NCT03420781

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

Statistical Analysis Plan Amendment 1 Date: 09Dec2020

1 Title Page

RLM-MD-03

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

STATISTICAL ANALYSIS PLAN - Abbreviated Clinical Study Report

Final: 1 October, 2020
Amendment #1: 9 December, 2020

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2.1 List of Tables

2.2 List of Figures

3 List of Abbreviations

AE	adverse event
DG	diabetic gastroparesis
DGSSD	Diabetic Gastroparesis Symptom Severity Diary
DGSSS	Diabetic Gastroparesis Symptom Severity Score
DGSSS-SR	DGSSS Study Responder
GEBT	Gastric emptying breath test
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
eDiary	electronic diary
ITT	intent to treat
mITT	modified intent to treat
[redacted]	
PCS	potentially clinically significant
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
RW	randomized withdrawal
SAE	serious adverse event
SAP	statistical analysis plan
SI	*Le Système International d'Unités* (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

4 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/or specified in the final protocol of Study RLM-MD-03 (version dated 12 Dec 2017) and the most recent amendment (version dated 4 Mar 2019).

However, the study was early terminated 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 1 October 2020. The major change to the SAP is to add descriptive analyses for the primary and secondary 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

Approximately 960 participants will enter this study at 700 study sites (globally), based on the assumption that 80% of participants who complete the lead-in pivotal registration studies RLM-MD-01 or RLM-MD-02 will elect to continue receiving the double-blind study treatment. Approximately 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 randomized withdrawal period (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.

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 BID 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 their [redacted] compliance, and use of rescue medication. After Visit 4/Week 12, 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/Week 24 through Visit 7/Week 40 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 treatment or switch to placebo BID treatment. Participants who received placebo during the Treatment Period will be allocated to receive relamorelin 10 µg BID. 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.

Study schematic and schedule of evaluations for Study RLM-MD-03 are presented in Figure 4.1–1 and Table 4.1–1 respectively.

Figure 4.1–1. RLM-MD-03 Study Schematic

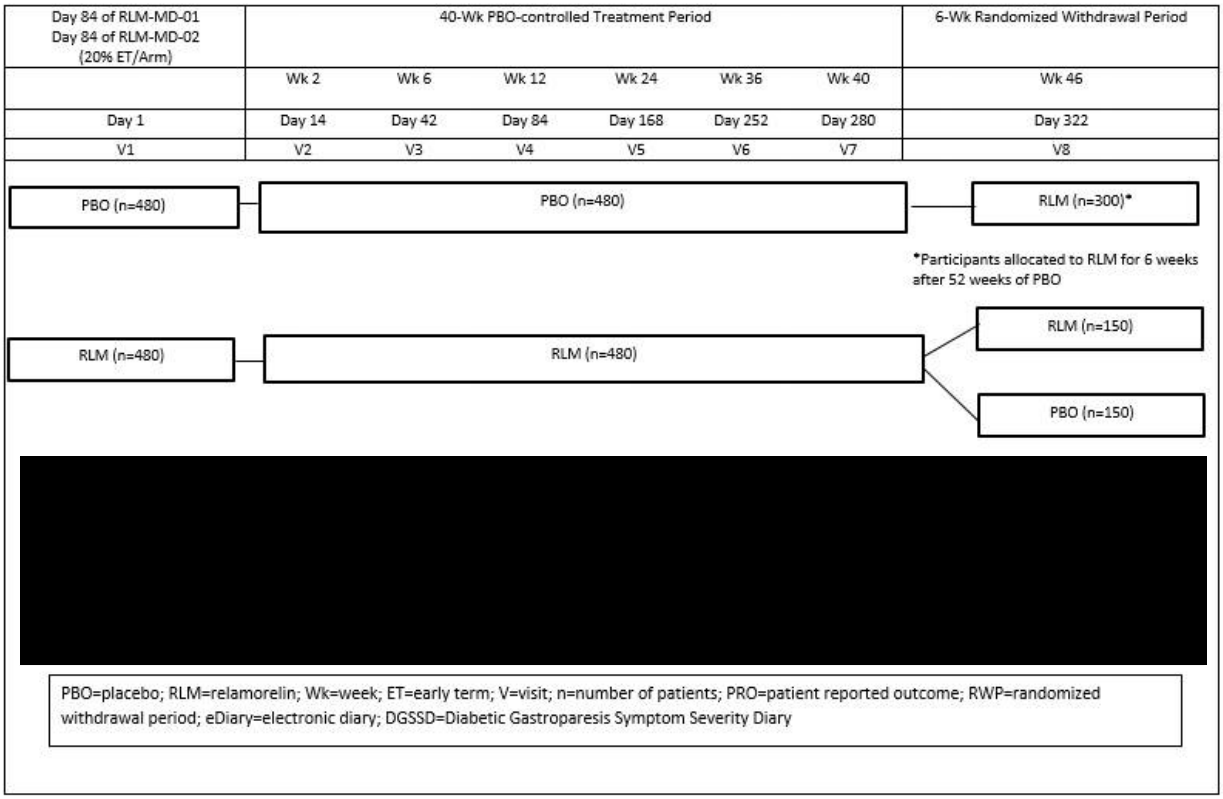
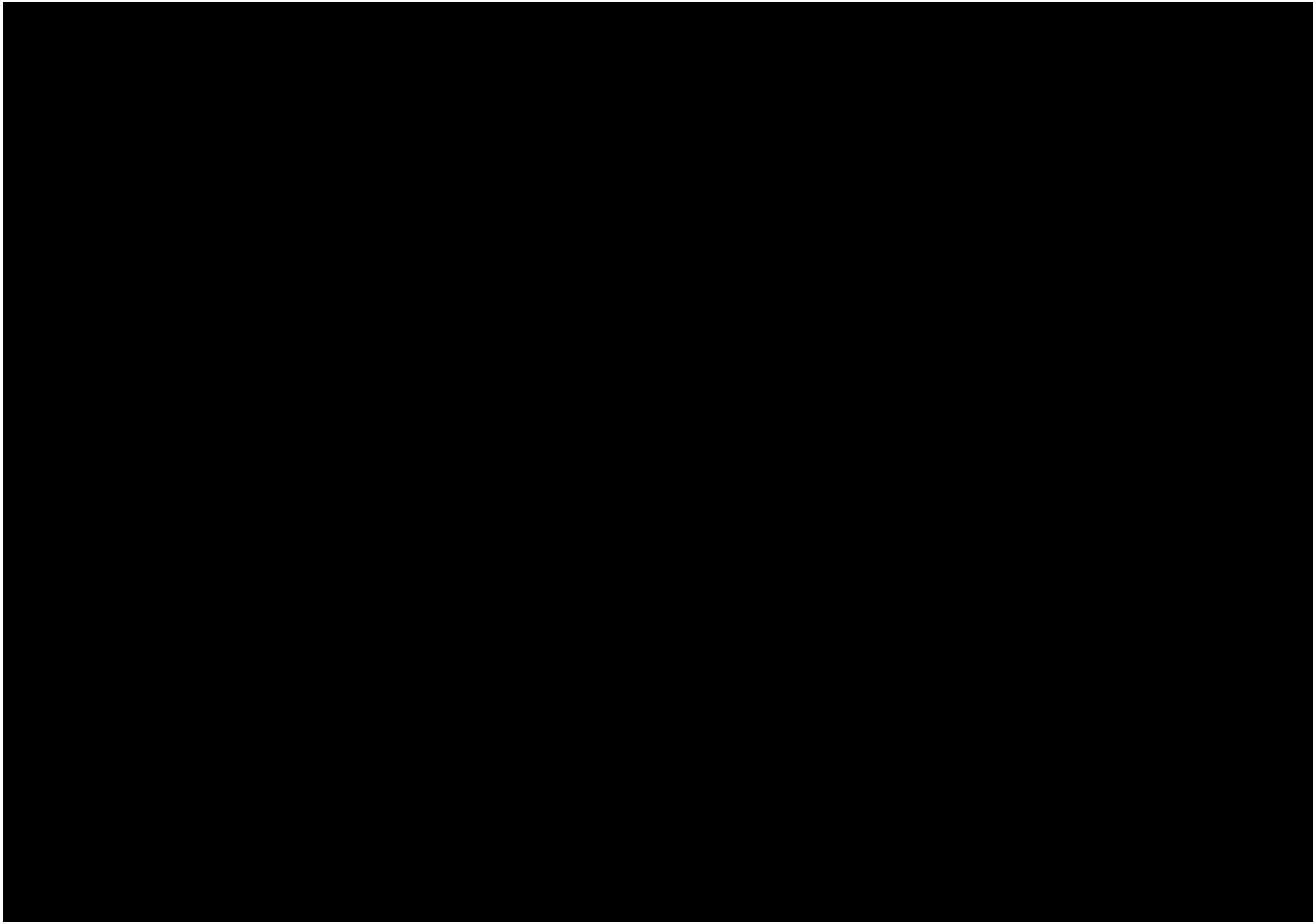


Table 4.1–1. Schedule of Activities: Study RLM-MD-03



5 Objectives

The primary objectives are:

- 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 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
    - Bloating
    - Postprandial fullness
- 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 RLM-MD-02 and 12 weeks from the current study) in participants with DG with respect to vomiting frequency

The secondary objectives are:

- 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 RLM-MD-02 and 12 weeks from the current study) in participants with DG with respect to the following individual symptoms of the Diabetic Gastroparesis Symptom Severity Score (DGSSS):
    - Nausea
    - Abdominal Pain
    - Bloating
    - Postprandial fullness
- 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 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
    - Bloating
    - Postprandial fullness

- 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 RLM-MD-02 and 40 weeks from the current study) in participants with DG with respect to vomiting frequency

- 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

6 Populations for Analyses

6.1 Screened Population

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

6.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all participants who enter the 40-week Treatment Period (ie, participants who are dispensed study treatment at Visit 1 of this study).

6.3 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) Population will consist of all participants in the ITT population who have ≥ 1 postbaseline assessment of DGSSD.

6.4 Safety Population

The Safety Population will consist of all participants in the ITT population who received ≥ 1 administration of study treatment.

The Safety Population will be used for all safety analyses. Participants will be analyzed according to the treatments they are planned during the study.

6.5 Randomized Withdrawal Population

The Randomized Withdrawal (RW) Population will consist of all participants who are re-randomized or assigned to a treatment of the RW Period and receive ≥ 1 administration of study treatment during the RW Period. For the RW Period, there are 3 treatment sequences as follows:

1. Placebo - 10 μg (Placebo BID in the Treatment Period, followed by Relamorelin 10 μg BID in the RW Period)

2. 10 μg - 10 μg (Relamorelin 10 μg BID in the Treatment Period, followed by Relamorelin 10 μg BID in the RW Period)

3. 10 μg - Placebo (Relamorelin 10 μg BID in the Treatment Period, followed by placebo BID in the RW Period)

For the analyses based on RW Population, participants will be analyzed according to the treatments they are planned in the lead-in studies RLM-MD-01 and RLM-MD-02 and the RW period.

7 Participant Disposition

Screen failures (ie, participants who signed informed consent form, but did not enter the 40-week Treatment Period (ie, participants who were not dispensed study treatment at Visit 1 of this study)) and the associated reasons will be tabulated by treatment group and pooled across treatment group for the Screened Population. The number and percentage of participants who complete the double-blind Treatment Period and of participants who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the ITT Population. The reasons for premature discontinuation from the double-blind Treatment Period as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group and pooled across treatment groups. All participants who prematurely discontinue during the double-blind Treatment Period will be listed by discontinuation reason.

Similar to the double-blind Treatment Period, the number and percentage of patients who are re-randomized into the RW Period, complete the RW Period, and prematurely discontinue from the RW Period will be presented overall and by treatment sequence for the RW Population. Reason for premature discontinuation from the RW Period as recorded on the trial completion forms of the eCRFs will be summarized (number and percentage) by treatment sequence.

The number and percentage with significant protocol deviations in the double-blind Treatment Period and in RW Period will be presented by treatment group and overall and by treatment sequence for the ITT Population and the RW Population, respectively.

8 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, age group, race, ethnicity, sex, geographic region), using the demographic and baseline data from lead-in studies RLM-MD-01 and RLM-MD-02, will be summarized in total and by treatment group for the Safety Population and RW Population.

Abnormalities in participants' medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities,* version 23.1 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 from the lead-in studies RLM-MD-01 and RLM-MD-02. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of double-blind study treatment in this study.

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 Extent of Exposure

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

10 Efficacy Analyses

The efficacy analyses for the double-blind Treatment Period will be based on the mITT Population. For the RW Period, the efficacy analyses will be based on the RW Population. Since the study was early terminated, only descriptive analyses for the primary and secondary efficacy endpoints will be performed.

Most efficacy parameters will be derived from the DGSSD, a 7-item, patient-reported daily diary designed to assess the severity of 6 core signs and symptoms of DG—nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety—and the frequency of vomiting episodes. For purposes of the analyses, weekly values will be calculated from the daily e-diary data. For weeks with less than 4 days of available DGSSD data, weekly values will be set to missing. The Day 1 for the efficacy endpoints in the double-blind treatment period of this study is the Day 84 of lead-in studies RLM-MD-01/02. Day 1 for the efficacy endpoints in the RW period is the re-randomization date.

For all analyses, the baseline is the baseline value from the lead-in study RLM-MD-01 or RLM-MD-02, derived from the DGSSD, will be the average of the two weekly values from the two-week Run-in period of the lead-in studies.

10.1 Primary Efficacy Endpoints

- **Change from Baseline to Week 12 in Weekly DGSSS:** Baseline is the baseline value from the lead-in study RLM-MD-01 or RLM-MD-02 and Week 12 is the 12th week of the 40-week Treatment Period (Days 78 to 84).

- **Vomiting Week-12 Responder**: Vomiting Week-12 Responder is defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the first 12 weeks of the 40-week Treatment Period.

A participant will be considered as Vomiting Week 12 non-Responder if the weekly number of vomiting episodes is missing from the diary for any of the last 6 weeks of the first 12 weeks of the 40-week Treatment Period.

10.2 Secondary Efficacy Endpoints

- Nausea Week 12 responder: Nausea responder defined as a participant who has a $\geq$ 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

- Abdominal pain Week 12 responder: Abdominal pain responder defined as a participant who has a $\geq$ 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

- Bloating Week 12 responder: Bloating responder defined as a participant who has a $\geq$ 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

- 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

- Change from Baseline to Week 40 in Average Weekly DGSSS: Average weekly scores are derived as the average of the weekly scores from Week 37 to Week 40

- Change from Baseline to Week 46 in Average Weekly DGSSS: Average weekly scores are derived as the average of the weekly scores from the six weeks of the Randomized Withdraw Period

- Change from Baseline to Week 40 in Vomiting Frequency: Average weekly number of vomiting episodes are derived as the average of the weekly number of vomiting episodes from Week 37 to Week 40

- Change from Baseline to Week 46 in Vomiting Frequency: Average weekly number of vomiting episodes are derived as the average of the weekly number of vomiting episodes from the six weeks of the Randomized Withdraw Period

- 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 37 to Week 40)

11 Safety Analyses

The safety analysis for the double-blind Treatment Period will be performed using the Safety Population. For the RW Period, the safety analysis will be performed using the RW Population. The safety parameters will include adverse events (AEs), clinical laboratory, electrocardiogram, and vital sign parameters.

The Day 1 for the safety analyses in the double-blind treatment period is the date of the first double-blind study treatment in this study. Day 1 for the safety analyses in the RW period is the re-randomization date.

11.1 Adverse Events

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) for the study if it was present after the first dose of study intervention or was present before the date of the first dose of study intervention and increased in severity or became serious after the first dose of study treatment during the study. 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 study intervention and within 30 days of the last dose of study intervention in the study. An AE that occurs more than 30 day after the last dose of study drug in the study will not be counted as a TEAE for the study.

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

All TEAEs related summary will be presented by treatment group for the Treatment Period and by treatment sequence for the RW Period separately. A TEAE will only be counted in the double-blind treatment period if it starts between the date of the first dose of study treatment (inclusive) in the double-blind treatment period and the date of the first dose of study treatment (exclusive) in the RW period or within 30 days of the date of the last dose of study treatment in the double-blind treatment period if the patient did not enter the RW period. A TEAE will only be counted in the RW period if it starts on or after the first dose of study treatment in the RW period and within 30 days of the date of the last dose of study treatment in the RW period.

The number and percent of participants with TEAEs, TEAEs leading to discontinuation from study, Deaths, SAEs and TESAEs will be presented by treatment group for the Treatment Period, and by treatment sequence for the RW Period separately.

The number and percentage of participants reporting TEAEs in each treatment group for the Treatment Period, by treatment sequence for the RW Period, will be tabulated by system organ class (SOC) and preferred term and further categorized by the investigator's assignment of 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. Additionally, the number and percentage of participants reporting treatment related TEAEs and treatment related TESAEs in each treatment group for the Treatment Period, by treatment sequence for the RW Period, will be tabulated by system organ class (SOC) and preferred term.

In addition, separate tabular displays for participants who died, participants with SAEs, 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 postbaseline clinical laboratory values will be tabulated by treatment group for the Treatment Period and by treatment sequence for the RW Period. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for periods. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value by treatment group for the Treatment Period and by treatment sequence for the RW 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 Interim Analysis

No interim analysis is planned for this study.

13 Determination of Sample Size

The study is early terminated; and the original study primary objectives are no longer applicable. The original study design considers the enrollment of this study depending 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.

14 Statistical Software

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

15 Data Handling Conventions

15.1 Analysis Weeks and Visit Time Windows for Efficacy Analysis

15.1.1 Analysis Weeks for Efficacy Analysis

Table 15.1.1–1 below presents the analysis weeks assigned for the efficacy analysis of the participant daily diary data related to DGSSD. These analysis weeks will be used in the calculations for all week-based endpoints (eg, weekly DGSSS, weekly vomiting frequency, individual symptoms weekly scores etc.).

Table 15.1.1–1. Analysis Time Windows for Efficacy Analysis

Period	***Analysis Week***	***Begins***	***Ends***
Treatment Period	Week 1	Day 1, Day 84 of lead-in studies RLM-MD-01/02	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 k	Day (k-1)x7 + 1	Day k x 7
		.....	
	Week 40	Day 274	Day 280 (or Day of last dose)
RW	Week 1	RW Day 1, the day of re-randomization	RW Day 7
	Week 2	RW Day 8	RW Day 14
	Week 3	RW Day 15	RW Day 21
	Week 4	RW Day 22	RW Day 28
	Week 5	RW Day 29	RW Day 35
	Week 6	RW Day 36	RW Day 42 (or Day of last RW dose)

For the RW Period, diary day is calculated as (diary date - date of re-randomization + 1). For the Treatment Period, diary day is calculated as (diary date – the date of Day 1 in Treatment Period + 1).

15.2 Derived Efficacy Variables

Weekly scores for nausea, abdominal pain, postprandial fullness, bloating, vomiting severity and early satiety will be the average of the corresponding non-missing daily scores if a participant has at least 4 non-missing daily scores during each week (See section 15.1 for definition of analysis weeks). Weekly score will be set to missing if there are less than 4 days with non-missing 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.

Weekly assessment for vomiting frequency is calculated as the total number of vomiting episodes during a week (normalized for the number of days with non-missing responses). i.e.:

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

The weekly number of vomiting episodes is set to missing if there are less than 4 days with non-missing diary data during the week.

15.3 Repeated or Unscheduled Assessments of Safety Parameters

All postbaseline assessments will be used for PCS value determination, and all assessments will be presented in the data listings.

15.4 Missing Date of the Last Dose of Study Treatment

When the date of the last dose of study drug is missing in specific period, 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 in the specific period will be used as the last dose date.

15.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of study drug 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 study drug, 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.

15.6 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 study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.

- If the year is prior to the year of the date of the first dose of study drug, 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 study drug, 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 study drug, then the date of the first dose of study drug will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, 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 study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, 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 after the date of the first dose of study drug, the date of the first dose of study drug will be assigned to the missing start date.

- If the stop date is before the date of the first dose of study drug, the stop date will be assigned to the missing start date.

16 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 References

There are no references.

Electronic Signatures

User	Date	Justification
[redacted]	10-Dec-2020 21:38:50 (GMT)	Manager Approval
[redacted]	10-Dec-2020 17:11:43 (GMT)	Subject Matter Expert Approval
[redacted]	10-Dec-2020 22:20:03 (GMT)	Document Originator Approval
[redacted]	10-Dec-2020 17:45:16 (GMT)	Subject Matter Expert Approval
[redacted]	09-Dec-2020 20:55:43 (GMT)	Subject Matter Expert Approval