NCT03420781

Study ID: Study ID: RLM-MD-03

Title: A 46-week, Double-blind, Placebo-controlled, Phase 3 Study with a 6-week Randomized-withdrawal Period to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Protocol Amendment 2 Date: 10 March 2021

Title Page

Protocol Title: A 46-week, Double-blind, Placebo-controlled, Phase 3 Study with a 6-week Randomized-withdrawal Period to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Brief Protocol Title: Diabetic Gastroparesis Study with Randomized-withdrawal Period

Protocol Number: RLM-MD-03

Amendment Number: 2

Product: Relamorelin

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND: [redacted]

EudraCT: 2017-002143-15

Emergency Telephone Number: Refer to study contacts list

Serious Adverse Event Reporting Email/Fax Number:
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Allergan Medical Safety Physician: Refer to study contacts list

Allergan Signatory: [redacted] Vice President, Clinical Development-GI

Protocol Amendment 2 Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	29 Mar 2018
Original Protocol	12 Dec 2017

Amendment 2 (04 Mar 2019)

Overall Rationale for Amendment 2:

This summary includes changes made to Protocol RLM-MD-03 from Protocol Amendment 1 (Dated 29 Mar 2018; details provided in Section 12.19). The purpose of Protocol Amendment 2 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 primary endpoint to specify "change from baseline at Week 12"; defined Vomiting Week 12 Responder for primary endpoint; Deleted DGSSS Week 40 Responder as a secondary endpoint	[redacted]
Section 1 Synopsis, Section 5.2 Participant and Study Completion, Section 12.9/Appendix 9 Study Tabular Summary	Increased the number of sites from approximately 400 to approximately 700	
Section 2 SOA	Added ECG assessment at Visit 4	
Section 4.2 Clinical Hypotheses	First 2 clinical hypotheses modified	
Section 6.1 Inclusion Criteria	Inclusion criterion #2: Added a cross reference to Appendix 3	
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.	
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.	

Section Number	Description of Change	Rationale
Section 7.7.1, Table 7-2 Prohibited Medications	Provided more specific guidelines for prohibiting anti-emetics; added 5HT4 agonists to table; added tramadol as an opioid example	[redacted]
Section 7.7.3 Rescue Medicine	Clarifications made to text; Removed antihistamines as an example of an anti-emetic drug	
Section 8 Discontinuation/Withdrawal Criteria; Section 12.8. Appendix 8: Standard Discontinuation Criteria	Removed: "non-compliance with study treatment"	
Section 8.1.1 Temporary Discontinuation	Added requirement for the investigator to contact the sponsor under specific conditions.	
Section 9.2.4 Regulatory Reporting Requirements for SAEs	Details added to second bullet for clarity	
Section 9.2.7.1 Hy's Law	Editorial changes for clarity	

Section Number	Description of Change	Rationale
Section 9.2.7.2 Inadequate Control of Diabetes: Hyperglycemia and Hypoglycemia	Added the phrase "Inadequate Control of Diabetes" to section title.	[redacted]
Section 9.2.8 Medication Errors	Specified 10 µg BID or 20 µg/day as maximum recommended dose. Deleted statement referencing a dose of greater than 150 µg BID to be considered an overdose.	
Section 10.3.1 Key Statistical Methodology, Table 10-2	CFB MMRM methodology and description added to table; MMRM defined in footnotes of table.	
Section 10.3.2.1 Key Endpoints, Table 10-3	Updated DGSSS key endpoint, along with description, timing, and methodology; Deleted DGSSS Week 40 Responder as a secondary endpoint	
Section 10.3.2.2 Missing Data	Updated language with regards to the key endpoints	
[redacted]		
Section 10.3.5 Interim Analyses	Added a requirement for a DSMB to review interim safety data at defined intervals throughout the study.	
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 Visits 4 and 6; other footnotes renumbered accordingly.	
Section 12.3 Appendix 3 Study Governance Considerations	Made un-numbered subsections level 3 headings Reorganized subsections 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.	

Section Number	Description of Change	Rationale
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.	[redacted]
Section 12.3.9 Publication Policy	Added bullet about relevant country requirements	
Section 12.4 Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Made un-numbered subsections level 3 headings	
Section 12.4 Appendix 4 AE Definitions	Revised procedures for reporting AESIs; specified that specific DG manifestations will be captured in the DGSSS and not in the eCRF	
Section 12.4.1 Definition of AE	Identified specific AESIs.	
Section 12.5 Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information	Added more options to Highly Effective Methods That Are User Independent; added example of bilateral tubal occlusion; moved list of "Acceptable Methods" to table from text; updated footnote b to specify that 2 **acceptable** methods of contraception should be used during treatment (as opposed to 2 highly effective methods). 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 interaction with study intervention.	
Section 12.9, Appendix 9 Study Tabular Summary	Corrected trial length from 52 to 46 weeks	

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.

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1. Synopsis

Protocol Title: A 46-week, Double-blind, Placebo-controlled, Phase 3 Study with a 6-week Randomized-withdrawal Period to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Brief Title: Diabetic Gastroparesis Study with Randomized-withdrawal Period

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 gastric emptying (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 hyperglycaemia, especially if treated with insulin.

In Phase 2 studies, the pharmacodynamic effect of relamorelin was confirmed in larger numbers of participants with DG. 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, including supporting evidence from Study RLM-MD-03.

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	Primary
• To compare the efficacy of relamorelin with that of placebo after 12 weeks of treatment in this study (ie, after a total of 24 weeks of treatment—12 weeks from lead-in study RLM-MD-01 or from lead-in study RLM-MD-02 ***and*** 12 weeks from the current study) in participants with DG with respect to the following core signs and symptoms of DG: • Nausea • Abdominal pain • Postprandial fullness • Bloating	• Change from Baseline to Week 12 of this study in the weekly Diabetic Gastroparesis Symptom Severity Score (DGSSS)
• To compare the efficacy of relamorelin with that of placebo after 12 weeks of treatment in this study (ie, after a total of 24 weeks of treatment—12 weeks from lead-in study RLM-MD-01 or from lead-in study RLM-MD-02 ***and*** 12 weeks from the current study) in participants with DG with respect to vomiting frequency	• Vomiting Week-12 Responder, defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the first 12-week Treatment Period
Secondary	Secondary
• To compare the efficacy of relamorelin with that of placebo after 12 weeks of treatment in this study (ie, after a total of 24 weeks of treatment—12 weeks from lead-in study RLM-MD-01 or from lead-in study RLM-MD-02 ***and*** 12 weeks from the current study) 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) Week-12 Responder
• To compare the efficacy of relamorelin with placebo after 40 weeks of treatment in this study (ie, after a total of 52 weeks of treatment—12 weeks from the lead-in study RLM-MD-01 or lead-in study RLM-MD-02 ***and*** 40 weeks from the current study) in participants with DG with respect to the following core signs and symptoms of DG: • Nausea • Abdominal pain • Postprandial fullness • Bloating	• Change from Baseline (CFB) to Week 40 in the average weekly DGSSS
• To compare the efficacy of relamorelin with placebo	• Vomiting Frequency at Week 40 • CFB to Week 40 in the average weekly number of

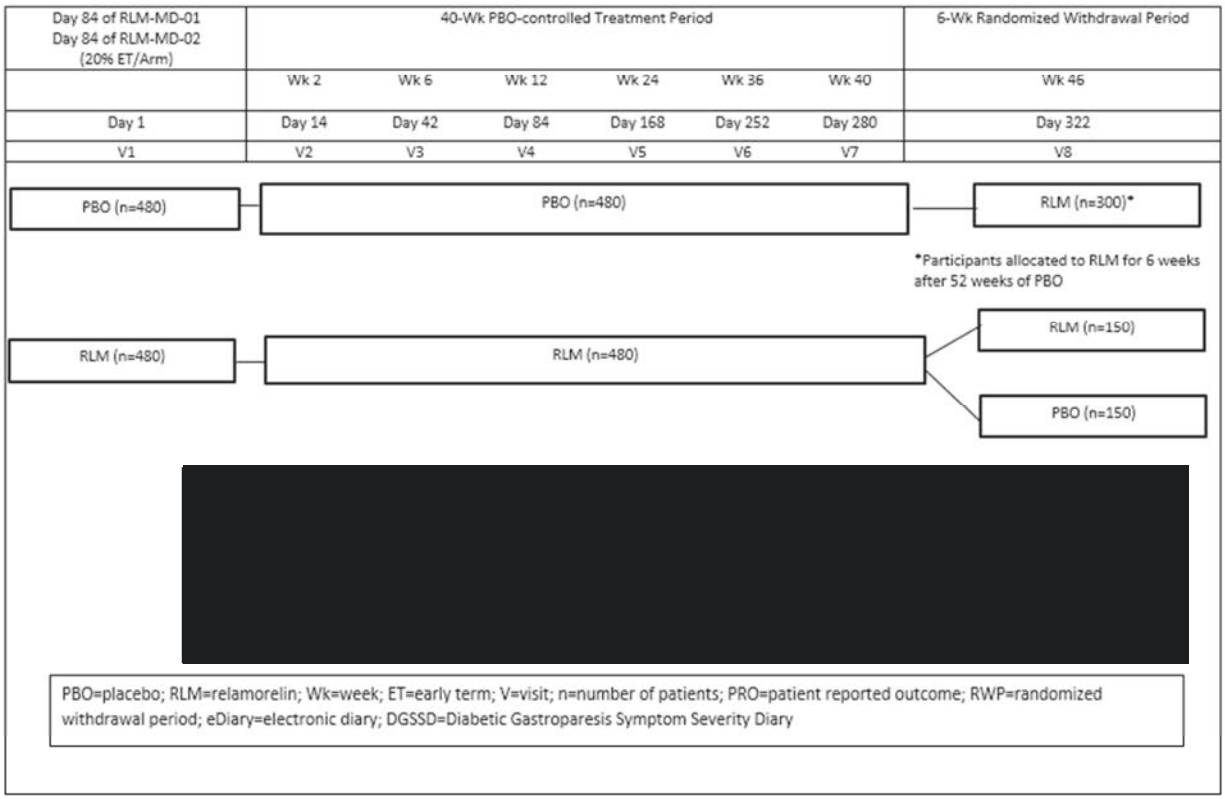
Objectives	Endpoints
after 40 weeks of treatment in this study (ie, after a total of 52 weeks of treatment—12 weeks from the lead-in study RLM-MD-01 or lead-in study RLM-MD-02 ***and*** 40 weeks from the current study) in participants with DG with respect to vomiting frequency	vomiting episodes
• To demonstrate maintenance of efficacy after continuation versus discontinuation after 52 weeks of relamorelin treatment during the 6-week Randomized Withdrawal Period (RWP) • To compare the safety of relamorelin with placebo in participants with DG	• CFB to end of RWP in the average weekly DGSSS • CFB to end of RWP in the number of vomiting episodes • AEs, clinical laboratory values, vital signs, electrocardiograms (ECGs), HbA1c, and anti-relamorelin antibodies

Overall Study Design:

- Global, multicenter, double-blind, placebo-controlled, parallel-group study with a randomized-withdrawal period (RWP),
- Treatment Groups: Relamorelin 10 µg or placebo subcutaneously (SC) BID,
- Study Duration: 46 weeks, consisting of a 40-week Treatment Period followed by a 6-week RWP:
    - 40-week Treatment Period: Participants who meet entry criteria at the end of either lead-in study RLM-MD-01 or RLM-MD-02 will continue to receive the same blinded treatment with relamorelin 10 µg or placebo that they received during the lead-in study Treatment Period. They will continue to use the electronic hand-held device for reporting of [redacted] compliance and rescue-medication use throughout the Treatment Period, and for completion of the Diabetic Gastroparesis Symptom Severity Diary (DGSSD) daily during the first 12 weeks (84 days) of the Treatment Period until Visit 4 and during each 4-week period before Visits 5, 6 and 7.

- 6-week RWP: At the end of the 40-week Treatment Period, participants who were on relamorelin will be randomized (1:1) either to continue relamorelin study treatment or switch to placebo study treatment. Participants who received placebo during the Treatment Period will be allocated to receive relamorelin 10 µg. Participants will continue to use the electronic hand-held device daily for reporting of their symptoms via the DGSSD as well as their [redacted] compliance, and use of rescue medication.

Figure 1-1 RLM-MD-03 Study Schematic



Number of Participants:

Approximately 960 participants, based on assumption that 80% of participants who enter lead-in study RLM-MD-01 or lead-in study RLM-MD-02 will complete the study and enter this study.

Study Population:

Key Inclusion Criteria:

1. Participant met all inclusion/exclusion criteria of either Protocol RLM-MD-01 or Protocol RLM-MD-02 and successfully completed the study

2. Able to provide written informed consent (IC) prior to any study procedures and willing and able to comply with study procedures

3. In the opinion of the investigator, the participant demonstrated adequate compliance with the study procedures in RLM-MD-01 or RLM-MD-02

Key Exclusion Criteria:

1. Participant is not willing or able to abide by the restrictions regarding concomitant medicine use

2. Participant is planning to receive an investigational drug (other than study treatment) or investigational device at any time during Study RLM-MD-03

3. Participant has an unresolved AE or a clinically significant finding on physical examination, clinical laboratory test, or 12-lead ECG that, in the investigator's opinion, would limit the participant's ability to participate in or complete the study

4. Any other reason that, in the investigator's opinion, would confound proper interpretation of the study or expose a participant to unacceptable risk, including renal, hepatic or cardiopulmonary disease

5. Participant is directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, other study staff member, or employee of Allergan, Inc.; or the participant is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or the participant is enrolled in this study at another clinical study site

Number of Sites:

Approximately 700 sites globally (the combined sites from lead-in studies RLM-MD-01 and RLM-MD-02)

2. Schedule of Activities (SoA)

[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 1α (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 et al, 2004; Trudel et al, 2003; and Murray et al, 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, 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 et al, 2015; Acosta et al, 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 and negatively affect function (Parkman et al, 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 et al, 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 et al, 2011; Parkman et al, 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 et al, 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 et al, 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 et al, 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 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 hyperglycaemia, especially if treated with insulin.

In Phase 2 studies, the pharmacodynamic effect of relamorelin was confirmed in larger numbers of participants with DG, and, beneficial effects on the symptoms of DG were also observed. Safety and tolerability were shown at therapeutic doses, including the 10 µg 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, including supportive evidence from study RLM-MD-03.

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, specifically to assess the effect of long-term treatment.

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 twice daily (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 enrollment in the Phase 2b Study RM-131-009, DG participants 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 episodes were 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 advantage. 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 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 relamorelin 10 µg BID group.

With respect to laboratory findings, in some participants, glycemic control appeared to be negatively affected by the introduction of relamorelin. There were trends in increasing hemoglobin A1c (HbA1c) values after the initiation of relamorelin, which changed little 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 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 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 that of placebo after 12 weeks of treatment in this study (ie, after a total of 24 weeks of treatment—12 weeks from lead-in study RLM-MD-01 or from lead-in study RLM-MD-02 ***and*** 12 weeks from the current study) in participants with DG with respect to the following core signs and symptoms of DG:
  • Nausea
  • Abdominal pain
  • Postprandial fullness
  • Bloating
	• Change from Baseline to Week 12 of this study in the weekly Diabetic Gastroparesis Symptom Severity Score (DGSSS)

• To compare the efficacy of relamorelin with that of placebo after 12 weeks of treatment in this study (ie, after a total of 24 weeks of treatment—12 weeks from lead-in study RLM-MD-01 or from lead-in study RLM-MD-02 ***and*** 12 weeks from the current study) in participants with DG with respect to vomiting frequency	• Vomiting Week-12 Responder, defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the first 12-week Treatment Period.
Secondary	Secondary

• To compare the efficacy of relamorelin with placebo after 12 weeks of treatment in this study (ie, after a total of 24 weeks of treatment—12 weeks from lead-in study RLM-MD-01 or from lead-in study RLM-MD-02 ***and*** 12 weeks from the current study) 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) Week-12 Responder

Objectives	Endpoints

• To compare the efficacy of relamorelin with placebo after 40 weeks of treatment in this study (ie, after a total of 52 weeks of treatment—12 weeks from the lead-in study RLM-MD-01 or lead-in study RLM-MD-02 ***and*** 40 weeks from the current study) in participants with DG with respect to the following core signs and symptoms of DG:
  • Nausea
  • Abdominal pain
  • Postprandial fullness
  • Bloating
	• Change from Baseline (CFB) to Week 40 in the average weekly DGSSS

• To compare the efficacy of relamorelin with placebo after 40 weeks of treatment in this study (ie, after a total of 52 weeks of treatment—12 weeks from the lead-in study RLM-MD-01 or lead-in study RLM-MD-02 ***and*** 40 weeks from the current study) in participants with DG with respect to vomiting frequency	• Vomiting Week-40 Responder • CFB to Week 40 in the average weekly number of vomiting episodes
• At the end of the 6-week randomized-withdrawal period (RWP), to demonstrate maintenance of efficacy among participants who were switched from relamorelin to placebo vs participants who continued relamorelin treatment	• CFB to end of RWP in the average weekly DGSSS • CFB to end of RWP in the number of vomiting episodes
• 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. Endpoint Definitions

Endpoint definitions are provided in Section 10.3.2.1.

4.2. 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 Week-12 Responder" status, defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the 12-week Treatment Period.

3. A greater proportion of DG participants receiving relamorelin than DG participants receiving placebo will achieve "Week-12 Responder" status for the individual symptoms comprising the DGSSS (nausea, abdominal pain, bloating, post-prandial fullness), defined as experiencing a clinically meaningful ≥ 2-point improvement in the symptom severity score during each of the last 6 weeks of the first 12 weeks of the Treatment Period.
4. Improvements in DGSSS and number of vomiting episodes will be seen through Week 40 (ie, Week 52 [the combination of treatment duration of the current study and the 12-week treatment duration from either lead-in study RLM-MD-01 or lead-in study RLM-MD-02]).
5. Participants who are treated with relamorelin during the Treatment Period, and randomized to relamorelin during the RWP will experience maintenance of effect of treatment compared to participants who are randomized to placebo in the RWP.

5. Study Design

5.1. Overall Design

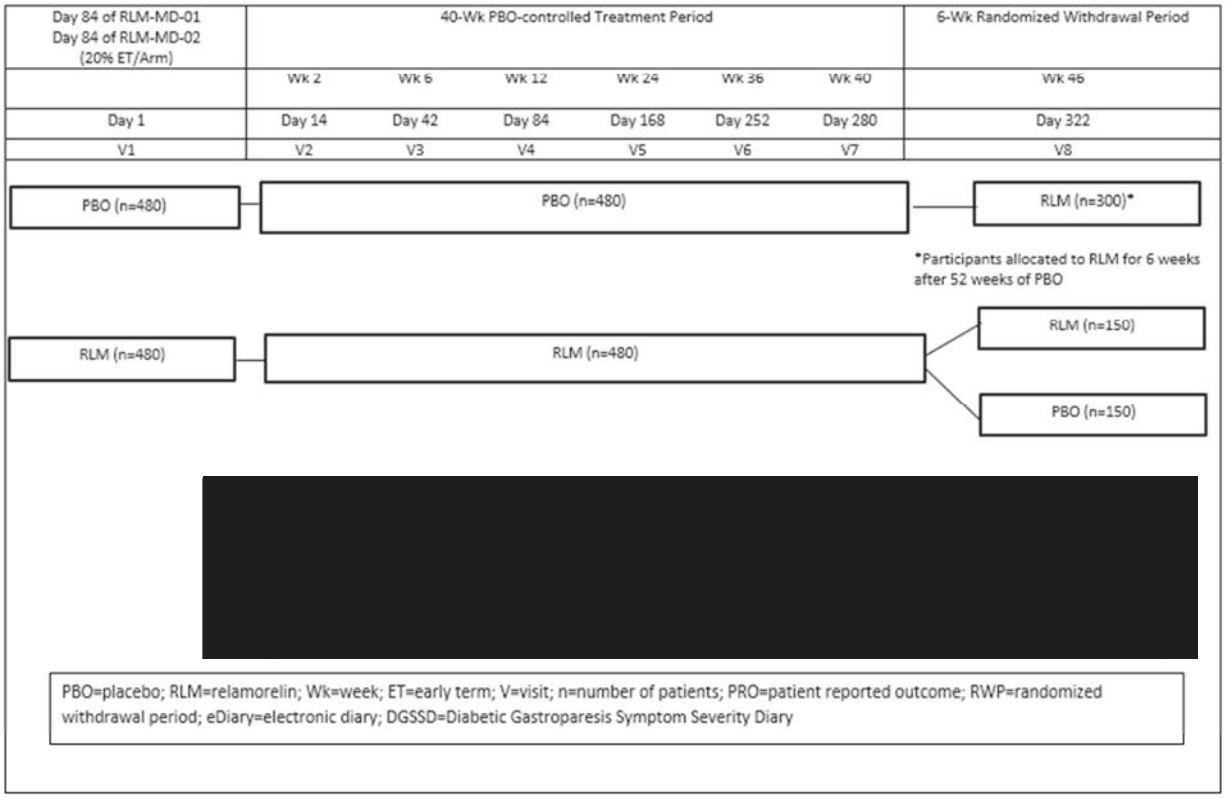
- Global, multicenter, double-blind, placebo-controlled, parallel-group
- Treatment Groups: Relamorelin 10 µg or placebo; BID, SC
- Study Duration: 46 weeks
- Study Periods:

    - 40-Week Treatment Period: Participants who meet entry criteria at the end of either lead-in study RLM-MD-01 or RLM-MD-02 will continue to receive the same blinded treatment with relamorelin 10 µg or placebo that they received during the Treatment Period of the lead-in study and continue to use the electronic hand-held device for the first 12 weeks (84 days) of the Treatment Period as they did in the lead-in study for daily reporting of their symptoms via the Diabetic Gastroparesis Symptom Severity Diary (DGSSD) as well as [redacted] compliance, and use of rescue medication. After Day 84 (Visit 4), participants will continue daily reporting of compliance and use of rescue medication, but will report their symptoms via the DGSSD, [redacted] only during the 4 weeks preceding subsequent visits (Visit 5 through Visit 7 or Early Termination).

- 6-Week RWP: At the end of the 40-week Treatment Period, participants who were on relamorelin will be randomized (1:1) either to continue relamorelin study treatment or switch to placebo study treatment. Participants who received placebo during the Treatment Period will be allocated to receive relamorelin 10 µg. Participants will continue to use the electronic hand-held device daily for reporting of their symptoms via the DGSSD as well as their [redacted] compliance, and use of rescue medication.

See Figure5-1 for a Study Schematic.

Figure 5-1 RLM-MD-03 Study Schematic



Study Population:

Participants who successfully complete lead-in study RLM-MD-01 or lead-in study RLM-MD-02 and meet enrollment criteria for this study shall constitute the study population. Their 40-week treatment assignment will have been determined by randomization during the lead-in study.

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.

5.2. Participant and Study Completion

Approximately 960 participants will enter this study at approximately 700 sites (globally), based on the assumption that 80% of participants who complete RLM-MD-01 or RLM-MD-02 will elect to continue receiving study treatment (480 participants to receive relamorelin and 480 participants to receive placebo) for an additional 40 weeks in the Treatment Period, and 6 weeks in the subsequent RWP. In the RWP, participants who received relamorelin in the Treatment Period will be re-randomized 1:1 to either continue relamorelin or switch to placebo; participants who received placebo in the Treatment Period will all switch to relamorelin. A total of 600 participants are expected to complete the study. 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 322 days of treatment, and the last visit (Visit 8). 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 medical safety physician (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 for inclusion of a long-term placebo-controlled safety study (12 months, with appropriate pre-specified provisions for rescue medications) as part of the development plan.

Several design features have been incorporated in the current study to minimize bias, including double-blind design and random assignment of participants, helping to 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.

A RWP has been added to the end of the Treatment Period to comply with CDER recommendation, made in the GP draft guidance, that a RWP follow the treatment period to address the need for maintenance treatment to prevent GP sign or symptom recurrence.

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 tested 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 effects, while the 10 µg BID dose achieved near maximal reductions. 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 the following criteria apply:

1. Participant met all inclusion/exclusion criteria of either Protocol RLM-MD-01 or Protocol RLM-MD-02 and successfully completed the study

2. 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)

3. In the opinion of the investigator, the participant demonstrated adequate compliance with the study procedures in Study RLM-MD-01 or RLM-MD-02

6.2. Exclusion Criteria

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

1. Participant is not willing or able to abide by the restrictions regarding concomitant medicine use

2. Participant is planning to receive an investigational drug (other than study treatment) or investigational device at any time during Study RLM-MD-03

3. Participant has an unresolved AE or a clinically significant finding on physical examination, clinical laboratory test, or 12-lead ECG that, in the investigator's opinion, would limit the participant's ability to participate in or complete the study

4. Any other reason that, in the investigator's opinion, would confound proper interpretation of the study or expose a participant to unacceptable risk, including renal, hepatic or cardiopulmonary disease

5. Participant is directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, other study staff member, or employee of Allergan, Inc.; or the participant is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or the participant is enrolled in this study at another clinical study site.

6.3. Rationale for Inclusion and Exclusion Criteria

The Inclusion and Exclusion Criteria are meant to create a population of participants that is well characterized as having DG with symptoms that require chronic treatment. This population, having previously participated in RLM-MD-01 or RLM-MD-02, will have received study treatment for at least 12 weeks before entering this study, during which the safety and efficacy of an additional 40 weeks of treatment will be assessed; the effect of withdrawal of relamorelin will also be evaluated.

6.4. 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.

6.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. The determination as to whether a participant meets inclusion/exclusion criteria of RLM-MD-03 is made at the final visit (Visit 7) in lead-in study RLM-MD-01 or lead-in study RLM-MD-02.

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 per the study protocol.

7.1. Treatments Administered

Participants are to self-administer double-blind study treatment twice daily, [redacted]

Participants should rotate injection sites in the abdomen.

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	Study treatment will be provided in a single unit carton. Each carton will be labeled as required per country requirement.	Study treatment will be provided in a single unit carton. Each carton will be labeled as required per country requirement.
Manufacturer	Baxter (Prefilled Cartridge) Allergan (Assembled Pen)	Baxter (Prefilled Cartridge) Allergan (Assembled Pen)
Injection Device	Utilize Multi-dose Pen Injector for the administration of the study treatment or placebo. Refer to the Relamorelin Pen Investigational Directions for Use for detailed instructions on use of the injection device. Each pen injector is to be used for 28 days.	Utilize Multi-dose Pen Injector for the administration of the study treatment or placebo. Refer to the Relamorelin Pen Investigational Directions for Use for detailed instructions on use of the injection device. Each pen injector is to be used for 28 days.

7.1.1. Study Supplies

1. The Allergan-manufactured medical devices (or devices manufactured for Allergan by a third party) 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 the 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 Section 12.7).

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

At the start of lead-in studies RLM-MD-01 or RLM-MD-02, all participants will have been centrally assigned to randomized study treatment to be taken during the Treatment Period of this study using an interactive web response system (IWRS).

At Visit 7/Week 40 (the beginning of the RWP), participants taking relamorelin during the Treatment Period will be re-randomized to either relamorelin or placebo using IWRS. Participants taking placebo during the Treatment Period will all be allocated to relamorelin treatment for the 6 weeks following the end of the Treatment Period. Before this study is initiated, the log-in information and directions for the IWRS will be provided to each site.

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 40-week Treatment Period and the 6-week RWP. 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

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.

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.

[redacted]

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.

[redacted]

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 except for diabetes mellitus (see Section 7.7.2 Permitted Treatments) 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 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.

Table 7-2 provides a list of drug classes and treatments that are prohibited during the study. These Drug Classes/Treatments were washed out prior to participants entering RLM-MD-01 and RLM-MD-02, and continue to be prohibited in RLM-MD-03.

Table 7-2 Prohibited Medications

Drug Class/Treatment
Pro-motility agents: Metoclopramide, macrolide antibiotics (eg, azithromycin, clarithromycin, erythromycin), domperidone, prucalopride, or other drugs considered to be GI pro-motility agents
Anticholinergics: Drugs with an anti-cholinergic mechanism of action as the basis of their therapeutic benefit, not those that have anti-cholinergic activity as a side effect
Anti-emetics (Used for more than 1 day a week, or participant 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)
Amylin analogue: pramlintide
5HT4 agonists (cisapride, tegaserod, and prucalopride)
Opioids[a] **(**including tramadol**)**
Glucagon-like peptide-1 (GLP-1) agonists: Exenatide, liraglutide, etc.
Botulinum toxin injections (eg, Botox®) by pyloric injection only; injection of Botox in other parts of the body is allowed

[a] Exception to prohibition: An opioid prescribed for severe pain following a surgical operation, dental procedure, or injury may be taken as directed for up to 72 hours a maximum of two times during the study.

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 after entering the Treatment Period or RWP, may receive a single day of treatment per week with an anti-emetic drug, but should avoid such treatment, if possible, 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 in the study.

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

Participants who complete the study 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
- Lack of efficacy
- Lost to follow-up
- Other
- Investigator or physician decision
- Pregnancy
- Protocol deviation

- 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. [redacted]

[redacted]

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, behavioural, 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 (Section 2) 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.

[redacted]

[redacted]

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.

[redacted]

9.1. Efficacy Assessments

9.1.1. Key Efficacy Assessment – DGSSD

The primary efficacy assessment is 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 (Appendix 13) and the frequency of vomiting episodes.

DGSSD entries are to be made daily at the same time every evening on the electronic hand-held device during the 12-week period before Visit 4 of the Treatment Period, the 4-week periods before Visits 5, 6, and 7 of the Treatment Period, and throughout the 6 weeks of the

Randomized-withdrawal Period. Planned timepoints for all efficacy assessments are provided in the SoA (Section 2).

The severity of DG symptoms is 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).

An overall assessment of the severity of non-vomiting symptoms is derived from the weekly DGSSS, which is the sum of the weekly averages of DGSSD items of nausea, abdominal pain, postprandial fullness, and bloating. Weekly assessments are calculated from a participant's daily DGSSD responses.

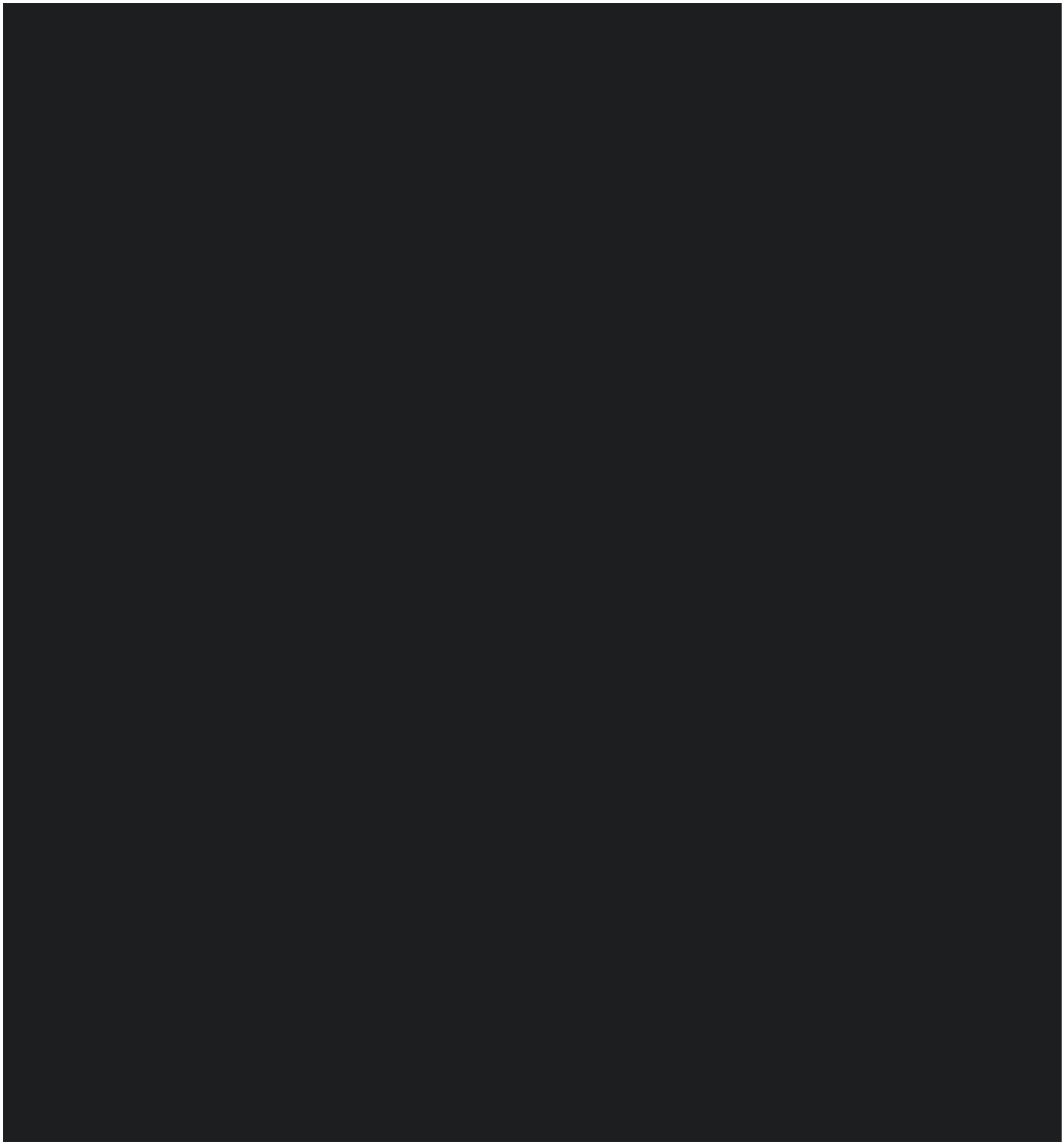
The DGSSS ranges from 0 to 40, with the worst possible DGSSS for the 4 DG symptoms being 40, and the best possible DGSSS being 0. Psychometric analyses have shown that a decrease in the DGSSS by ≥ 10 points and a decrease in individual symptom scores by ≥ 2 points is recognized as a clinically meaningful improvement in DG symptoms by affected patients (Psychometric Evaluation, RTI Health, 2017).

Vomiting frequency will be captured daily on the electronic hand-held device. Participants will be asked to indicate the number of vomiting episodes experienced in the day since the previous entry made, with information to be provided as to what constitutes a "vomiting episode" in order to ensure accurate reporting. 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.

Weekly assessment of vomiting frequency is derived as the normalized total number of vomiting episodes during a week. This is defined as:

> Weekly normalized number of vomiting episodes = (total number of vomiting episodes in the week)*(7 days / [number of days with non-missing responses in the week])

[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 8) or Early Termination Visit, at the time points specified in the SoA (Section 2). Ongoing AEs at the end of study RLM-MD-01 and RLM-MD-02, and new AEs that occur after the signing of the ICF for RLM-MD-03 are considered to be AEs in RLM-MD-03.

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 AEs and SAEs 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 AEs/SAEs and non-serious AEs of special interest ([AESI] as defined in Appendix 4) will be followed until resolution, stabilization, until 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 Section 12.5.
- 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:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (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. [redacted]

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 DG 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

For this study, any dose of study treatment greater than 150 µg BID within a 24-hour time period will be considered an 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 at the visits indicated on the SoA (Section 2); height to be measured only at Visit 1 of lead-in study RLM-MD-01 or RLM-MD-02.

Any abnormality noted during the physical examination performed at Visit 7 (or an early termination visit that occurs prior to Visit 7) 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. Any abnormality noted during the physical examination performed at Visit 8 (or an early termination visit that occurs after Visit 7) that was not present during the physical examination at Visit 7 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 (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, 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 (Section 2).

    - 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. 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 will provide each participant with test strips and all supplies necessary for testing finger-stick capillary blood glucose with the glucose monitor previously provided in lead-in study RLM-MD-01 or RLM-MD-02. 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 fasting blood glucose, 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

Pharmacokinetic parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

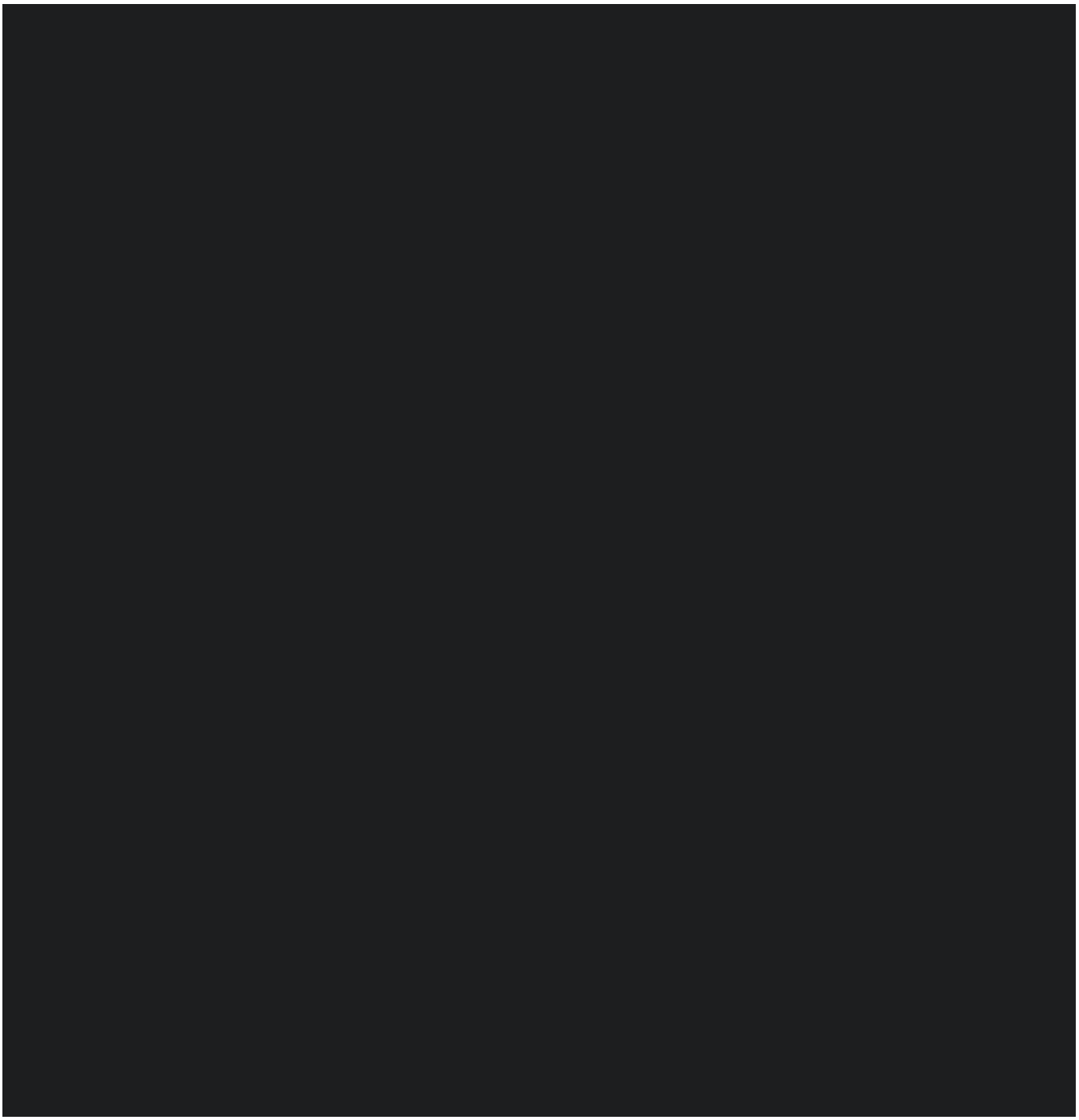
9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not used in the study.

[redacted]



10. Statistical Considerations

10.1. Sample Size Determination

Enrollment in this study is dependent upon the drop-out rates in the pivotal studies RLM-MD-01 and RLM-MD-02. Assuming 300 participants per arm in each study and a drop-out rate of 20% in each of the pivotal studies, it is expected that approximately 960 participants (480 participants in each arm) will enter the study. Further, assuming that the drop-out rate will also be 20% by Week 12 in this study, it is expected that there will be 384 participants per treatment group at Week 12. This sample size will provide 99% power to detect a statistically significant difference in response rate between treatment and placebo in both the 4-symptom composite DGSSS endpoint (assuming a placebo rate of 14% and a treatment rate of 35%) and in the vomiting response endpoint (assuming a placebo rate of 11% and a treatment rate of 26%.) at Week 12. The assumed response rates were those calculated from study RM-131-009.

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 participants who sign the ICF
Intent-to-treat (ITT)	All participants who enter the 40-week Treatment Period
Modified intent-to-treat (mITT)	All participants in the ITT Population who have ≥ 1 postbaseline assessment of DGSSD
Safety	All participants in the ITT Population who received ≥ 1 administration of study treatment

10.3. Statistical Analyses

The statistical analysis plan (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 SAP. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects without multiplicity adjustment. All confidence intervals will be 2-sided 95% CIs, unless stated otherwise.

Table 10-2 Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories ○ Participants with ≥ 1 qualifying event counted once per individual category

Categorical descriptives	• Number and percentage of participants in individual categories
	  ○ Participants with ≥ 1 qualifying event counted once per individual category
	• N1 if percentage denominator ≠ number of participants in the population (standard percentage denominator)
	  ○ N1 = participants with nonmissing baseline value

Event descriptives	• Number and percentage of events in individual categories ○ Events counted individually for each instance • Percentage denominator = total number of events
Shift analysis	• Number and percentage of participants in individual baseline and postbaseline categories • Percentage denominator = number of participants in individual baseline categories • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit
Continuous descriptives	• N1, mean, standard deviation, 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

CFB ANCOVA	• Continuous descriptives and standard error (SE) for baseline, postbaseline, and CFB values
	• Estimates derived from mixed model for CFB value controlling for factors (treatment group, region) and covariates (baseline value)
	  ○ Least squares (LS) means and standard errors
	  ○ LS mean differences, standard errors, and confidence intervals vs placebo
	  ○ P-values from contrast t-test comparing treatment group vs placebo
	• N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit

CFB MMRM	• Continuous descriptives and standard error (SE) for baseline, postbaseline, and CFB values
	• MMRM model with geographic region, treatment, week, treatment-by-week interaction as factors, baseline and baseline-by-week interaction values as covariates
	• Estimates derived from mixed model for CFB value controlling for factors (treatment group, region) and covariates (baseline value)
	  ○ Least squares (LS) means and standard errors
	  ○ LS mean differences, standard errors, and confidence intervals vs placebo
	  ○ P-values from contrast t-test comparing treatment group vs placebo
	• N1 = participants with nonmissing

Methodology	Description

Responder	• Categorical descriptives for responders and non-responders
	  ○ Nonresponders include:
	  ▪ Participants who do not meet responder criteria
	  ▪ Participants with no postbaseline values
	• Risk differences and Wald confidence intervals vs [placebo/active comparator]
	• Estimates derived from Cochran-Mantel-Haenszel (CMH) model controlling for factors (treatment group, region)
	  ○ Mantel-Haenszel (MH) odds ratios (ORs) and confidence intervals vs placebo
	  ○ P-values comparing treatment group vs placebo
	• N1 = all participants unless otherwise specified

ANCOVA = analysis of covariance; CFB = change from baseline; MMRM = mixed-effects model with repeated measures.

10.3.2. Efficacy Analyses

10.3.2.1. Key Endpoints

Table 10-3 displays the primary and secondary efficacy endpoints that will be analyzed for the mITT population. For all analyses, the baseline is the baseline value from the lead-in study RLM-MD-01 or RLM-MD-02. All other efficacy endpoints and analyses will be defined in the SAP.

Table 10-3 Key Endpoints

Key Endpoints	Description	Timing	Methodology
Primary			
CFB to Week 12 in weekly DGSSS	Change from baseline to week 12 of this study in the weekly DGSSS. Weekly score at Week 12: Average score from Days 78 to 84.	Days 78 to 84	CFB MMRM
Vomiting Week 12 Responder	Vomiting responder defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the first 12 weeks of the Treatment Period.	Last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Responder
Secondary			
Nausea Week 12 Responder	Nausea responder defined as a participant who has a ≥ 2-point improvement in the weekly symptom score at each of the last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Responder
Abdominal Pain Week 12 Responder	Abdominal pain responder defined as a participant who has a ≥ 2-point improvement in the weekly symptom score at each of the last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Responder

Table 10-3 Key Endpoints

Key Endpoints	Description	Timing	Methodology
Bloating Week 12 Responder	Bloating responder defined as a participant who has a ≥ 2-point improvement in the weekly symptom score at each of the last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Responder
Postprandial Fullness Week 12 Responder	Postprandial Fullness responder defined as a participant who has a ≥ 2-point improvement in the weekly symptom score at each of the last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Last 6 weeks of the first 12 weeks of the 40-week Treatment Period	Responder
DGSSS at Week 40	Change from baseline to Week 40 in average weekly DGSSS. Average weekly scores are derived as the average of the weekly scores from the four weeks prior to Week 40 (Visit 7) in this study.	Week 36 - Week 40	CFB ANCOVA
Vomiting Frequency at Week 40	Change from baseline to Week 40 in average weekly number of vomiting episodes derived as the average of the weekly number of vomiting episodes during the four weeks prior to Week 40 (Visit 7) in this study.	Week 36 - Week 40	CFB ANCOVA
Vomiting Week-40 Responder	Vomiting responder defined as a participant with zero weekly vomiting episodes during each of the last 4 weeks of the 40-week Treatment Period	Week 36 - Week 40	Responder
DGSSS at Week 46	CFB to end of RWP in the average weekly DGSSS. Average weekly scores are derived as the average of the weekly scores from the six weeks of the RWP.	Week 41 - Week 46	CFB ANCOVA
Number of Vomiting Episodes at Week 46	CFB to end of RWP in the average weekly number of vomiting episodes. Average weekly scores are derived as the average of the weekly number of vomiting episodes from the six weeks of the RWP.	Week 41 - Week 46	CFB ANCOVA

10.3.2.2. Missing Data

Participants with a missing weekly value for either of the key endpoints (symptom Week 12 responders or vomiting frequency) during any of the last 6 weeks of the first 12 weeks of the 40-week Treatment Period will be analyzed as a non-responder for the particular endpoint for the Week-12 responder analyses.

Participants with a missing weekly value for either of the key endpoints (symptom Week 40 responders or vomiting frequency) during any of last 4 weeks of the 40-week Treatment Period will be analyzed as a non-responder for the particular endpoint for the Week-40 responder analyses.

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 hypoglycemia-related events
- Clinical laboratory assessments
    - Potential Hy's law cases
- Vital signs
- ECGs
- Study-specific assessments
    - HbA1c

[redacted]

10.3.5. Interim Analyses

In addition to the above, monitoring of participant 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

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
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
DG	diabetic gastroparesis
DGSSD	Diabetic Gastroparesis Symptom Severity Diary
DGSSS	Diabetic Gastroparesis Symptom Severity Score
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

GE	gastric emptying
GI	gastrointestinal
GP	gastroparesis
HbA1c	glycosylated hemoglobin A1c
HEOR	health economics outcomes research
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormonal replacement therapy
IC	informed consent
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
MSP	medical safety physician
NRS	numerical rating scale

[redacted]

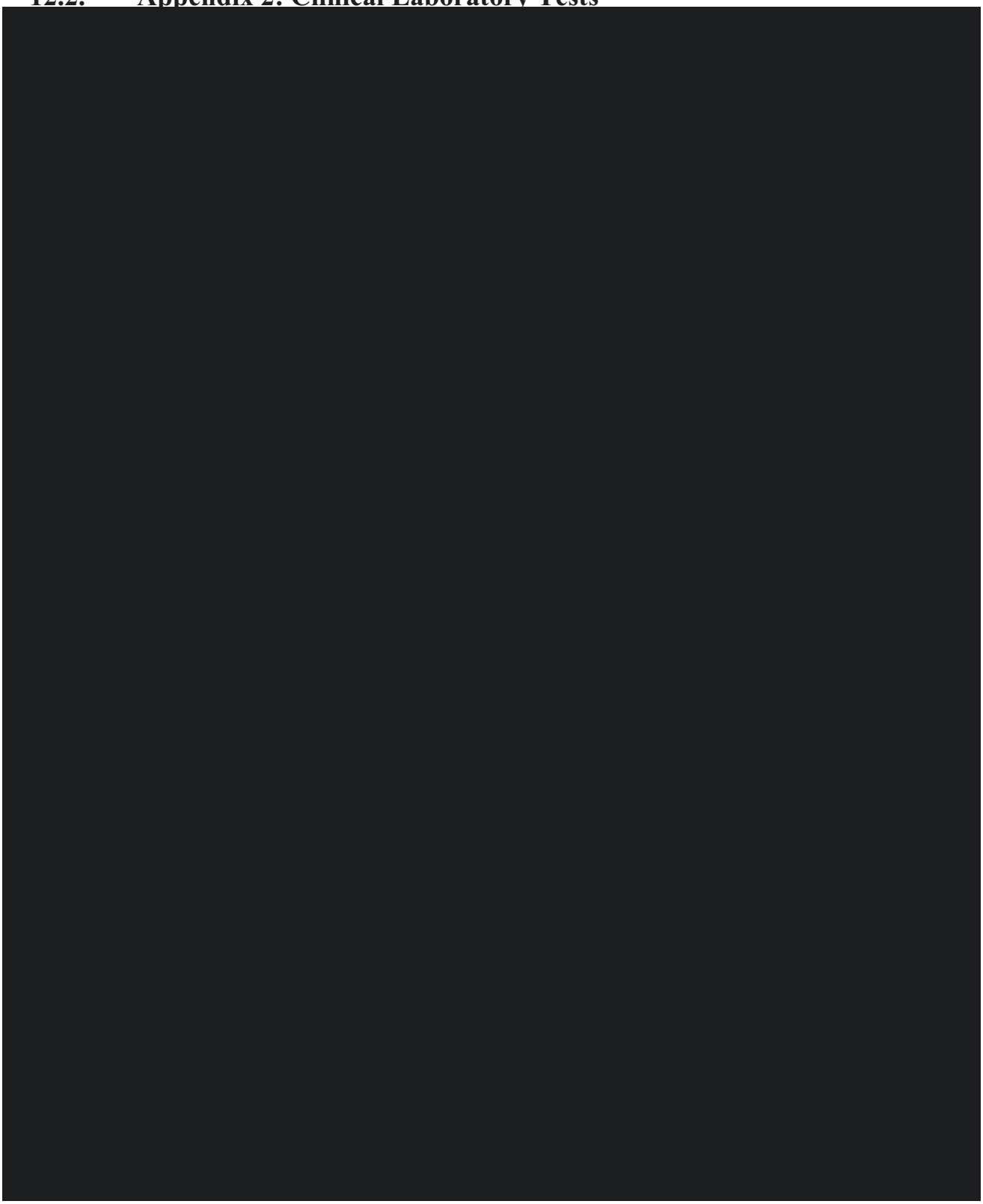
[redacted]

QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using Fridericia formula
RLM	relamorelin
RWP	randomized withdrawal period
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)

[redacted]

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
ULN	upper limits of normal
US	United States of America
WOCBP	women of childbearing potential

12.2. Appendix 2: Clinical Laboratory Tests



12.3. Appendix 3: Study Governance Considerations

12.3.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

12.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

12.3.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of IC that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written IC was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the IC must also sign the ICF.
- Written documentation must be obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection Consent [European sites]).
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Additionally, in accordance with relevant country requirements, written IC is to be obtained from each participant prior to enrollment into the study. The IC form includes explanation of the following:

1. That the study involves research
2. The objectives of the study
3. The study procedures
4. The expected duration of the participant's participation in the study
5. The approximate number of participants involved in the study
6. The reasonably foreseeable risks or inconveniences to the participant
7. The alternative procedures or courses of treatments that may be available to the participant, and their important potential benefits and risks
8. The compensation and/or treatment available to the participant in the event of study-related injury

9. That the participant's participation in the study is voluntary and that the participant may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the participant is otherwise entitled

10. That the participant will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study

11. The foreseeable circumstances and/or reason under which the participant's participation in the study may be terminated

12. That the monitors, auditors, the IRB, and the regulatory authorities may provide direct access to the participant's original medical records. In such cases, the confidentiality of the participant should be protected, and by signing and sealing an IC form, the participant is authorizing such access.

13. If the results of the study are published, the participant's identity will remain confidential.

14. The anticipated expenses, if any, to the participant for participating in the study

15. The anticipated prorated payment, if any, to the participant for participating in the study

16. The name, title, and address of the investigator to contact

17. The person(s) to contact for further information regarding the clinical study and the rights of participants, and whom to contact in the event of study-related injury

18. The type of the IRB engaged in the assessment and deliberation about the acceptability of the study, items subject to the assessment of each IRB, and other IRB-related items relating to the study

19. The participant's responsibilities

Participants who are rescreened are required to sign a new ICF.

12.3.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.3.5. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.3.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

12.3.7. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.3.8. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect cooperation between the investigator or multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In the case of a multicentre study, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- In accordance with relevant country requirements, a report of the results of this study may be published or sent to the appropriate health authorities in any country in which the

study intervention may ultimately be marketed, but the participant's name will not be disclosed in these documents. The participant's name may be disclosed to the sponsor of the study, Allergan Japan K.K., or the governing health authorities (ie, PMDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

12.4.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

AE of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study treatment/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESIs have been identified for the study interventions in this protocol (see also Section 9.2.7):

1. Hy's law cases
2. Inadequate control of diabetes: hyperglycaemia and hypoglycaemia
3. MACE

Serious AESIs should be reported to the sponsor within 24 hours via the SAE form.

[redacted]

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • The following events are considered to be manifestations of diabetic gastroparesis and will be captured in the DGSSS but they will not be reported as AEs or SAEs: nausea, abdominal pain, upper abdominal pain, vomiting, postprandial fullness, bloating, and early satiety.

If the investigator considers these manifestations to have a reasonable possibility of relationship to the study treatment/device(s) then they should be reported as AEs or SAEs.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

12.4.2. Definition of SAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred, or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.3. Recording an AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the

individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before**

the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

12.4.4. Reporting of SAEs

SAE Reporting to the Sponsor via e-mail, fax, or telephone

- Email is the preferred method for transmission of SAE information to the sponsor.

[redacted]

- Facsimile transmission of SAE information is also acceptable.

[redacted]

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

- Contacts for SAE reporting can be found in the Study Reference Manual.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

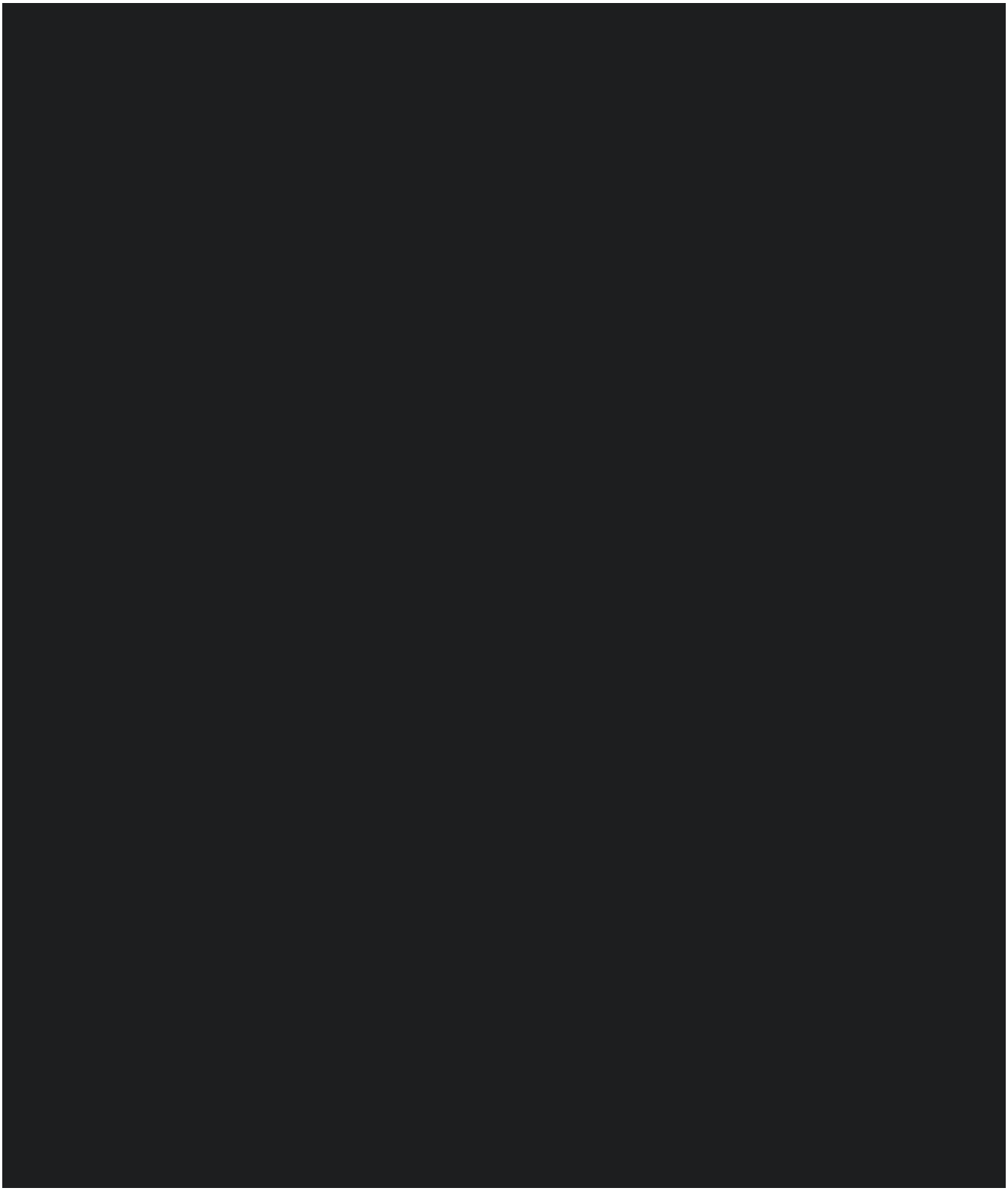
Women in the following categories are not considered WOCBP:

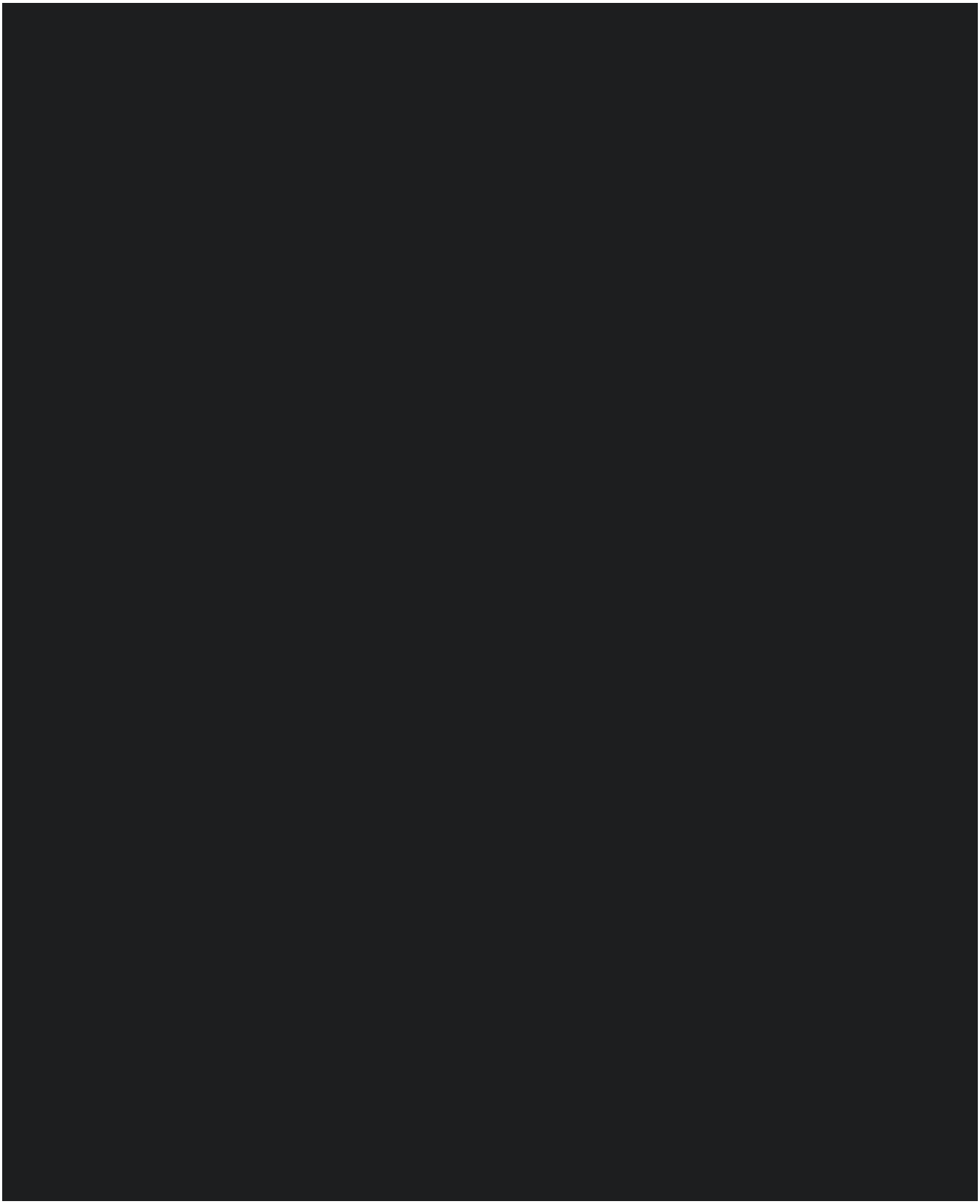
1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

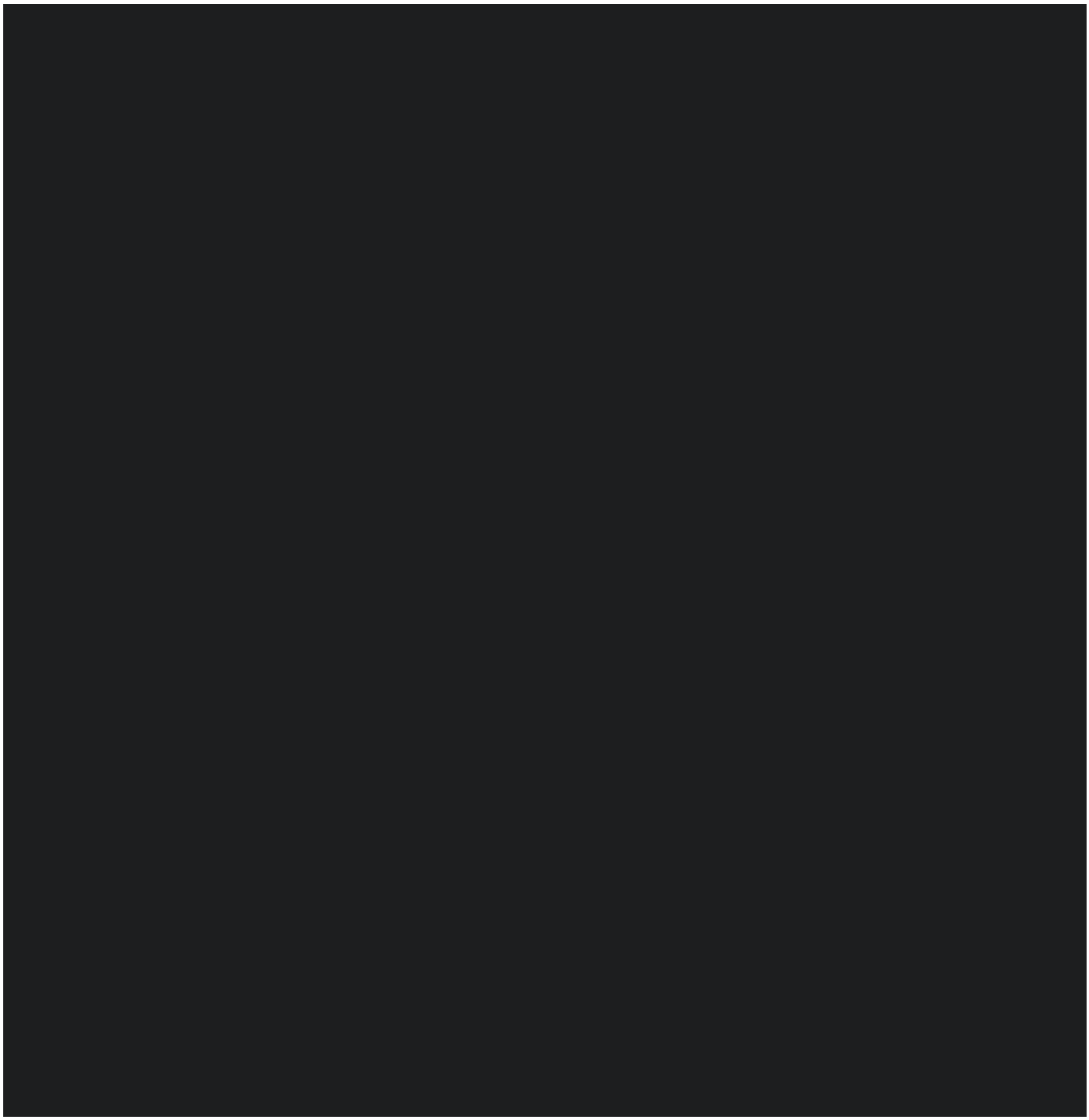
   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

[redacted]







12.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Hy's law cases are considered AESIs. Potential Hy's Law criteria are as follows:

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

All cases that qualify as potential Hy's law cases (AESI) must be reported to Allergan [redacted]

Investigational product must be discontinued if any of the following criteria are met:

- ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

The participant may be re-challenged with study treatment only after consultation with the Allergan MSP. For participants who are not re-challenged with study treatment, the participant should be discontinued from the study and complete the Early Termination Visit. Participants should receive appropriate follow-up as per standard of care.

Potential Hy's Law Cases

Sites must report every participant who meets the potential Hy's law criteria if this occurs within the time the participant signs the ICF until 30 days after the last dose of study treatment.

A laboratory alert for potential Hy's laws cases will be in place, and the investigators and Allergan will be notified immediately when the above criteria have been met. Any potential Hy's laws case should be considered an SAE and also reported as an AE of Special Interest.

[redacted] Every effort to determine the cause of the liver abnormalities must be made, and close monitoring should be initiated in conjunction with the

Allergan MSP and in accordance with the FDA “Guidance for Industry: Drug Induced Liver Injury - Pre-Marketing Clinical Evaluation” July 2009.

12.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 7.1 for the list of sponsor medical devices).

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting

[redacted]

12.8. Appendix 8: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [Modified from ICH E2A] Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Failure to meet randomization criteria	An indication that the participant has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a participant to follow-up
Other	Different than the one(s) previously specified or mentioned (NCI)
Investigator or physician decision	A position, opinion or judgment reached after consideration by the investigator with reference to participant (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential participant who does not meet one or more criteria required for participation in a trial

CDISC Submission Value	CDISC Definition
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by participant	An indication that a study participant has removed itself from the study (NCI)

12.9. Appendix 9: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A 46-week, Double-blind, Placebo-controlled, Phase 3 Study with a 6-week Randomized-withdrawal Period to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis
	Clinical Study Sponsor	Allergan Sales
	Trial Phase Classification	Phase 3 Trial
	Trial Indication	Diabetic Gastroparesis
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	46 weeks
	Planned Country of Investigational Sites	Global
	Planned Number of Subjects	Approximately 960, based on assumption that 80% of participants who enter RLM-MD-01 and RLM-MD-02 will complete these studies and enter this study. Number of Sites: approximately 700 sites (globally)
	FDA-Regulated Device Study Indicator	No
	FDA-Regulated Drug Study Indicator	No
	Pediatric Study Indicator	No
Subject information	Diagnosis Group	Diabetes mellitus
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	none
	Sex of Participants	Both
	Stable Disease Minimum Duration	3 months

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	relamorelin
	Intervention Type	drug
	Pharmacological Class of Invest. Therapy	synthetic ghrelin analogue
	Dose per Administration	10 µg
	Dose Units	Pre-Filled Cartridge in Multi-Dose Pen Injector
	Dosing Frequency	BID
	Route of Administration	subcutaneous injection
	Current Therapy or Treatment	treatment
	Added on to Existing Treatments	No
	Control Type	Placebo
	Comparative Treatment Name	none
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Trial is Randomized	Yes
	Randomization Quotient	1:1
	Trial Blinding Schema	Double blind
	Stratification Factor	Not applicable
	Adaptive Design	No
	Study Stop Rules	Not stated