NCT03383146

Study ID: RLM-MD-04

Title: A 52-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients With Diabetic Gastroparesis

Statistical Analysis Plan Amendment 1 Date: 15Dec2020

1.0 Title Page

RLM-MD-04

A 52-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Participants with Diabetic Gastroparesis

STATISTICAL ANALYSIS PLAN - Abbreviated Clinical Study Report

Final: 28 September, 2020
Amendmend #1: 15 December, 2020

2.0 Table of Contents

2.1 List of Tables

3.0 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
CDC	Center for Disease Control
[redacted]	
CFB	change from baseline
DG	diabetic gastroparesis
DGSSD	Diabetic Gastroparesis Symptom Severity Diary
DGSSS	Diabetic Gastroparesis Symptom Severity Score
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
EOS	end of study
[redacted]	
GEBT	gastric emptying breath test
HbA1c	glycosylated hemoglobin A1c
[redacted]	
ITT	intent to treat
[redacted]	
PCS	potentially clinically significant
[redacted]	
PT	Preferred Term
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RM	rescue medication
RLM	Relamorelin
SAE	serious adverse event
SI	*Le Système International d'Unités* (International System of Units)
SoA	Schedule of activities
SOC	system organ class
T1DM	type I diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event

TESAE	treatment-emergent serious adverse event
WOCBP	women of childbearing potential

4.0 Introduction

The statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in the protocol RLM-MD-04, Amendment 3 (dated 29 Apr 2019).

However, the study was early/prematurely terminated on 04 September 2020 and only an abbreviated study report will be applied to this study to report only some safety analyses and along with some basic trial characteristics data summaries.

This SAP amendment is based on the SAP dated 28 September 2020. The major change to the SAP is to add descriptive analyses for the key efficacy endpoints for the results posting on ClinicalTrials.gov and EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) and add the COVID-19 data listing.

4.1 Study Design

Overall Study Design:

- Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group
- Treatment Group: Relamorelin 10 μg or placebo subcutaneously twice daily
- Study Duration: 52-week Double-blind Treatment Period
- Participants who meet study entry and randomization criteria will be randomized in a 2:1 ratio to blinded treatment with relamorelin 10 μg or placebo, and will use an electronic hand-held device for reporting of their symptoms, treatment satisfaction, compliance, and use of rescue medication.

Planned enrollment for this study is 600 participants assigned to study treatment (400 to relamorelin and 200 to placebo). A total of 300 participants are expected to complete the study (200 relamorelin- and 100 placebo-treated participants).

Two different groups of participants may enter into the study, rollover participants and de novo participants.

1. Rollover participants are those who met all Screening and Run-in Period criteria in lead-in Study RLM-MD-01 or lead-in Study RLM-MD-02 (including compliance with dosing and data entry into the Diabetic Gastroparesis Symptom Severity Diary (DGSSD) during the lead-in study Run-in Period), but were not randomization-eligible at the end of the lead-in study Run-in Period. They are eligible for randomization in Study RLM-MD-04 if:

    - They had no vomiting episodes recorded in the DGSSD and had an average daily Diabetic Gastroparesis Symptom Severity Score (DGSSS) ≥ 12 at the end of the lead-in study Run-in Period.

OR

- They had vomiting episodes recorded in the DGSSD but had an average daily DGSSS of ≥ 12 and < 16 at the end of the lead-in study Run-in Period.

Rollover participants will enter the study at Visit 1 (Randomization); they will not undergo Screening (Visit –2) or Run-in Visit (Visit –1) procedures.

De novo participants are those who undergo screening and Run-in procedures in Study RLM-MD-04. De novo participants are eligible for randomization if they meet all Screening and Run-in Period criteria for Study RLM-MD-04, including:

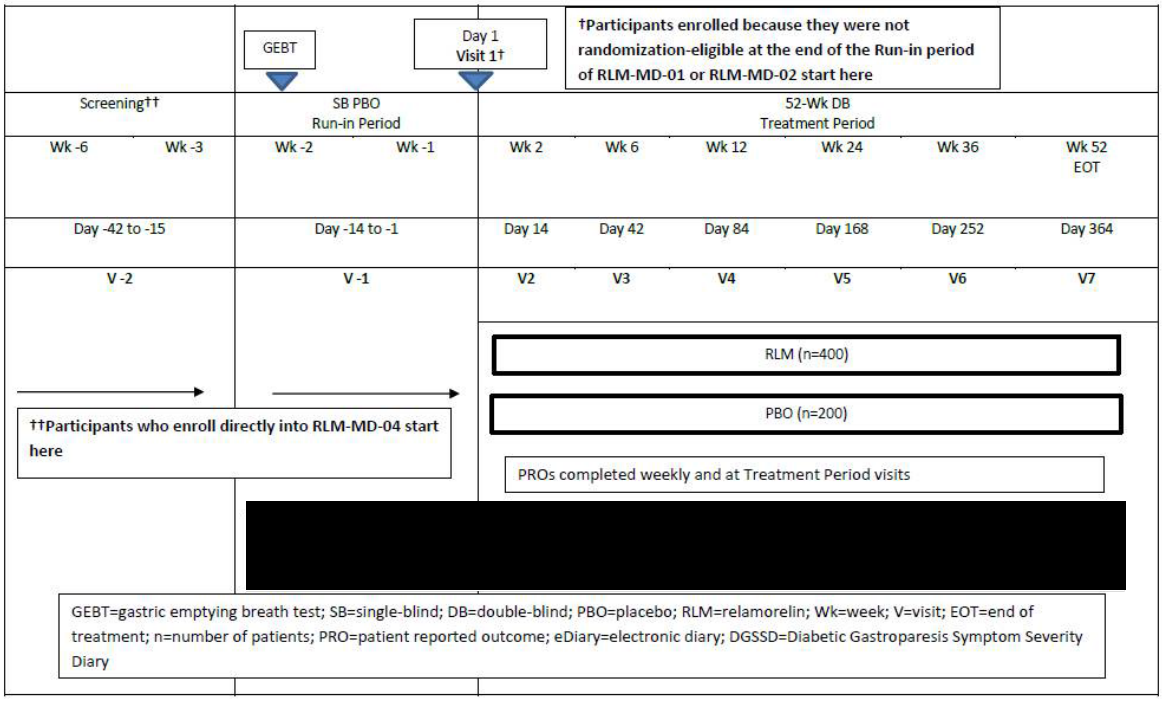
At the Screening Visit (Visit -2):

- Male or female aged 18 years and older;
- T1DM or T2DM with controlled and stable blood glucose levels and HbA1c ≤ 11%;
- Symptoms suggestive of DG for at least 3 months (one of which must be nausea), with mechanical obstruction of the gastrointestinal tract as the cause of symptoms having been ruled out;
- History of nausea and/or at most a single episode of vomiting in the 2 weeks prior to Screening (Visit -2), as ascertainied by participant history

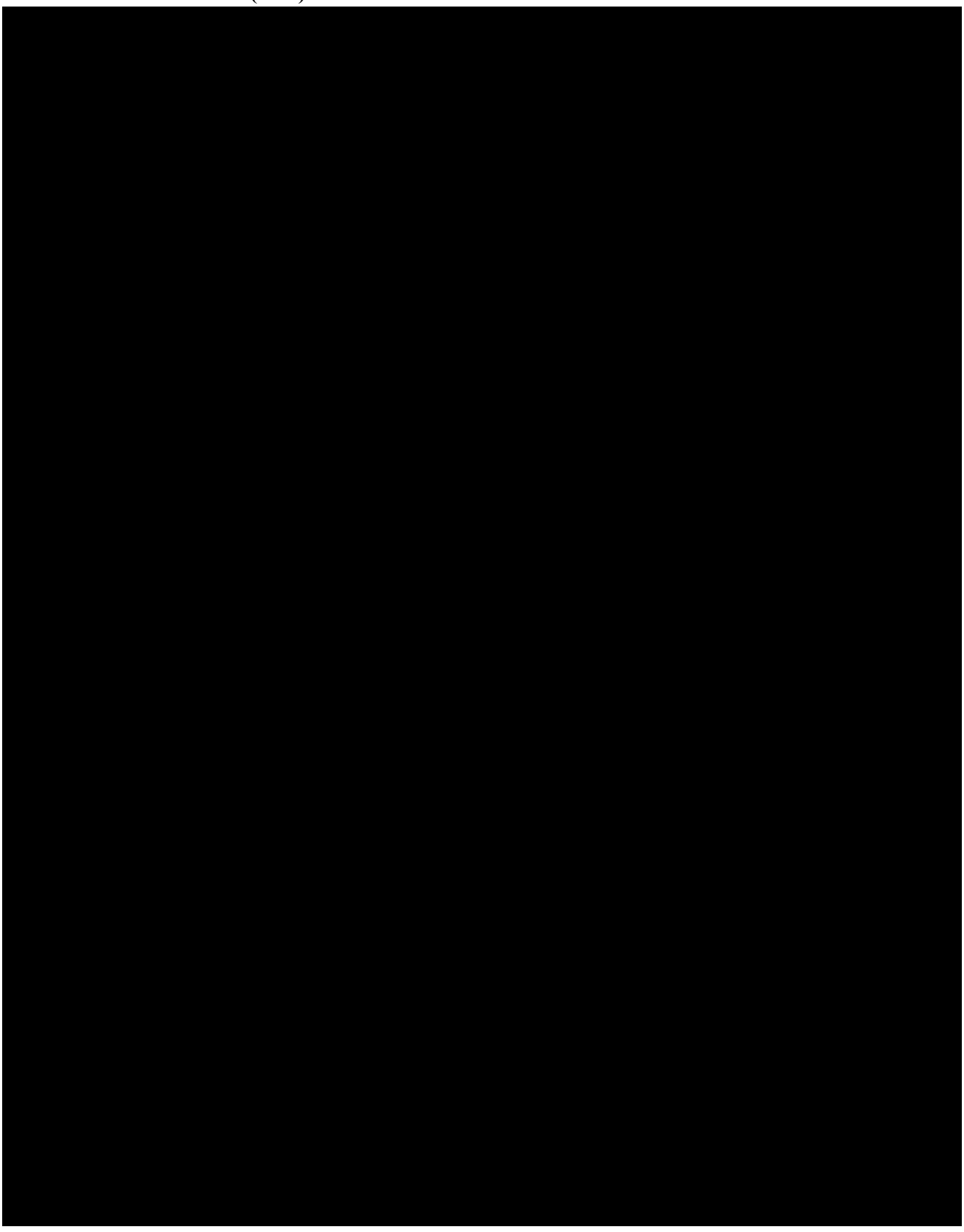
At the End of the Run-in Period:

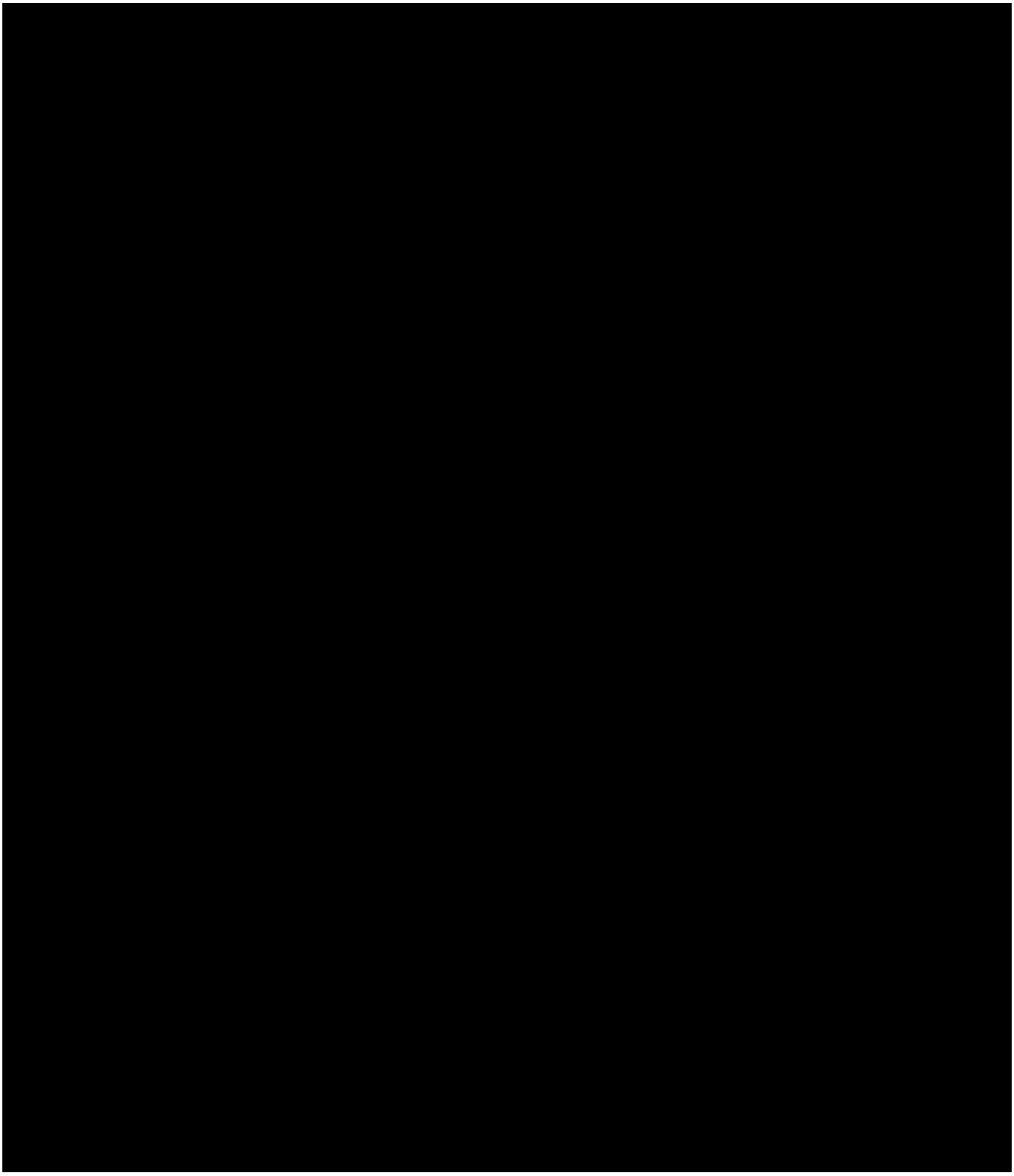
- Evidence of compliance during the Run-in Period with both the use of the electronic hand-held device for entry of data and with twice daily SC injections of the study treatment;
- No treatment with GI promotility agents during the Run-in Period;
- A score of >= 12 for the average of the daily DGSSS measured during the Run-in Period.

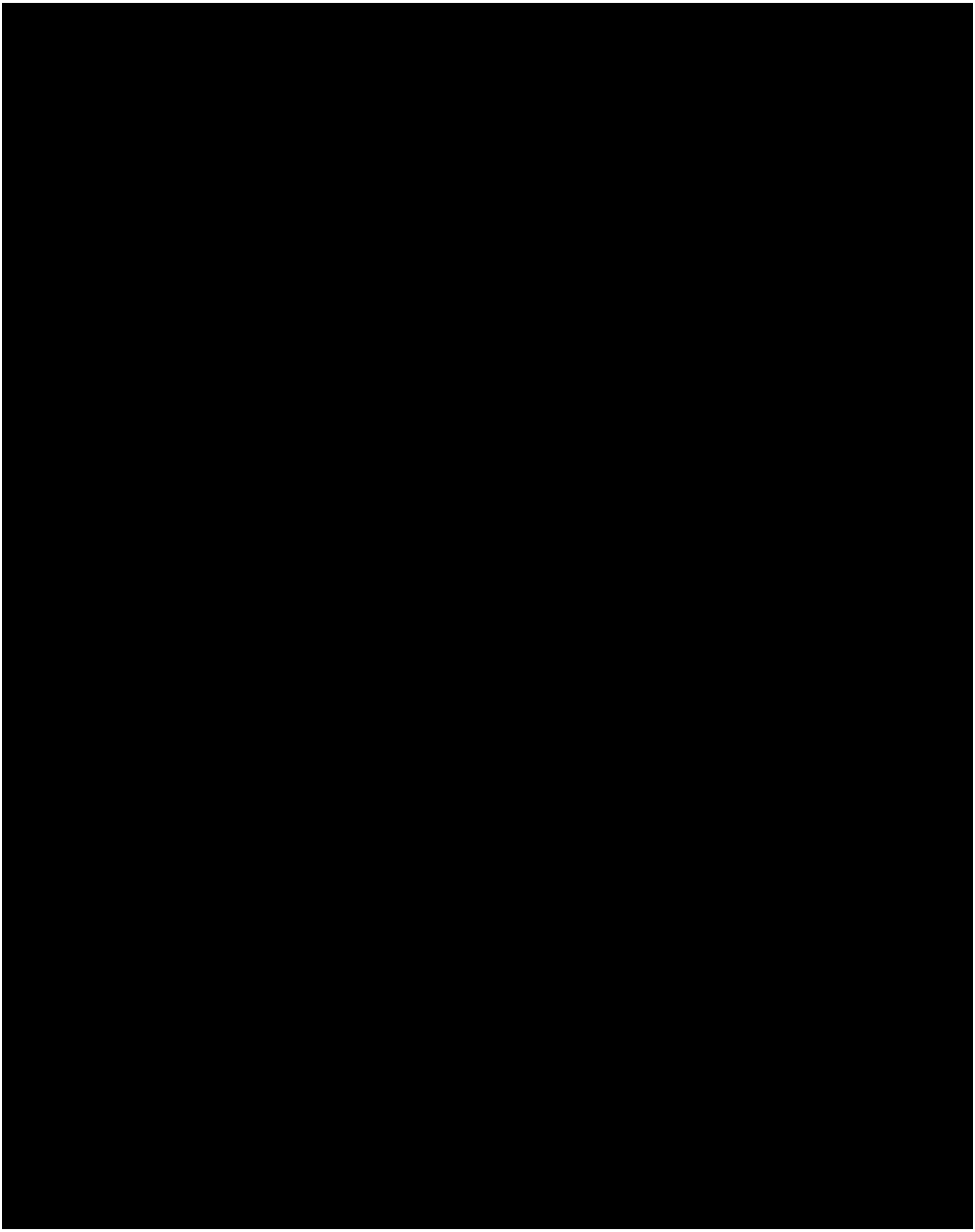
Study Schematic:

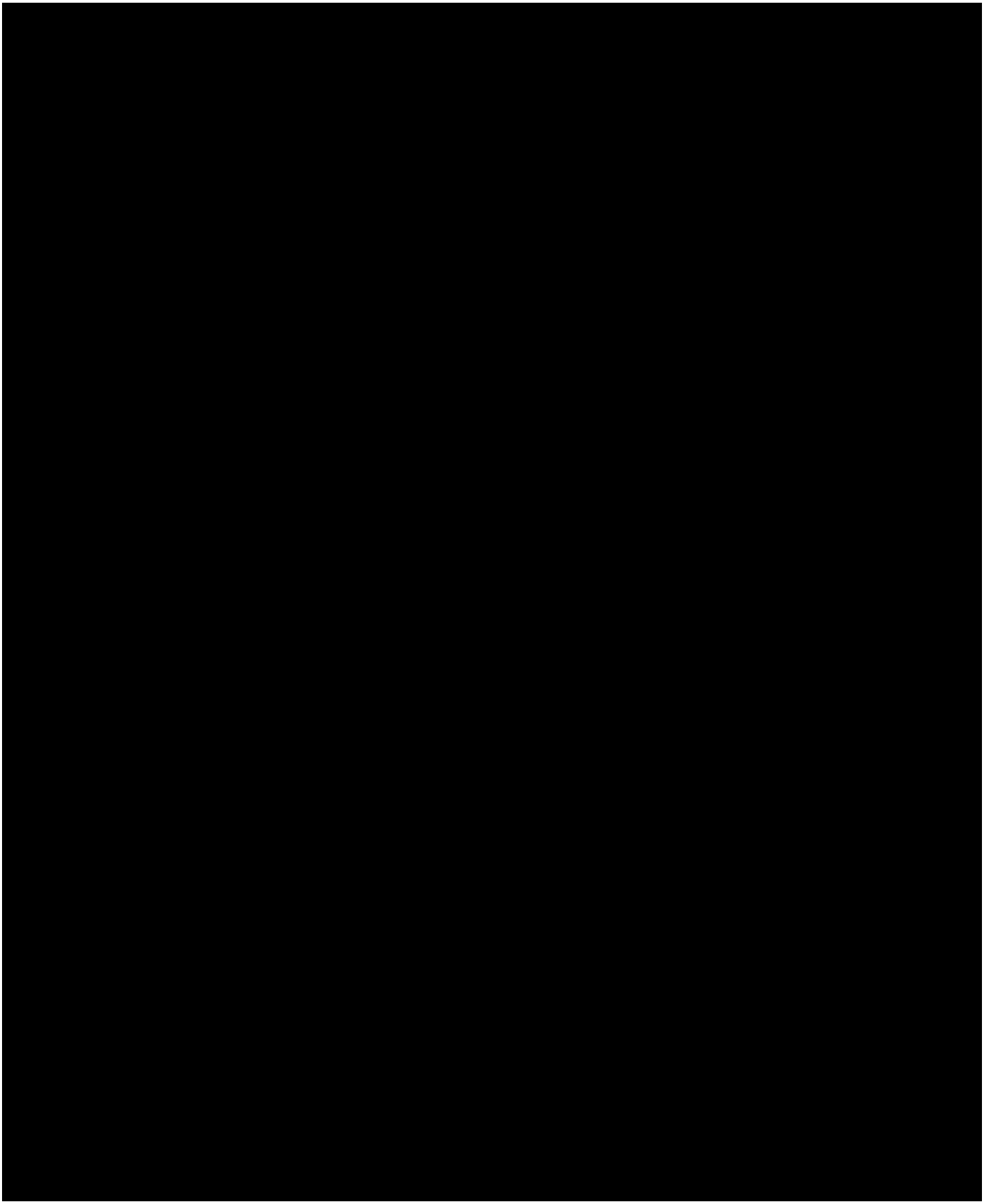


Schedule of Activities (SoA)









5.0 Objectives

Key Objectives	Key Endpoints
• To compare the efficacy of relamorelin with that of placebo in participants with DG with respect to a composite of the following core signs and symptoms of DG: o Nausea o Abdominal pain o Postprandial fullness o Bloating	• Change from baseline to Week 12 in the weekly DGSSS • Change from baseline to Week 52 in weekly average DGSSS
• To compare the safety of relamorelin with that of placebo in participants with DG	• AEs, clinical laboratory values, vital signs, ECGs, HbA1c, and anti-relamorelin antibodies
Other Objectives	**Other Endpoints**
• To assess relamorelin treatment effect on individual symptoms of DG such as nausea, abdominal pain, bloating, postprandial fullness, early satiety, and vomiting frequency	• Change from baseline to Week 12 and Week 52 in the following: o Nausea o Abdominal pain o Bloating o Postprandial fullness o Early satiety o Vomiting frequency

6.0 Populations for Analyses

6.1 Screened Population

The Screened Population will consist of all participants who sign informed consent.

6.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all randomized participants.

6.3 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) Population will consist of all randomized participants with ≥ 1 postbaseline assessment of DGSSD. It is a subset of the ITT Population.

6.4 Safety Population

The Safety Population will consist of all participants who receive ≥ 1 administration of study treatment.

The Safety Population will be used for all safety analyses. Participants will be analyzed according to the treatment they actually received during the Double-blind Treatment Period. In case a participant receives relamorelin 10 μg and placebo alternatively during the study, the participant will be included in the relamorelin 10 μg group for purpose of safety analyses.

7.0 Participant Disposition

The number and percentage of participants screened will be tabulated by de novo participants and rollover participants from lead-in studies RLM-MD-01 and RLM-MD-02 for the Screened Population.

The number and percentage of participants who complete the study and of participants who prematurely discontinue will be presented by treatment group and overall for the ITT Population. All participants who prematurely discontinue will be listed by discontinuation reason.

The number and percentage with significant protocol deviations will be presented by treatment group and overall for the ITT Population.

8.0 Demographics and Other Baseline Characteristics

Demographic parameters (e.g., age, age group, race, ethnicity, sex, geographic region) will be summarized by treatment group and overall for the Safety Population.

Abnormalities in participants' medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities,* version 23.0 or newer. A data listing for medical and surgical histories will be presented.

Prior medication is defined as any medication started before the date of the first dose of double-blind study treatment. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of double-blind study treatment.

The *WHO Drug Dictionary*, Version B2 March 2017 or newer, will be used to classify prior and concomitant medications by WHO Drug Anatomical/Therapeutic/Chemical (ATC) category and drug preferred name. A data listing for prior and concomitant medications will be presented.

9.0 Extent of Exposure

A listing of the investigational product dosing records will be provided for ITT population.

10.0 Efficacy Analyses

The main efficacy assessment is the Diabetic Gastroparesis Symptom Severity Diary (DGSSD), a 7-item, patient-reported daily diary designed to assess the severity of 6 core signs and symptoms of DG—nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety—and the frequency of vomiting episodes. The severity of DG symptoms are assessed using a 0 to 10 numerical rating scale (NRS), on which 0 = "no" or "not at all uncomfortable" (ie, absence of the DG symptom) and 10 = "worst possible" or "most uncomfortable" (ie, worst experience of the DG symptom).

The Diabetic Gastroparesis Symptom Severity Score (DGSSS) is an overall assessment of the severity of non-vomiting symptoms. It is the sum of the four individual DGSSD items of nausea, abdominal pain, postprandial fullness and bloating. The score ranges from 0 to 40.

Participants report their symptoms daily from Visit 1/Baseline to Visit 4/Week 12, and for each of the 4 weeks preceding Visits 5/Week 24, Visit 6/Week 36, and Visit 7/Week 52 in the DGSSD.

Baseline values for DGSSD based parameters are derived from the DGSSD assessment collected during the Run-in Period as the average of the two weekly values of Week -2 and Week -1.

There are two key efficacy endpoints as follows:

Key Endpoints	Description	Timing
CFB to Week 12 in weekly DGSSS	Change from baseline to Week 12 in weekly DGSSS	Week 12
CFB to Week 52 in weekly average DGSSS	Change from baseline in average of the weekly average DGSSS from Weeks 49 to 52	Week 49-Week 52

Since the study was early terminated, only descriptive analyses for the key efficacy endpoints will be performed.

11.0 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs), clinical laboratory, electrocardiogram, vital sign parameters.

11.1 Adverse Events

All AEs and serious AEs (SAEs) will be collected from the signing of the informed consent form (ICF) until 30 days after the final visit in the study (Visit 7) or Early Termination Visit at the time points specified in the SoA. For rollover participants, ongoing AEs from lead-in Studies RLM-MD-01 and RLM-MD-02, and new AEs that occur after the signing of the ICF for RLM-MD-04 are considered to be AEs in RLM-MD-04.

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities (MedDRA),* version 23.0 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of double-blind study intervention. However, an AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE. Per case report form instructions, a new AE record will be created with a new AE onset date for any AE that worsens. Therefore, TEAEs can simply be identified as those AEs with recorded onset date on or after the date of the first dose of double-blind study intervention and within 30 days of the last dose of double-blind study intervention.

An AE will be considered a treatment-emergent SAE (TESAE) if it is a TEAE that also is an SAE.

The number and percentage of participants with TEAEs, death, TESAE, treatment related TEAE, TEAEs leading to treatment discontinuation, and TEAEs leading to discontinuation from study will be presented by treatment group.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by descending percentage in Relamorelin group, by system organ class (SOC), preferred term, and severity. If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the greatest severity for the summarization by severity.

The number and percentage of participants reporting treatment-related TEAE, TESAEs, treatment related TESAE, and having TEAEs leading to discontinuation of the study in each treatment group will be summarized by system organ class and preferred term.

In addition, listings for participants who died, participants with AEs, participants with TESAEs, participants with TEAEs leading to discontinuation from study will be presented.

11.2 Clinical Laboratory Parameters

Clinical laboratory test values from all assessments (including those from unscheduled or repeat assessments) will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11.2–1.

The number and percentage of participants who have PCS post-baseline clinical laboratory values will be tabulated by treatment group for the Double-blind Treatment Period. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 post-baseline assessment for the Double-blind Treatment Period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS post-baseline value for the Double-blind Treatment Period.

Table 11.2–1. Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	***SI Unit***	***Lower Limit***	***Higher Limit***
CHEMISTRY			
Albumin	g/L	< 0.9 * LLN	> 1.1 * ULN
Alanine Aminotransferase (ALT)	U/L	—	≥ 3 * ULN
Alkaline Phosphatase	U/L	—	≥ 3 * ULN
Aspartate Aminotransferase (AST)	U/L	—	≥ 3 * ULN
Calcium	mmol/L	< 0.9 * LLN	> 1.1 * ULN
Chloride	mmol/L	< 0.9 * LLN	> 1.1 * ULN
Cholesterol	mmol/L	—	> 1.6 * ULN
Creatinine	µmol/L	—	> 1.3 * ULN
Potassium	mmol/L	< 0.9 * LLN	> 2.0 * ULN
Glucose, Fasting	mmol/L	< 0.9 * LLN	> 2.5 * ULN
Glycohemoglobin A1C	%		Increase of ≥ 0.5%
Glycohemoglobin A1C	%		Increase of ≥ 1%
Sodium	mmol/L	< 0.9 * LLN	> 1.1 * ULN
Total Bilirubin	µmol/L	—	> 1.5 * ULN
Total Protein	g/L	< 0.9 * LLN	> 1.1 * ULN
Triglycerides, Fasting	mmol/L	—	≥ 3 * ULN
Urea (BUN)	mmol/L	—	> 1.2 * ULN
Magnesium	mmol/L	< 0.9 * LLN	> 1.1 * ULN
Bicarbonate	mmol/L	< 0.9 * LLN	> 1.1 * ULN
Phosphate	mmol/L	< 0.9 * LLN	> 1.1 * ULN
Uric Acid	µmol/L	< 0.9 * LLN	> 1.1 * ULN
HEMATOLOGY			
Basophils Absolute Cell Count	10^9/L	—	> 3 * ULN
Eosinophils Absolute Cell Count	10^9/L	—	> 3 * ULN
Hematocrit	Ratio	< 0.9 * LLN	> 1.1 * ULN
Hemoglobin	g/L	< 0.9 * LLN	> 1.1 * ULN
Lymphocytes Absolute Cell Count	10^9/L	< 0.8 * LLN	> 1.5 * ULN
MCH	PG	—	> 3 * ULN
MCHC	G/L	—	> 3 * ULN
MCV	fL	< 0.9 * LLN	> 1.1 * ULN
Monocytes Absolute Cell Count	10^9/L	—	> 3 * ULN
Neutrophils Absolute Cell Count	10^9/L	< 0.8 * LLN	> 1.5 * ULN
Platelet Count	10^9/L	< 0.5 * LLN	> 1.5 * ULN

Table 11.2–1. Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	***SI Unit***	***Lower Limit***	***Higher Limit***
Red Blood Cell Count (Erythrocyte Count)	10^{12}/L	< 0.9 * LLN	> 1.1 * ULN
White Blood Cell Count	10^{9}/L	< 0.7 * LLN	> 1.5 * ULN
URINALYSIS			
pH		< 0.9 * LLN	> 1.1 * ULN
Specific Gravity		—	> 1.1 * ULN

LLN: Lower limit of normal value provided by the laboratory.
ULN: Upper limit of normal value provided by the laboratory.

11.3 Vital Signs

A listing for vital signs (heart rate (HR), respiratory rate, systolic and diastolic blood pressure (BP), temperature, and body weight) at each visit will be presented.

11.4 Electrocardiogram

A listing for electrocardiographic(ECG) parameters (HR, RR interval, PR interval, QRS interval, QT interval, and QTc) at each assessment time point will be presented. The QTc will be calculated using Fridericia and/or Bazett correction.

11.5 COVID-19

A listing of participants with visits impacted due to COVID-19 for the ITT population will be provided.

12.0 Interim Analysis

There is no interim analysis planned for this study.

13.0 Determination of Sample Size

The study is early terminated; and the original study primary objectives are no longer applicable. The original study design of this protocol is for those participants who screen failed either of the two pivotal registration studies (ie, Studies RLM-MD-01 and RLM-MD-02). The original study design was to achieve 600 participants from these screen failures (assuming approximately 2800 participants will be screened for the two pivotal studies together) who will be randomized in a 2:1 ratio (for Relamorelin vs Placebo) to this study. For the originally designed two primary endpoints (original protocol dated October 6, 2017, amendments #1 and #2 dated December 20, 2017 and March 29, 2018, respectively), 600 randomized participants would provide at least 90% power for both the 4-symptom composite DGSSS responder endpoint (assuming a placebo rate of 14% and a treatment rate of 35%) and the vomiting responder endpoint (assuming a placebo rate of 11% and a treatment rate of 26%). For the redesigned key efficacy endpoint, change from baseline in 4-symptom DGSSS composite score at Week 12 (Protocol amendment #3 dated April 29, 2019), the planned sample size of 600 participants would provide more than 90% power in detecting a clinical meaningful difference, assuming Relamorelin provides additional 3.8 points of improvement as compared to Placebo.

14.0 Statistical Software

Statistical analyses will be performed using version 9.4 (or newer) of SAS on a Linux operating system.

15.0 Data Handling Conventions

15.1 Analysis Weeks for Efficacy Analysis

Table below presents the analysis weeks assigned for the efficacy analysis of the participant daily diary data related to DGSSD.

Table 15.1.1–1 Analysis Week Windows for Efficacy Analysis

Period	***Analysis Week***	***Begins[a]***	***Ends[a]***
Pretreatment (Baseline[b])	Week -2	Day -14	Day -8
	Week -1	Day -7	Day -1
Treatment	Week 1	Day 1, day of randomization	Day 7
	Week 2	Day 8	Day 14
	Week 3	Day 15	Day 21
	Week 4	Day 22	Day 28
	Week 5	Day 29	Day 35
	Week 6	Day 36	Day 42
	Week 7	Day 43	Day 49
	Week 8	Day 50	Day 56
	Week 9	Day 57	Day 63
	Week 10	Day 64	Day 70
	Week 11	Day 71	Day 77
	Week 12	Day 78	Day 84
	Week 21	Day 141	Day 147
	Week 22	Day 148	Day 154
	Week 23	Day 155	Day 161
	Week 24	Day 162	Day 168
	Week 33	Day 225	Day 231
	Week 34	Day 232	Day 238
	Week 35	Day 239	Day 245
	Week 36	Day 246	Day 252
	Week 49	Day 337	Day 343
	Week 50	Day 344	Day 350
	Week 51	Day 351	Day 357
	Week 52	Day 358	Day 364

a Relative to the date of randomization; Day 1 = the day of randomization.

b Baseline values for efficacy parameters will be derived as average of the two pretreatment weeks.

For the Double-blind Treatment Period, diary day is calculated as (diary date - date of randomization + 1). For the Pretreatment Period, diary day is calculated as (diary date - date of randomization).

15.2 Derived Efficacy Parameters

15.2.1 Weekly DGSSS

Weekly scores for nausea, abdominal pain, postprandial fullness, bloating, and vomiting severity will be the average of the corresponding nonmissing daily scores if a participant has at least 4 nonmissing daily scores during a week (See section 15.1115.1 for definition of analysis weeks). Weekly score will be set to missing if there are less than 4 days with nonmissing diary data during a week.

Weekly DGSSS is derived as the sum of the weekly DGSSD items of nausea, abdominal pain, postprandial fullness, and bloating. The range of DGSSS is from 0 to 40 with 40 indicating the worst possible. If any one of weekly items of nausea, abdominal pain, postprandial fullness, and bloating is missing, then the weekly DGSSS will be set to missing.

If any of the weekly values during the Run-in Period (Week -2 and/or Week -1) is missing, baseline for the DGSSD items (nausea, abdominal pain, postprandial fullness, bloating, and vomiting severity) will be the average of the scores reported during the seven days -consecutive or not- preceding Day 1.

The Week 52 weekly average DGSSS is the average of the weekly DGSSS from Weeks 49 to 52.

15.3 Visit Time Windows for Safety Analysis

No analysis visit window is needed for safety parameters. The nominal visit or eCRF visit will be used for listings.

15.4 Repeated or Unscheduled Assessments of Safety Parameters

If a participant has repeated assessments before the start of double-blind treatment with investigational product, the results from the final assessment made before the date of the first dose will be used as baseline.

However, all post-baseline assessments will be used for PCS value determination, and all assessments will be presented in the data listings.

15.5 Missing Date of the Last Dose of Study Treatment

When the date of the last dose of the double-blind investigational product is missing, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts have been made, the last diary date will be used as the last dose date.

15.6 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of double-blind investigational product, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of double-blind investigational product, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.7 Missing Date Information for Adverse Events

The following imputation rules apply to cases in which the start date is incomplete (ie, partial missing) for AEs.

Missing day and month

- If the year is the same as the year of the date of the first dose of double-blind investigational product, then the day and month of the date of the first dose of double-blind investigational product will be assigned to the missing fields.

- If the year is prior to the year of the date of the first dose of double-blind investigational product, then December 31 will be assigned to the missing fields.

- If the year is after the year of the date of the first dose of double-blind investigational product, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year are the same as the month and year of the date of the first dose of double-blind investigational product, then the date of the first dose of double-blind investigational product will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of double-blind investigational product or if both years are the same but the month is before the month of the date of the first dose of double-blind investigational product, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of double-blind investigational product or if both years are the same but the month is after the month of the date of the first dose of double-blind investigational product, then the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, then the following algorithm is used to impute the start date:

- If the stop date is on or after the date of the first dose of double-blind investigational product, the date of the first dose of double-blind investigational product will be assigned to the missing start date.

- If the stop date is before the date of the first dose of double-blind investigational product, the stop date will be assigned to the missing start date.

16.0 Changes to Analyses Specified in Protocol

The study was early terminated and only an abbreviated study report will be applied to this study, for which only minimum efficacy analyses will be implemented. As such, this document is an abbreviated statistical analysis plan for only selected study disposition, demographics, safety parameters and selected descriptive efficacy analyses.

17.0 References

There are no references.

Electronic Signatures

User	Date	Justification
[redacted]	16-Dec-2020 01:23:35 (GMT)	Document Originator Approval
[redacted]	15-Dec-2020 20:23:50 (GMT)	Manager Approval
[redacted]	15-Dec-2020 20:29:15 (GMT)	Subject Matter Expert Approval
[redacted]	15-Dec-2020 21:16:33 (GMT)	Subject Matter Expert Approval
[redacted]	15-Dec-2020 21:51:48 (GMT)	Subject Matter Expert Approval