a Screening Period of up to 4 weeks, a 2-week Run-in Period, and a 12-week Treatment Period:
    - Run-in Period: Participants who meet initial study entry criteria during the Screening Period will enter a 2-week Run-in Period, during which they will self-administer placebo twice daily SC. Using an electronic hand-held device, participants will report their symptoms via the Diabetic Gastroparesis Symptom Severity Diary (DGSSD) as well as their [redacted] compliance, and use of rescue medication.

- 12-week Treatment Period: Participants who meet study entry criteria at the end of the Run-in Period, will be randomized 1:1 to blinded treatment with relamorelin 10 µg or placebo, and will continue to use the electronic hand-held device for reporting of their symptoms via the DGSSD as well as their [redacted] compliance, and use of rescue medication.

Assuming they meet entry criteria, participants who successfully complete this study are eligible, to enter a placebo-controlled, long-term safety and efficacy study (Study RLM-MD-03) during which they will receive study treatment for an additional 46 weeks.

Figure 1: RLM-MD-02 Study Schematic



Number of Participants:

Approximately 2500 participants will be screened to achieve 600 participants randomly assigned to study treatment (300 per treatment group). A total of 480 participants are expected to complete the study (240 per treatment group).

Study Population:

- Screening: Males and females aged 18 years and older; T1DM or T2DM with controlled and stable blood glucose levels and HbA1c ≤ 11%; symptoms suggestive of DG for at least 3 months, with mechanical obstruction of the gastrointestinal (GI) tract as the cause of symptoms having been ruled out; history of at least 2 vomiting episodes.

- During the Run-in Period: at least 1 vomiting episode and delayed GE by gastric emptying breath test (GEBT)

- After Run-in Period: Evidence of compliance during the Run-in Period with the use of the electronic hand-held device for entry of data, with twice daily SC injections of the study treatment, no treatment with GI promotility agents during the Run-in Period, at least 1 vomiting episode reported during the 2-week Run-in Period, and a score of ≥ 16 for the average of the daily Diabetic Gastroparesis Symptom Severity Score (DGSSS) assessments measured during the Run-in Period.

Number of Sites:

Approximately 350 sites (globally)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. Introduction

Relamorelin (also known as RM-131) is a novel, potent, and selective synthetic penta-peptide ghrelin analogue, which is being developed for treatment of diabetic gastroparesis (DG).

Ghrelin, a 28 amino-acid peptide, is produced predominantly by specialized cells of the stomach and pancreas, and has been demonstrated to be a central modulator of energy homeostasis. It is the natural ligand for the Growth Hormone Secretagogue 1 α (GHS1α) receptor, a potential target for treatment of clinical conditions associated with impaired gastric motility and energy balance. Administration of ghrelin has been shown to promote gastric motility in mice, rats, dogs, and humans (Dornonville 2004; Trudel 2003; and Murray 2005). It can increase body weight, attributed to a combination of enhanced food intake, increased gastric emptying (GE), and increased food assimilation, coupled with a transient increase in growth hormone (GH), which promotes nutrient incorporation into tissues.

Relamorelin has similar characteristics to native ghrelin but with enhanced efficacy, plasma stability, and circulating half-life. As a ghrelin mimetic, it acts as a potent prokinetic agent, as evidenced by significant effects on GE as well as effects on overall colonic transit (Acosta 2015, Acosta 2016).

Gastroparesis (GP) is a disorder characterized by delayed GE, such that movement of food from the stomach to the small intestine is delayed. The pathophysiology of GP has not been fully elucidated but seems to involve abnormalities in the autonomic nervous system (vagus nerve), smooth muscle cells, enteric neurons, and interstitial cells of Cajal; in DG, change in the type of macrophages in the gastric musculature suggest a role for inflammation as a cause of delayed GE.

Diabetes mellitus, either type 1 or 2 (T1DM/T2DM), is considered to be the most common, specifically identifiable cause of GP. This complication is a result of chronically elevated blood glucose levels, which are known to damage nerve structure in general, and the vagus nerve in particular, and negatively affect function (Parkman 2004).

DG is a chronic condition that requires prolonged treatment. Core signs and symptoms of DG are nausea, abdominal pain, post-prandial fullness, bloating, vomiting, and early satiety (a feeling of fullness after eating just a few bites) (Camilleri 2013). These symptoms can be debilitating and, when uncontrolled, have a significant negative impact on patient quality of life and functioning, including work productivity (Camilleri 2011, Parkman 2011). Serious adverse sequelae of DG include: potentially life-threatening dehydration due to persistent vomiting, gastroesophageal reflux disease (GERD) that can advance to esophagitis, formation of bezoars, difficulty managing blood glucose levels, and malnutrition due to poor absorption of nutrients or a low-calorie intake (U.S. Department of Health and Human Services, 2012). Aside from the impact on patients, these events often lead to hospitalization (Koch 2016), resulting in a high economic burden for health care systems.

DG complicates management of blood glucose for both T1DM and T2DM patients due to carbohydrates being delivered to and therefore absorbed from the small intestine at unpredictable times (Rayner 2001). As a result, diabetic patients with DG often have poorly controlled diabetes, frequently with alternating hypo- and hyperglycaemia, especially if treated with insulin.

Little data on the incidence and prevalence of GP are available; however, an older epidemiology study of diagnosed GP (defined as typical symptoms plus confirmed delayed GE by scintigraphy) showed prevalence of 24.3 per 100,000 inhabitants and incidence of 6.3 per 100,000 persons per year in Olmstead County, MN from 1996 to 2006 (Jung 2008). This study reported that age-adjusted prevalence of GP was approximately 4 times greater for women than men (37.8 versus 9.6 cases per 100,000 persons). It has been reported that 30% to 50% of diabetic patients have delayed GE, while the prevalence of the specific symptoms of GP (nausea and vomiting) is lower, with approximately 10% of patients with diabetes being affected (Hopkins Medicine, 2013). According to Bharucha (2015), in a restricted community-based study of GP in DM, the average cumulative incidence of symptoms and delayed GE over 10 years was higher in T1DM (5%) than in T2DM (1%) and controls (1%). It is expected that the incidence of DG will increase worldwide in proportion to the increase in T2DM due to increasing obesity.

3.1. Study Rationale

Previous non-clinical and Phase 1 studies have shown relamorelin to have a potent prokinetic effect on the stomach, accelerating GE in both healthy volunteers and participants with diabetic gastroparesis (DG).

GP is a disorder characterized by signs and symptoms of nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety along with delayed GE, such that movement of food from the stomach to the small intestine takes longer than normal and occurs with unpredictable timing. Diabetes mellitus, either type 1 or 2 (T1DM or T2DM), is considered to be the most common identifiable cause of GP. This complication is a result of chronically elevated blood glucose levels, which are known to damage nerve structure and function. DG complicates management of blood glucose for both T1DM and T2DM patients due to carbohydrates being delivered to and therefore absorbed from the small intestine at variable times after ingestion. As a result, diabetic patients with DG often have poorly controlled diabetes, frequently with alternating hypo- and hyperglycemia, especially if treated with insulin.

In Phase 2 studies, the pharmacodynamic effect of relamorelin was confirmed in larger numbers of participants with DG, and in addition, beneficial effects on the symptoms of DG were observed. Safety and tolerability were shown at therapeutic doses, including the 10 µg twice daily (BID) dose to be studied in Phase 3 studies, supporting the decision to obtain confirmatory evidence of safety and efficacy of relamorelin in Phase 3, and specifically in Study RLM-MD-02.

A significant unmet medical need exists for a safe and effective treatment of patients with DG whose quality of life is impacted by their disease and for whom the current standard of care is

Relamorelin
suboptimal; therefore, the sponsor is performing this study to further the development of relamorelin for the treatment of DG.

3.2. Background

Relamorelin is being developed for the treatment of patients with DG to address the existing unmet need for an effective and safe/tolerable treatment, attested to by the FDA's granting of fast-track designation to relamorelin for the treatment of DG in adults. It is a member of an established class of compounds, ghrelin agonists, but if granted regulatory approval, will be the first member of this class to attain marketing approval.

In clinical studies to date, 466 participants with T1DM or T2DM with DG have been exposed to relamorelin at doses up to 100 µg administered BID by subcutaneous (SC) injection for 12 weeks.

In a randomized, placebo-controlled, multiple-dose Phase 2a study (RM-131-004), participants with T1DM and T2DM, and DG received 28 days of double-blind treatment with relamorelin. GE was accelerated and compared to placebo, relamorelin 10 µg BID significantly decreased the vomiting severity score and mean number of weekly vomiting episodes in participants with vomiting at baseline and produced improvement in the 4 individual DG symptoms of nausea, abdominal pain, bloating and early satiety as well as significant improvement in the composite endpoint of the 4 symptoms (p=0.043). The safety and tolerability profile of relamorelin in Study RM-131-004 was generally good.

The results in Study RM-131-004 helped the sponsor select the target patient population for enrolment in the Phase 2b Study RM-131-009, DG patients with vomiting at baseline, and encouraged assessment of a wider range of relamorelin doses.

Study RM-131-009 was a randomized, double-blind, placebo-controlled, stratified, multiple dose, multi-national study with 10 µg BID, 30 µg BID and 100 µg BID doses of relamorelin. A total of 393 participants with T1DM or T2DM, who had both delayed GE and moderate to severe symptoms of GP were enrolled and treated. The Phase 2b study confirmed a statistically significant effect of relamorelin over placebo on GE for the 10 µg and 30 µg doses. Vomiting frequency was reduced from baseline to Week 12 by approximately 75% in all relamorelin dose groups; however, there was also a strong, previously unobserved placebo effect on vomiting frequency (reduction of approximately 70%) that precluded statistical significance of the relamorelin effect that was observed. Results for the key secondary endpoint, a composite score of 4 DG symptoms (nausea, abdominal pain, bloating and early satiety) showed benefit of treatment with relamorelin compared to placebo although the difference was not statistically significant; the same was true for an exploratory endpoint, a composite score of 4 DG symptoms that included postprandial fullness instead of early satiety.

Relamorelin was generally safe and well tolerated among participants with T1DM or T2DM and DG. There were more reports of diarrhea and hyperglycemia-related events on relamorelin compared to placebo; hypoglycemia was infrequently reported (1.2% incidence in the placebo

Relamorelin
and relamorelin 100 µg groups only). Twenty-three serious adverse events (SAEs) were reported in the 289 participants treated with the 3 doses of relamorelin and 8 in the 104 participants treated with placebo. The number and characteristics of the reported SAEs reflected the advanced underlying disease state of this DG population with long-standing T1DM or T2DM and other common co-morbidities and only 2 of the SAEs (cardiac failure congestive and diabetes mellitus inadequate control) were assessed by the investigator as possibly related to study treatment, both in the 100-µg treatment group. Three adverse events (AEs) of diabetic ketoacidosis were reported, one event on each relamorelin dose. A total of 20 relamorelin-treated participants and 3 placebo-treated participants discontinued study treatment because of a treatment-emergent AE; only 3 in the relamorelin10 µg BID group.

With respect to laboratory findings, in some participants glycemic control may have been negatively affected by the introduction of relamorelin. There were trends in increasing haemoglobin A1c (HbA1c) values after the initiation of relamorelin, which increased slightly after approximately 8 weeks, and dose-related trends in fasting hyperglycemia. Otherwise, no clinically relevant abnormalities were seen for other laboratory tests, including liver function tests, electrocardiograms (ECGs), physical examination findings, and injection site reactions; anti-drug antibodies (ADAs) were not found.

A detailed description of the chemistry, pharmacology, efficacy, and safety of relamorelin is provided in the investigator's brochure (Relamorelin Investigator's Brochure).

3.3. Benefit/Risk Assessment

Based on information about relamorelin obtained to date, the benefits of study participation are expected to include accelerated GE and clinically meaningful improvement in the symptoms of DG, including nausea, abdominal pain, postprandial fullness, bloating, vomiting frequency, early satiety, and vomiting severity. A potential risk of treatment is worsening of glycemic control, including the possibility of diabetic ketoacidosis occurring. However, preventive measures, including special laboratory assessments to allow early recognition by investigators and participants of rising glucose levels, are being included in this protocol so that early remedial action (eg, adjustment of medication and diet) may be taken to minimize increase in glucose levels; this might increase the incidence of hypoglycemic reactions, especially in participants with T1DM. See Section 5 Study Design for details of study procedures, dose, and study design justification.

More detailed information about the known and expected benefits and risks and reasonably expected AEs associated with relamorelin are provided in the investigator's brochure (Relamorelin Investigator's Brochure); information about the investigational directions for use (DFU) for the pen injector, the device that will be used to administer study treatment are also provided.

4. Objectives and Endpoints

Objectives	Endpoints
Primary	Primary

• To compare the efficacy of relamorelin with placebo in participants with DG with respect to a composite of the following core signs and symptoms of DG:
  • Nausea
  • Abdominal pain
  • Postprandial fullness
  • Bloating
	• Change from Baseline to Week 12 in the weekly DGSSS. Baseline is defined as the average of the 2 weekly DGSSS from the 2-week placebo Run-in Period.

• To compare the efficacy of relamorelin with placebo in participants with DG with respect to vomiting frequency	• Vomiting Responder, defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the 12-week Treatment Period
Secondary	Secondary

• To compare the efficacy of relamorelin with placebo in participants with DG with respect to the following individual symptoms of the DGSSS:
  • Nausea
  • Abdominal Pain
  • Postprandial fullness
  • Bloating
	• Individual Symptom (ie, nausea, abdominal pain, postprandial fullness, and bloating) Responder, defined as a participant with at least a 2-point decrease in the change from baseline on the weekly average of the symptom severity (at its worst) during each of the last 6 weeks of the 12-week Treatment Period

• To compare the safety of relamorelin with placebo in participants with DG	• AEs, clinical laboratory values, vital signs, ECGs, HbA1c, and anti-relamorelin antibodies

4.1. Clinical Hypotheses

The clinical hypotheses are:

1) DG participants receiving relamorelin compared with DG participants receiving placebo will experience greater improvement in DGSSS.
2) A greater proportion of DG participants receiving relamorelin than DG participants receiving placebo will achieve “Vomiting Responder” status, defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the 12-week Treatment Period.

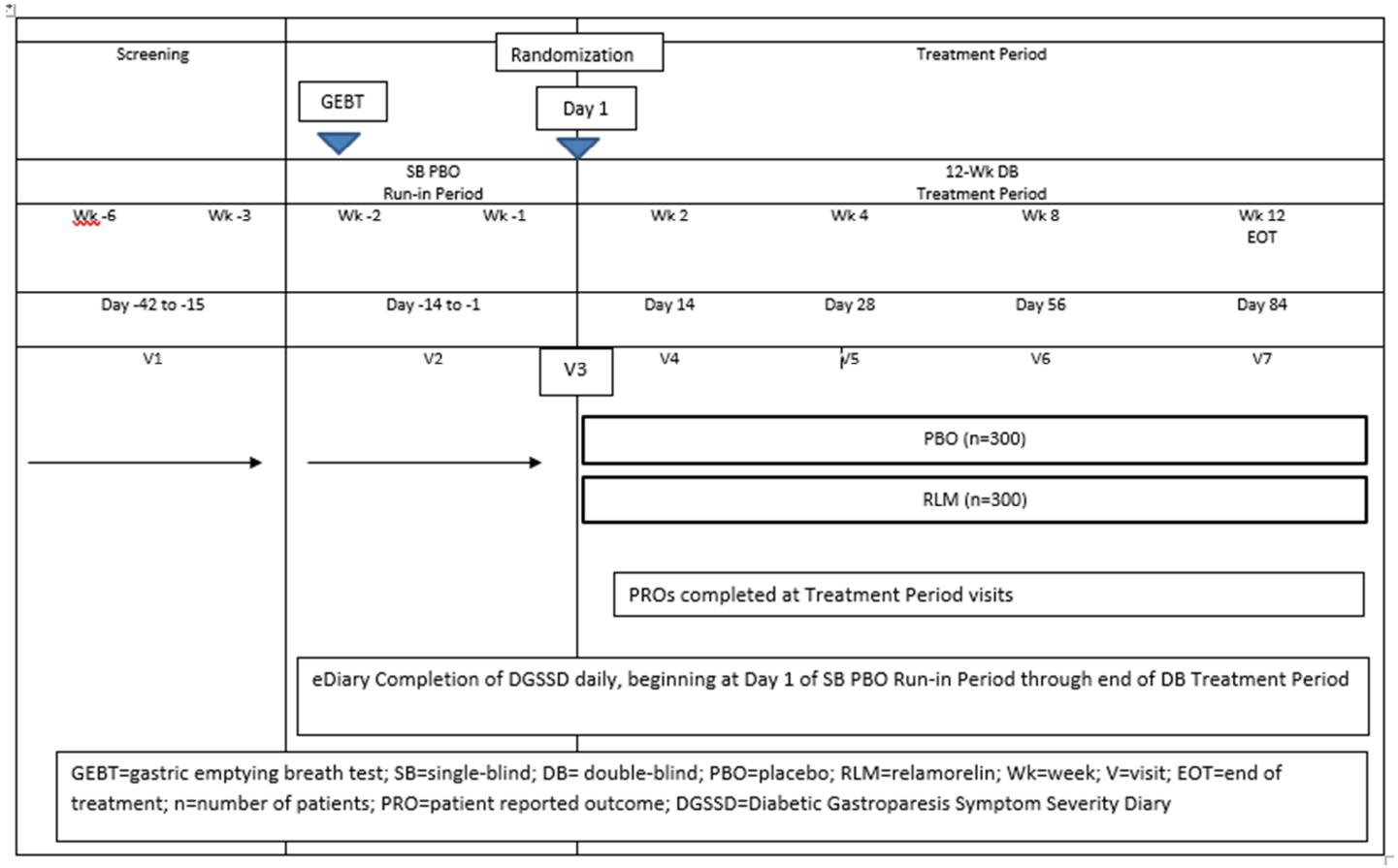
5. Study Design

5.1. Overall Design

- Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group
- Treatment Groups: Relamorelin 10 µg or placebo, twice daily, SC
- Study Duration: Up to 18 weeks, including a 12-week Treatment Period
- Study Periods: A Screening Period of up to 4 weeks, a 2-week Run-in Period, and a 12-week Treatment Period as follows:
    - Run-in Period: Participants who meet initial study entry criteria during the Screening Period will enter a 2-week placebo Run-in Period, during which they will self-administer single-blind placebo twice daily, SC. Using an electronic hand-held device, participants will report their symptoms via the Diabetic Gastroparesis Symptom Severity Diary (DGSSD) as well as their [redacted] compliance, and use of rescue medication.
    - 12-week Treatment Period: Participants who meet entry criteria at the end of the Run-in Period, will be randomized 1:1 to blinded treatment with relamorelin 10 µg or placebo. Participants will continue to use the electronic hand-held device for reporting of their symptoms via the DGSSD as well as their [redacted] compliance, and use of rescue medication.

See Figure 2 for Study Schematic

Figure 2: RLM-MD-02 Study Schematic



Study Population:

- Screening: Males and females aged 18 years and older; T1DM or T2DM with controlled and stable blood glucose levels and HbA1c ≤ 11%; symptoms suggestive of DG for at least 3 months, with mechanical obstruction of the gastrointestinal (GI) tract as the cause of symptoms having been ruled out; history of at least 2 vomiting episodes.

- During the Run-in Period: At least 1 vomiting episode and delayed GE by gastric emptying breath test (GEBT)

- After Run-in Period: Evidence of compliance during the Run-in Period with the use of the electronic hand-held device for entry of data, with twice daily SC injections of the study treatment, no treatment with GI promotility agents during the Run-in Period, at least 1 vomiting episode reported during the 2-week Run-in Period; and a score of ≥ 16 for the average of the daily DGSSS assessments measured during the Run-in Period.

For studies conducted at US (IND) sites and non-US (non-IND) sites, data from IND and non-IND study sites will be pooled together for analysis.

Assuming they meet entry criteria, participants who successfully complete this study are eligible to enter a placebo-controlled, long-term safety and efficacy study (RLM-MD-03) during which they will receive study treatment for an additional 46 weeks.

5.2. Participant and Study Completion

Approximately 2500 participants will be screened at approximately 350 study sites (globally) to achieve 600 participants randomly assigned to study treatment (300 participants per treatment group). A total of 480 participants are expected to complete the study (240 participants per treatment group). See Section 10.1 for details on sample size determination.

5.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including at least 84 days of treatment, and the last visit (Visit 7). Independent of the end of study definition, all laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or MSP.

5.4. Scientific Rationale for Study Design

The sponsor has designed this randomized, double-blind, placebo-controlled, parallel-group study to follow regulatory recommendations for conduct of Phase 3 therapeutic confirmatory studies, specifically the ICH Harmonized Tripartite Guideline E8 (General Considerations for Clinical Trials, Current Step 4 version dated 20 July 2000) and Guideline E10 (Choice of Control Group and Related Issues in Clinical Trials, Current Step 4 version dated 17 July 1997). The study also has been designed to comply with recommendations made by the US FDA, Center for Drug Evaluation and Research (CDER) in the Draft Guidance for Industry, Gastroparesis: Clinical Evaluation of Drugs for Treatment, July 2015, including those for the minimum duration of studies to show efficacy (at least 12 weeks) and inclusion as part of the development plan of a long-term placebo-controlled safety study (12 months, with appropriate pre-specified provisions for rescue medications).

Several design features have been incorporated in the current study in an effort to minimize bias, including a placebo run-in and double-blind design. Random assignment of participants avoids bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment groups. The use of a placebo control permits prospective comparison between the relamorelin group and the control group. Furthermore, the placebo run-in period with collection of data (symptoms in a daily diary) was incorporated into this study to allow study personnel to assess compliance with and tolerability of these procedures prior to randomization, and to obtain robust baseline measurements prior to initiating study treatment dosing. The run-in period also allows the confirmation of vomiting symptoms in addition to a history of vomiting.

5.5. Justification for Dose

Study RM-131-009 was a 12-week Phase 2b, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of relamorelin in diabetic participants with moderate to severe DG. The doses included within the study were 10 µg BID, 30 µg BID, and 100 µg BID. In general, all doses tested within RM-131-009 appeared to demonstrate meaningful reductions in overall DG symptom scores including vomiting episodes, with acceptable safety and tolerability. The frequency of vomiting episodes was reduced from baseline over the 12-week Treatment Period to a similar extent for participants who received the 3 doses of relamorelin and placebo. Based upon the observed dose response of change-from-baseline symptom scores collected daily over the course of 12 weeks using the DGSSD, the 30 µg BID, and 100 µg BID doses demonstrated apparent maximal symptom score improvements, while the 10 µg BID dose achieved near maximal improvements. Of note, the twice-a-day regimen of relamorelin appears to be necessary for effective symptom relief; the 10 µg once daily study treatment did not demonstrate significant improvement in symptom relief compared to placebo after 28 days of dosing in Study RM-131-004.

Review of the safety laboratory data collected in RM-131-009 revealed an apparent dose-related increase in HbA1c values. Although the variability in HbA1c response was high across all treatments, the 30 µg BID and 100 µg BID doses demonstrated apparent maximal changes in HbA1c values, while the 10 µg BID dose resulted in an approximately half-maximal increase

after 12 weeks of study. Shorter durations of treatment (4 weeks) with 10 µg BID of relamorelin, as observed in Study RM-131-004, did not demonstrate this apparent increase in HbA1c in diabetic participants.

Based on the efficacy and safety data, the relamorelin dose selected for this study is 10 µg BID.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male and female participants aged 18 years or older at screening (Visit 1)

[redacted]

4. DG defined as at least a 3-month history prior to screening (Visit 1) of symptoms on an ongoing basis that are suggestive of GP[redacted]

[redacted]

[redacted]

10. Able to provide written informed consent (IC) prior to any study procedures and willing and able to comply with study procedures (as defined in Appendix 3)

[redacted]

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

[redacted]

3. Participants who are actively experiencing anorexia nervosa, binge-eating, bulimia, or other eating disorder at the time of Screening (Visit 1) are excluded regardless of when diagnosis was established.

4. History of intestinal malabsorption (including celiac disease even if well-controlled on a gluten-free diet) or pancreatic exocrine insufficiency; also, history of non-celiac gluten sensitivity

5. History of belching disorders, other nausea and vomiting disorders (eg, chronic nausea and vomiting syndrome, cyclic vomiting syndrome, cannabinoid hyperemesis syndrome), or rumination syndrome

[redacted]

10. Currently receiving parenteral feeding or presence of a nasogastric or other enteral tube for feeding or decompression

[redacted]

[redacted]

24. Functional dyspepsia diagnosed before the diagnosis of diabetes mellitus

[redacted]

their advanced symptoms and, therefore, are unlikely to benefit from further pharmacological intervention have been excluded. Although GP invariably affects negatively the ability of participants to achieve optimum diabetic control, an attempt to achieve stable and controlled blood glucose levels must be made by the patient prior to enrollment.

6.3. Lifestyle Restrictions

There are no specific dietary restrictions in the study. It is expected that participants are aware of the importance of maintaining reasonable consistency in timing and size of meals (and specifically carbohydrate intake) for achieving adequate control of hyperglycemia but appreciate that the presence of GP may make this difficult.

For timing of meals around the GEBT, refer to the Study Reference Manual.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. Screen failures can fail to meet criteria for random assignment to study treatment in the study either before or after participation in the Run-in Period.

Participants who do not meet the criteria for participation in this study (screen failure) before entering the Run-in Period may be rescreened once if the reason for screen failure is only because of Inclusion Criterion 3 "HbA1c ≤11.0% at Screening (Visit 1)." In this specific situation, the patient may be rescreened after at least one month and no more than 6 months of further effort to achieve improved glycemic control, as indicated by HbA1c being ≤11.0%.

Rescreening of a participant for any other reason is up to the discretion of the Sponsor and must be approved by the Sponsor prior to any rescreening procedures. The timeframe for rescreening is up to 6 months from the time of screen failure. Participants who enter the Run-in Period will not be allowed to be rescreened. Rescreening requires that a participant be assigned a new participant number and after repeating the Informed Consent Process, undergo all original screening assessments.

The sponsor may permit a participant with a positive UDS by immunoassay, at Screening (Visit 1) to continue in the Screening Period while confirmatory urine drug screen testing by a more specific method is carried out on an aliquot of the original urine sample. If the confirmatory test is negative, the initial positive urine drug screen will be considered to have been a false-positive urine drug screen and the participant can continue in screening. Confirmatory testing will be done at the discretion of the sponsor and must be approved by the sponsor prior to analysis. The significance of a positive UDS result for drugs prescribed for the participant (ie, barbiturates, benzodiazepines, amphetamines, but not opioids or cannabinoids) should be assessed by the investigator as to whether their stable-dose usage is clinically appropriate, and if so, should not be exclusionary; use of these prescribed drugs on an as-needed basis is not allowed.

Some participants who screen fail after completing the Run-in Period in this study may be eligible for entry into a parallel study (RLM-MD-04) but will still be considered screen failures in this study.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

7. Treatments

Study treatment is defined as any investigational treatments, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Participants are to self-administer double-blind study treatment twice daily, SC, with the first daily dose being administered within approximately 30 minutes before the morning meal [redacted] and the second daily dose within approximately 30 minutes before the evening meal [redacted] If a participant does not eat morning or evening meals, study treatment should be administered during typical meal times [redacted].

Should a participant miss a dose prior to either the morning or evening meal, he/she should adjust his/her study treatment administration as follows:

[redacted]

Study treatment will be dispensed as pen injectors with pre-filled cartridges of either relamorelin or placebo. Study treatment details are provided in Table 7-1.

Table 7-1: Study Treatment Details

Study Treatment	Relamorelin	Placebo
Dosage Formulation	Pre-Filled Cartridge in Multi-dose Pen Injector	Pre-Filled Cartridge in Multi-dose Pen Injector
Unit Dose Strength	10 µg dose	N/A
Route of Administration	Subcutaneous	Subcutaneous
Dosing Instructions	Administer twice daily	Administer twice daily
Packaging and Labeling	[redacted]	
Manufacturer	Allergan (Assembled Pen)	Allergan (Assembled Pen)
Injection Device	Utilize Multi-dose Pen Injector for the administration of the study treatment or placebo. [redacted]	Utilize Multi-dose Pen Injector for the administration of the study treatment or placebo.

7.1.1. Run-in Medications and Administration

Placebo (single-blind) should be self-administered twice daily [redacted] SC using the pen-injector.

7.1.2. Study Supplies

1. The Allergan-manufactured medical devices [redacted] provided for use in this study are: (1) Prefilled Cartridge, and (2) Multi-dose Pen Injector.

2. Instructions for medical device use are provided in Relamorelin Pen Investigational Directions for Use.

3. Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Appendix 7).

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

All participants will be centrally assigned to randomized study treatment using an interactive web response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

At the beginning of the 12-week Treatment Period, eligible participants will be randomized in a 1:1 ratio to blinded treatment with relamorelin 10 µg or placebo. Randomization will be stratified by geographic region.

Study treatment will be dispensed at the study visits indicated in the Schedule of Activities (SoA) (Section 2).

Returned study treatment should not be re-dispensed to the participants.

7.4. Blinding

The investigator, investigational staff, and participant will be fully blinded to study treatment during the 12-week Treatment Period; during the placebo Run-in Period, single-blind treatment with placebo is self-administered. All study treatment will be provided in identical pen injectors and cartons to maintain blinding of the study.

[redacted]

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

2. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance

with the labelled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

7.6. Treatment Compliance

Study treatment compliance will be closely monitored by assessing the participant's daily reporting of self-administered study treatment on the electronic hand-held device. Before dispensing new study treatment, study site personnel will make every effort to collect all unused study treatment. In the event of AE or intercurrent illness, dosing of study treatment can be stopped temporarily, for a maximum duration of 3 days. Should longer cessation of dosing be necessary, the investigator should contact the sponsor (Section 8.1.1).

The study centers will keep an accurate drug disposition record that specifies the amount of study treatment dispensed to each participant and the date of dispensing.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the electronic case report form (eCRF) along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

As much as possible, the dose and frequency of all concomitant medications taken for chronic conditions with the exception of diabetes mellitus (see Section 7.7.2) should be held stable during the study. The sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Prohibited Treatments

The classes of drugs prohibited in the study are, with the exception of SGLT-1 and SGLT-2 inhibitors, those that affect GI motility, either positively or negatively, and therefore could confound the assessment of the efficacy of study treatment on the signs and symptoms of DG. The SGLT-1 and SGLT-2 inhibitors are-prohibited for 3 days prior to the GEBT done at the start of the Run-in Period in all participants and in a subset of participants at a subset of sites at Visit 7

Relamorelin
or the Early Termination Visit. Their mechanism of action is through causing increased glycosuria, which may affect interpretation of the GEBT results.

Table 7-2 provides a list of drug classes and treatments that are prohibited during the study and require washout during the placebo Run-in Period.

Table 7-2: Prohibited Medications and Washout Requirements

[redacted]

7.7.2. Permitted Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

DG participants enrolled in this study will likely consist mostly of participants receiving one or more prescription medications for blood-glucose control. Good clinical practice allows for frequent adjustment of medication by participants and their health care providers to minimize large fluctuations in glycemia, and this practice is encouraged in this study. It should be remembered that certain diabetic drugs (see Table 7-2) delay GE and are prohibited during this study. Other therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.3. Rescue Medicine

Use of medications that may impact efficacy evaluations is strongly discouraged at any time after Visit 1 in the study. However, participants who experience severe symptoms of GP may receive a single day of treatment per week with an anti-emetic drug, but should avoid such treatment, if possible, during the 2-week Run-in Period, and on the day prior to and day of clinic visits during the Treatment Period. If a participant requires an anti-emetic drug (eg, 5-HT3 receptor antagonists, NK1 receptor antagonists) for more than 1 day a week, or requires an anti-emetic drug once weekly repeatedly (ie, for 3 consecutive weeks or more), the investigator should contact the sponsor to discuss the safety of the participant continuing study treatment.

The date of rescue-medication administration as well as the name and dosage regimen of the rescue medication should be recorded in the concomitant medications page of the eCRF.

7.8. Treatment after the End of the Study

Assuming they meet entry criteria, participants who successfully complete this study are eligible to enter a placebo-controlled, long-term safety and efficacy study (LTSES) (RLM-MD-03) during which they will receive study treatment for an additional 46 weeks.

Participants who prematurely discontinue from the study and participants who do not enter the long-term safety and efficacy study (Study RLM-MD-03) should follow up with the investigator regarding treatment at the end of the study.

8. Discontinuation/Withdrawal Criteria

Reasons for discontinuation from study treatment and/or the study may include the following:

- Adverse event
- Completed
- Death
- Failure to meet randomization criteria
- Lack of efficacy
- Lost to follow-up
- Other
- Investigator decision
- Pregnancy
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by participant

The reason for discontinuation should be clearly documented on the appropriate eCRF. Discontinuation of study treatment also requires discontinuation from the study. (See Appendix 8 for Standard Discontinuation Criteria/Definitions.)

8.1. Discontinuation of Study Treatment

Discontinuation of study treatment also requires discontinuation from the study. The following criteria should be evaluated:

- Special attention should be paid to the appearance of abnormal laboratory test results suggesting severe, drug-induced liver injury (DILI). Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a participant meets criteria for Hy's law (See Section 9.2.7.1 and Appendix 6) or if the investigator believes that it is in best interest of the participant.

- ECGs should be carefully analyzed for findings pointing to potentially important cardiac events (also see Section 9.2.7.3). If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using QTcB or QTcF) after enrollment, the investigator or qualified designee should determine if the participant can continue in the study and if any change in participant management is needed. Generally, a QTc value of > 500 msec or an increase from baseline of > 60 msec after start of study treatment should prompt discontinuation of the participant from the study. Review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

- Female participants who become pregnant during the study must be discontinued from treatment immediately and withdrawn from the study. See Section 9.2.5 Pregnancy and Appendix 5 for further details regarding follow-up of the participant through the pregnancy.

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation.

8.1.1. Temporary Discontinuation

In the event of AE or intercurrent illness, dosing of study treatment can be stopped temporarily, for a maximum duration of 3 days. Should longer cessation of dosing be necessary, the investigator should contact the sponsor. The investigator should also contact the sponsor should either recurrence of the AE that prompted discontinuation or the appearance of a new AE that requires discontinuation be experienced after reintroduction of treatment to discuss the safety of this participant continuing study.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. An early termination visit must be performed as soon as possible after the decision to withdraw has been made by the participant or the decision to withdraw the participant has been made by the investigator.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See the SoA for data to be collected at the time of study discontinuation.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed.
- Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately 63 mL (plus approximately an additional 64 mL only for participants in the PK and hormone subset). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

All primary and secondary efficacy assessments are derived from the DGSSD, a 7-item, patient-reported daily diary designed to assess the severity of 6 core signs and symptoms of DG—nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety—and the frequency of vomiting episodes (Appendix 15). DG symptoms are assessed using a 0 to 10 numerical rating scale (NRS), on which 0 = "no" or "not at all uncomfortable" (ie, absence of the DG symptom) and 10 = "worst possible" or "most uncomfortable" (ie, worst experience of the DG symptom).

DGSSD entries are to be made daily at the same time every evening on the electronic hand-held device beginning the first day of the Run-in Period and continuing throughout the Treatment Period. Planned timepoints for all efficacy assessments are provided in the SoA (Section 2).

9.1.1. Primary Efficacy Assessments

9.1.1.1. DGSSS Change from Baseline to Week 12 in the Weekly DGSSS

The change from baseline to Week 12 in the weekly DGSSS has been selected as a primary endpoint in this study.

DGSSS is derived as the sum of the daily DGSSD items of nausea, abdominal pain, postprandial fullness, and bloating. Weekly DGSSS is derived as the sum of the weekly averages of the DGSSD items of nausea, abdominal pain, postprandial fullness, and bloating. The worst possible DGSSS for the 4 DG symptoms is 40, and the best possible DGSSS is 0.

Baseline is the average of the 2 weekly DGSSS from the 2-week, placebo Run-in Period.

9.1.1.2. Vomiting Responder

Vomiting Responder, based on the number of vomiting episodes, has been selected as a primary endpoint in this study.

A Vomiting Responder is defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the 12-week Treatment Period. Vomiting is defined as throwing up

the contents of the stomach. This does not include retching or dry heaving (also known as dry vomiting) when no stomach contents are thrown up.

Vomiting frequency will be captured during the placebo Run-in Period and the 12-week Treatment Period. Participants will be asked to indicate the number of vomiting episodes experienced in the day since the previous entry made, with information provided as to what constitutes a "vomiting episode" in order to ensure accurate reporting.

9.1.2. Secondary Efficacy Assessment

9.1.2.1. DGSSS Individual Item Responders

The individual items assessing nausea, abdominal pain, bloating, and postprandial fullness will be assessed as secondary endpoints using the following response definition:

- Individual symptom response is defined as an improvement of ≥ 2-points in the weekly symptom scores for each individual item at each of the last 6 weeks of the 12-week Treatment Period

Psychometric analyses have shown that a decrease in individual symptom scores by ≥ 2 points is recognized as a clinically meaningful improvement in DG symptoms by affected patients (Psychometric Evaluation, RTI Health, 2017).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- No, my appetite has stayed the same

[redacted]

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be reported by the participant or noted by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the Informed Consent Form (ICF) until 30 days after the final visit in the study (Visit 7) or Early Termination Visit, at the timepoints specified in the SoA (Section 2).

Medical occurrences that begin before the start of study treatment but after obtaining IC will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AEs, and non-serious AEs of special interest ([AESI] as defined in Appendix 4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on AE/SAE follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators, including the head of the study center if required.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 7 days after the last dose.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.6. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purpose of study medication self-administration. In order to fulfill regulatory reporting obligations worldwide, the investigator is

responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 4 of the protocol.

9.2.6.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Incidents is provided in Appendix 7.

9.2.6.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2). This applies to all participants, including those who discontinue study treatment.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.6.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

9.2.6.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility, if needed, to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.2.7. Adverse Events of Special Interest

9.2.7.1. Hy's Law

Study site personnel must report every participant who meets potential Hy's Law criteria which are as follows:

- ALT or AST ≥ 3 × upper limits of normal (ULN) AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Typically, all analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the final protocol-defined study visit or the last known dose of study treatment (if the final visit does not occur).

A laboratory alert for potential Hy's laws cases will be in place. Investigators and the sponsor must be immediately notified when the above criteria have been met. A potential Hy's law case must be faxed to the sponsor's SAE/Pregnancy fax number on an Abnormal Liver Function Reporting Form (GPSE-PVOPS-F-01-28) and SAE form within 24 hours of learning of the potential Hy's law case to the SAE/Pregnancy fax number, even if no AE has occurred (Appendix 4). The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the MSP and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Additional details regarding liver safety assessments and follow up are provided in Appendix 6.

9.2.7.2. Inadequate Control of Diabetes: Hyperglycemia and Hypoglycemia

The irregular and delayed emptying of the stomach in DG has a major effect on the presentation of ingested carbohydrate to the small intestine for absorption, complicating the dosing of hypoglycemic agents (including insulin) used to manage glycemia. Participants should be closely monitored for changes to their diabetes control while in the study, and events related to hyperglycemia or hypoglycemia that are considered to be clinically significant should be reported as AEs (Section 9.2.1).

9.2.7.3. Major Adverse Cardiovascular Events

Patients with diabetic gastroparesis typically have long-standing diabetes mellitus, which predisposes them to develop macrovascular (and microvascular) complications. These include Major Adverse Cardiovascular Events (MACE), commonly defined as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and often also including revascularization (coronary or peripheral) procedures, and hospitalization for unstable angina pectoris.

In this study, occurrence of any of these events should be reported to the MSP within 24 hours of being made aware on the SAE form, followed by a complete report including narrative description of the event, test results, and copies of hospital records, if applicable. All reports of possible MACE will be adjudicated internally in a blinded fashion by a committee of qualified physicians on a periodic basis depending on the frequency of reported events. The functioning of the committee will be governed by charter.

9.2.8. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study treatment as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug/device
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study treatment.

Overdose: Unintentional administration of a quantity of the study treatment given per administration or per day that is above the maximum recommended dose (10 µg BID or 20 µg/day) according to the reference safety information or protocol for the study treatment or comparator as applicable. This also takes into account cumulative effects due to overdose.

Underdose: Unintentional administration of a quantity of the study treatment given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol. Since there is no clinical information on the efficacy of relamorelin at a dose less than 10 µg BID, a dose of 10 µg once daily should be considered an underdose.

9.3. Treatment of Overdose

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the MSP immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
3. Document the quantity of the excess dose as well as the duration of the overdose in the site's source documents for the participant.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the MSP based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 2).

9.4.1. Physical Examinations

Complete physical examinations (excluding pelvic exam in women and genital exam in men, and rectal exam in both genders) are to be performed. Symptom-directed (abbreviated) physical examinations, including evaluation of the injection sites for clinically significant reactions, will be conducted as required at other study visits.

Participants should be weighed with no shoes, in light clothing, without any outerwear; height to be measured only at Visit 1. The weight taken at Visit 2 is to be used for the GEBT and will not be recorded in the eCRF.

Any abnormality noted during the physical examination performed at Visit 7 or the early termination visit that was not present during the physical examination at Visit 1 should be reported as an AE if considered by the investigator to be clinically significant.

9.4.2. Vital Signs

- Heart rate (HR), respiratory rate, systolic and diastolic blood pressure (BP), and temperature will be assessed; the method for measuring temperature will be per the site's preference.
- BP and HR measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- BP and HR measurements should be preceded by at least 3 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

- Vital signs are to be taken before blood collection for laboratory tests.

9.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1 for QTc withdrawal criteria; also see Section 9.2.7.3 for Major Adverse Cardiovascular Events.

9.4.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 2) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or MSP.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

9.4.5. Hormonal Assessments

In a subset of participants (approximately 100 in total), at a subset of sites, investigation of the effects of study treatment on levels of hormones potentially affected by relamorelin will be carried out. These hormones are GH, insulin-like growth factor-1 (IGF-1), insulin, glucagon, c-peptide, adrenocorticotropic hormone (ACTH), and cortisol. The participants will be those who will undergo the PK assessment at selected sites. A single fasting blood specimen will be obtained for measurement of the hormones and fasting blood glucose (FBG) at the visits noted in the SoA (Section 2).

9.4.6. Self-monitoring of Blood Glucose

Participants will be strongly encouraged to carry out self-monitoring of blood glucose (SMBG) at home in order to achieve and maintain optimum glucose control during the study. This is almost always required by patients with T1DM and is good clinical practice in patients with T2DM. Sponsor may provide each participant with a glucose monitor, test strips, and all supplies necessary for testing finger-stick capillary blood glucose. It is recommended that this be done twice daily, pre-breakfast (fasting) and approximately 2 hours post-lunch or dinner (whichever is the larger meal).

Information from SMBG, in addition to that provided by values of HbA1c, and FBG, will be available to investigators for decision-making regarding adjustment of diabetic medications, diet, and exercise (or, alternatively, for decision-making regarding referral of the patient to his/her health care provider for the same purpose).

9.5. Pharmacokinetics

Sparse plasma samples of approximately 2 mL per sample will be collected at a subset of sites on a subset of participants to estimate concentrations of relamorelin. These sites will be selected by the sponsor to ensure the appropriate sample handling requirements can be met. In total, approximately 100 participants will be recruited to provide sparse samples.

The dosing of relamorelin and samples collected will occur at the following intervals:

- At Visit 3, administration of the first dose of study treatment will occur at the site, with the time and date recorded. PK samples will be collected within 0.5 hours before dose administration, between 0.5 hours and 1 hour after dose administration, and between 1.5 hours and 3.0 hours after dose administration.

- At Visit 4, Visit 5, Visit 6, and Visit 7, participants are to administer the morning dose of study treatment at home, and provide the site with the date and time of the dose administration. During these visits, a single PK sample will be collected between 0.5 hours and 6.0 hours after dose administration, dependent on the timing of the clinic visit. At the Early Termination Visit, a single PK sample will be collected irrespective of the time of the last dose administration.

In addition, plasma samples of approximately 4 mL will also be collected to assess the formation of anti-relamorelin antibodies in all study participants. Samples will be collected at Visit 3/Baseline, Visit 4, Visit 5, Visit 7, or Early Termination Visit.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

[redacted]

[redacted]

10. Statistical Considerations

10.1. Sample Size Determination

The sample size and statistical power for the DGSSSS endpoint was assessed by simulation. Data were simulated for the DGSSS over time under the assumption of a multivariate normal distribution and based on mean responses in Study RM-131-009 variance - covariance structure (Table 14.1 of the SAP). A missing completely at random (MCAR) dropout rate of 20% by Week 12 was assumed for each treatment.

Vomiting response rates were assumed to be those observed in Study RM-131-009 (26% and 11% for treatment and placebo respectively). Sample size was assessed using the POWER procedure in SAS.

The sample size of approximately 300 participants per arm will provide more than 90% power to reject at least one of the primary null hypotheses using the multiplicity approach described in Section 10.3 of the SAP.

10.2. Populations for Analyses

The analysis populations will consist of participants as defined in Table 10-1.

Table 10-1: Analysis Populations

Population	Definition
Screened	All screened participants who signed the ICF
Intent-to-treat (ITT)	All randomized participants
Modified intent-to-treat (mITT)	All randomized participants with ≥ 1 post-baseline assessment of DGSSD
Pharmacokinetic	All randomized participants who agreed to volunteer for sparse PK collection, and provided > 2 evaluable samples during the double-blind treatment period
Safety	All participants who received ≥ 1 administration of double-blind study treatment

10.3. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.3.1. Key Statistical Methodology

The methodologies defined in Table 10-2 apply as specified to individual endpoints defined in this protocol. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All CIs will be 2-sided 95% CIs, unless stated otherwise.

Table 10-2: Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories a. Participants with ≥ 1 qualifying event counted once per individual category
Categorical descriptives	• Number and percentage of participants in individual categories a. Participants with ≥ 1 qualifying event counted once per individual category • N1 if percentage denominator ≠ number of participants in the population (standard percentage denominator) a. N1 = participants with nonmissing baseline value
Event descriptives	• Number and percentage of events in individual categories a. Events counted individually for each instance • Percentage denominator = total number of events
Continuous descriptives	• N1, mean, SD, median, minimum, maximum • N1 = participants with nonmissing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit
Responder	• Categorical descriptives for responders and nonresponders a. Nonresponders include: i. Participants who do not meet responder criteria ii. Participants with no postbaseline values • Risk differences and Wald CIs vs [placebo/active comparator] • Estimates derived from Cochran-Mantel-Haenszel (CMH) model controlling for factors (treatment group, region) a. Mantel-Haenszel (MH) odds ratios (ORs) and CIs vs placebo b. P-values comparing treatment group vs placebo • N1 = all participants unless otherwise specified
CFB	• Continuous descriptives for CFB • Estimates derived from mixed-effects model with repeated measures including fixed effects for geographic region, treatment, week, treatment-by-week interaction, as well as baseline and baseline-by-week interaction values as the covariates a. LS mean and LS mean difference (CIs) between treatment group and placebo b. P-values comparing treatment group vs placebo

10.3.2. Efficacy Analyses

10.3.2.1. Primary and Secondary Endpoints

Table 10-3 displays the primary and secondary efficacy endpoints that will be analyzed for the mITT population. All other efficacy endpoints and analyses will be defined in the SAP.

Table 10-3: Primary and Secondary Endpoints

Primary Endpoints	Description	Timing	Methodology
CFB to Week 12 in weekly DGSSS	Change from baseline to Week 12 in weekly DGSSS	Week 12	CFB
Vomiting Responder	Vomiting responder during last 6 weeks of treatment	Last 6-weeks of Treatment Period	Responder
Secondary Endpoints			
Nausea Responder	Nausea responder during last 6 weeks of treatment	Last 6-weeks of Treatment Period	Responder
Abdominal Pain Responder	Abdominal Pain responder during last 6 weeks of treatment	Last 6-weeks of Treatment Period	Responder
Bloating Responder	Bloating responder during last 6 weeks of treatment	Last 6-weeks of Treatment Period	Responder
Postprandial Fullness Responder	Postprandial Fullness responder during last 6 weeks of treatment	Last 6-weeks of Treatment Period	Responder

10.3.2.2. Multiple Comparisons Procedure

To control the overall type-1 error rate of the study, a multiplicity adjustment will be applied to the primary and secondary endpoints. For that purpose, the hypotheses of interest will be grouped into the two families described below:

- Family 1:
    - Hypothesis H1: Comparison of relamorelin versus placebo in the change from baseline to Week 12 in weekly DGSSS
    - Hypothesis H2: Comparison of relamorelin versus placebo in Vomiting response rate
- Family 2:
    - Hypotheses H3-H6: Comparison of relamorelin versus placebo in the response rates of the individual symptoms comprising DGSSS (ie, nausea, abdominal pain, postprandial fullness, and bloating)

The multiple testing will be performed in two Steps as follows:

Step 1: Treatment comparisons to placebo in the DGSSS and vomiting response rates will be performed using the truncated Holm test at alpha=0.05. A truncation parameter of 0.5 will be used.

Step 2: If any of the comparisons at Step 1 is significant, the treatment comparisons to placebo in the individual symptoms response rates will be performed using the regular Holm test at a level alpha which depends on the unused alpha from Step 1.

Details for other efficacy analyses are provided in the SAP.

10.3.2.3. Missing Data

Participants with a missing weekly value for vomiting frequency or the individual symptoms comprising the DGSSS (ie, nausea, abdominal pain, postprandial fullness, and bloating) during any of the last 6 weeks will be analyzed as a non-responder for the endpoint.

Analysis for 2 primary endpoints based on multiple imputations (MI) as proposed by Little and Rubin (1987) will also be provided MI for weekly vomiting episodes, will be performed under both missing at random and the missing not at random (MNAR) assumptions, and MI for change from baseline in the weekly DGSSS will be performed only under MNAR assumption.

Detailed methods and procedures for the above outlined missing data-derived sensitivity analyses, planned or exploratory, will be documented in the final SAP prior to the study completion.

[redacted]

10.3.3. Safety Analyses

All safety analyses will be performed on the Safety Population.

The following safety categories will be summarized as appropriate (eg, categorical or continuous descriptives, shift tables) for the safety population and will be fully defined in the SAP.

- AEs
    - Clinically significant hyperglycemia- and hypoglycaemia-related events
- Clinical laboratory assessments
    - Potential Hy's law cases
- Vital signs
- ECGs
- Study-specific assessments
    - HbA1c

10.3.5. Interim Analyses

In addition to the above, monitoring of patient safety data will be performed by an independent Data and Safety Monitoring Board (DSMB). The DSMB will review interim safety data at defined intervals throughout the study. The DSMB will communicate their recommendations to the sponsor after each meeting but will serve in an advisory capacity only; the Board will not be empowered to stop the study or require changes in the protocol. Study conduct may be interrupted or terminated by the sponsor based on DSMB recommendation if safety data become available which appear to represent an undue risk to the study participants' health or well-being. Further details of the DSMB (composition, policy, and procedures) are specified in a separate DSMB Charter.

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All references are available upon request.

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12. Appendices

12.1. Appendix 1: Abbreviations

ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BP	blood pressure
[redacted]	
CDER	Center for Drug Evaluation and Research
CFB	change from baseline
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting
CSR	clinical study report
DFU	directions for use
DG	diabetic gastroparesis
DGSSD	Diabetic Gastroparesis Symptom Severity Diary
DGSSS	Diabetic Gastroparesis Symptom Severity Score
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram

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eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	early termination
EU	European Union
FBG	fasting blood glucose
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
[redacted]	
GE	gastric emptying
GEBT	gastric emptying breath test
GERD	gastroesophageal reflux disease
GHS1α	Growth Hormone Secretagogue 1 α
GH	growth hormone
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GP	gastroparesis
HbA1c	glycosylated hemoglobin A1c
HEOR	health economic outcomes research
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council on Harmonisation

IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
MACE	major adverse cardiovascular events
MI	multiple imputations
MMRM	mixed method for repeated measures
MNAR	missing not at random
MSP	medical safety physician
NRS	numerical rating scale
[redacted]	
PK	pharmacokinetic
PRO	patient-reported outcome
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using Fridericia formula
RLM	relamorelin
SAE	serious adverse event
SAP	statistical analysis plan

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SC	subcutaneous(ly)
SF-12v2	12-item Short Form Survey (version 2)
SGLT-1	sodium-glucose co-transporter-1
SGLT-2	sodium-glucose co-transporter-2
SMBG	self-monitoring of blood glucose
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UDS	urine drug screen
ULN	upper limits of normal
US	United States of America
WOCBP	women of childbearing potential

[redacted]

Electronic Signatures

User	Date	Justification