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Study ID: 3071-305-020

Title: Open-label Extension Study of Relamorelin for the Treatment of Diabetic Gastroparesis

Statistical Analysis Plan Date: 30Sept2020

1.0 TITLE PAGE

3071-305-020

Open-label Extension Study of Relamorelin for the Treatment of Diabetic Gastroparesis

STATISTICAL ANALYSIS PLAN - Synoptic Clinical Study Report

Final: 30 September 2020

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event special interest
BID	twice daily
BP	blood pressure
CRF	case report form
DG	diabetic gastroparesis
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
ET	early termination
ICF	informed consent form
LLN	lower limits of normal
MedDRA	Medical Dictionary for Regulatory Activities
OL	open-label
PCS	potentially clinically significant
[redacted]	
PT	preferred term
Q1, Q3	25 percentile, 75 percentile
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 ($QTcF = QT/(RR)^{1/3}$)
QT interval	Time between Q wave and T wave in heart's electrical cycle
RLM	relamorelin

SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SC	subcutaneous
SD	standard deviation
SI	*Le Système International d'Unités* (International System of Units)
SoA	schedule of activities
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limits of normal
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the safety data as outlined and/or specified in the final protocol of Study 3071-305-020 (version dated 17 Oct. 2018) and the most recent amendment 2 (Amendment 2 dated 17 Dec. 2019). Specifications of tables, figures, and data listings are contained in a separate document.

However, due to the early termination of the Relamorelin clinical development program by the sponsor for business reasons on 04 September 2020, all Relamorelin Phase 3 Studies including this open-label extension study 3071-305-020 will be early terminated. Only synoptic clinical study report (sCSR) for Study 3071-305-020 will be developed. To align with the regulatory requirements for sCSR, only selected key safety analyses will be specified in this SAP.

4.1 STUDY DESIGN

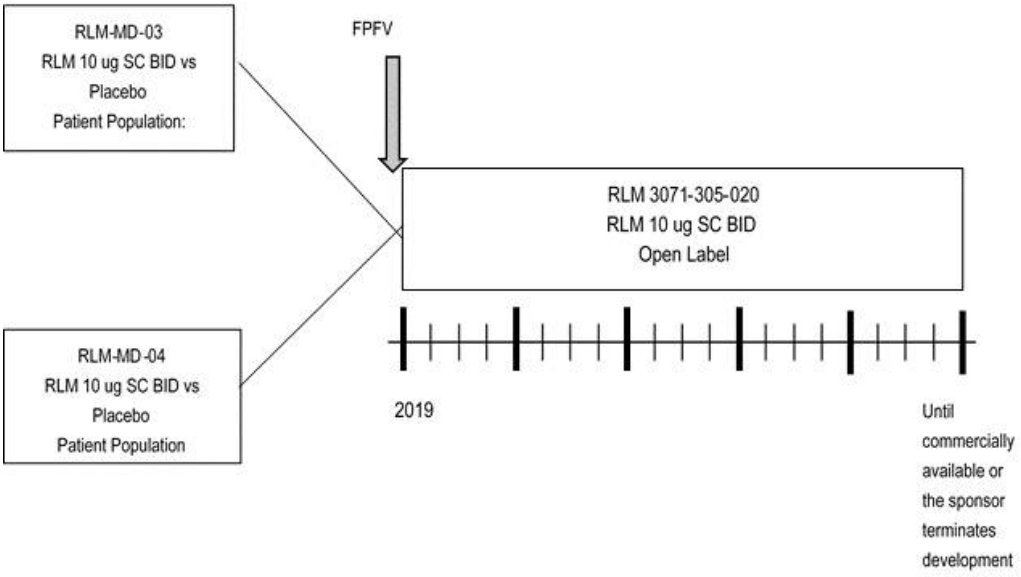
Study 3071-305-020 is an open-label, multicenter, multinational safety study in participants with diabetic gastroparesis (DG) who completed the Phase 3 studies, RLM-MD-03 or RLM-MD-04 and have no ongoing AEs from either lead-in study that, in the investigator's opinion, would preclude participation.

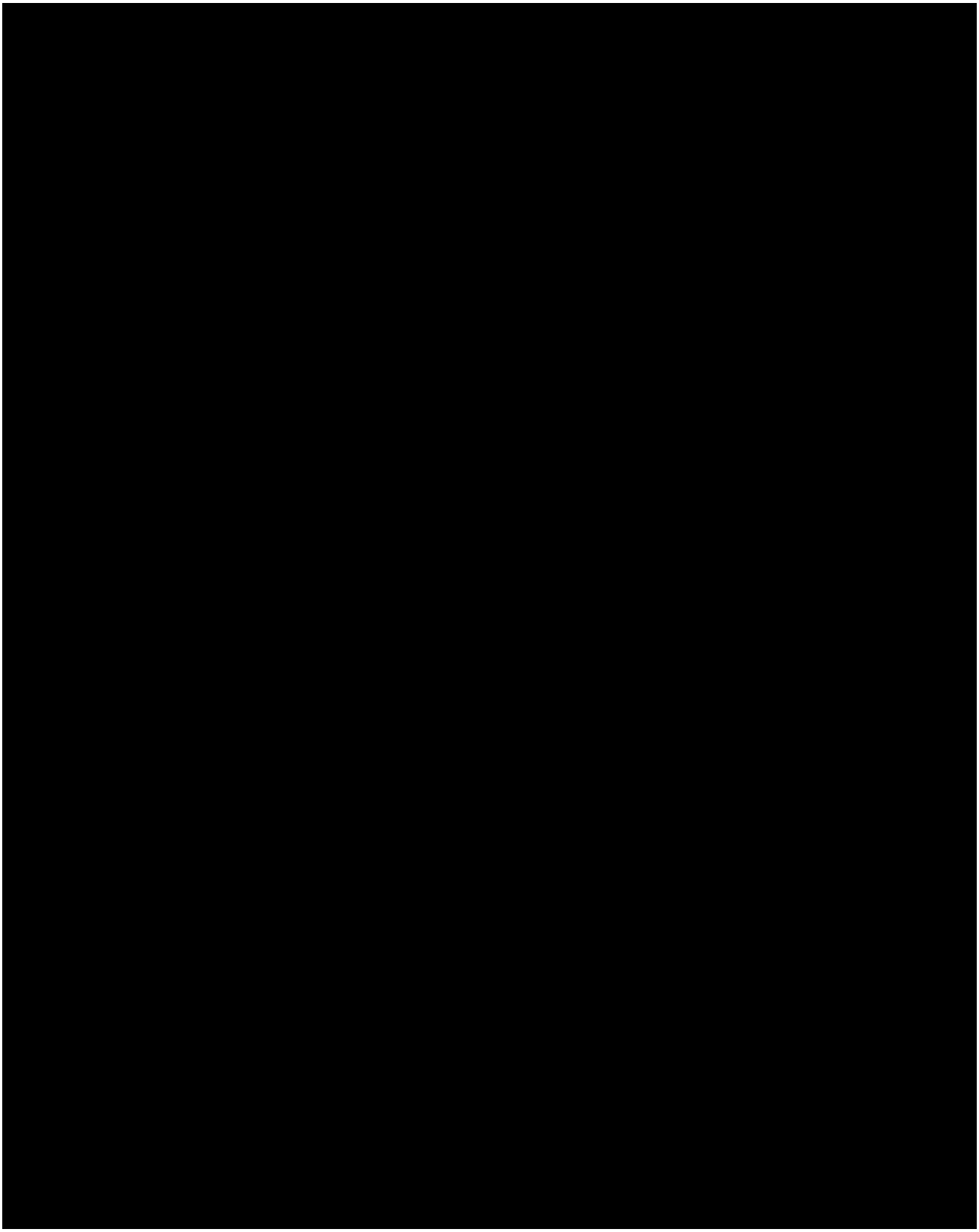
Participants may roll over from Studies RLM-MD-03 or RLM-MD-04 at approximately 700 sites. Written informed consent is to be obtained from each participant prior to enrollment into the study. Eligible adult participants will receive relamorelin (RLM) 10 µg subcutaneous (SC) twice daily (BID). Participants are to self-administer RLM and rotate injection sites in the abdomen.

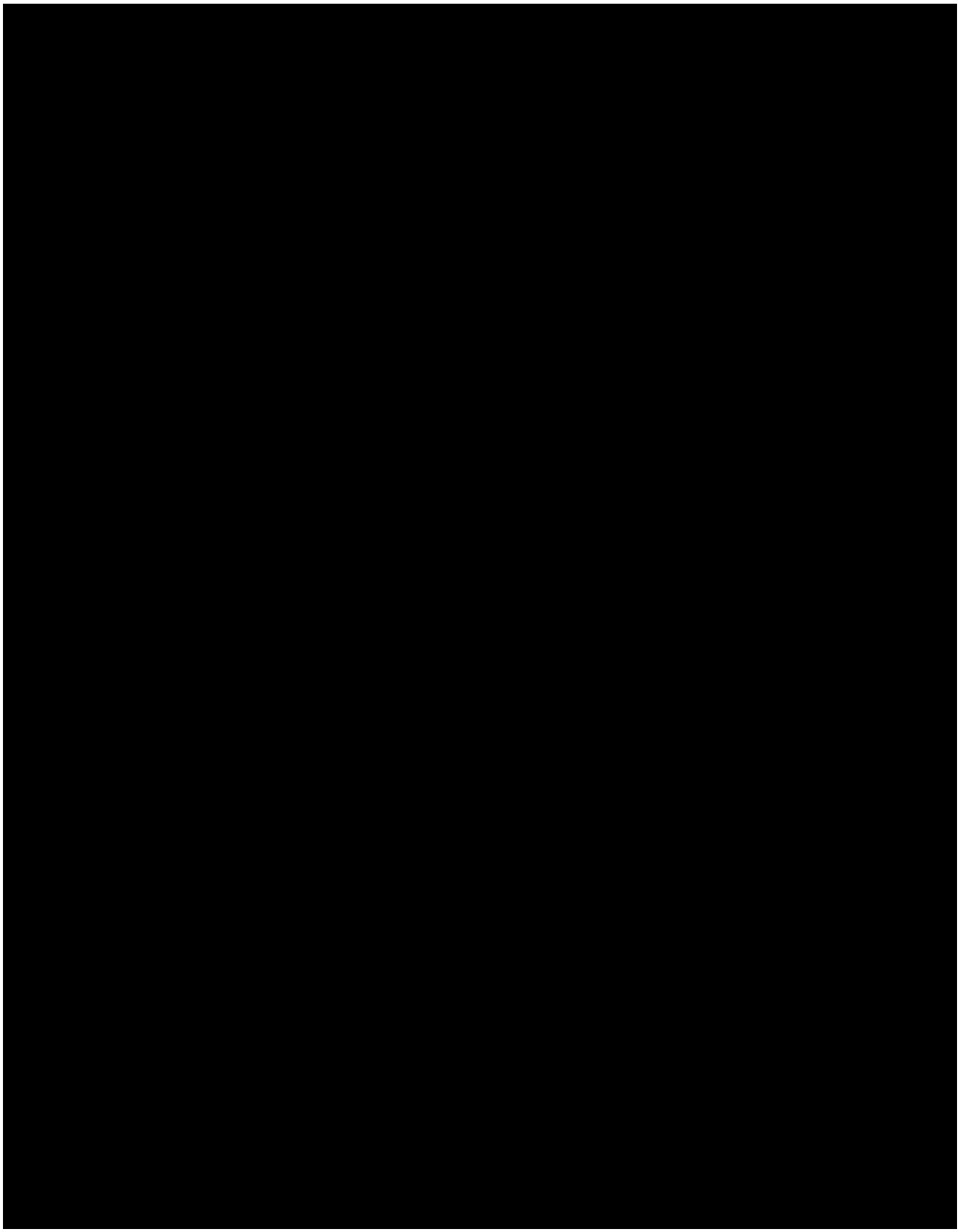
Participants who discontinued Studies RLM-MD-03 or RLM-MD-04 for any reason are not to be enrolled into this study. Participants who roll over to this continued-access study within 30 days (ie, ≤ 30) of completing their final visit assessments in either Study RLM-MD-03 or Study RLM-MD-04 do not need to complete baseline assessments; information from the final visit of Studies RLM-MD-03 or RLM-MD-04 will be used as the information for Visit 1 of this study. If a participant enters this continued-access study > 30 days after last visit in either lead-in study, visit 1 baseline assessments will be completed as shown in schedule of activities (SoA). A participant is considered to have completed the study if he/she has completed a final visit assessment.

Study schema and schedule of activities are presented in Figure 4-1 and Table 4–1 respectively.

Figure 4-1 Schema







5.0 OBJECTIVES

The primary objective of this study is to assess the safety of continued treatment with RLM for participants who previously completed the RLM-MD-03 or RLM-MD-04 study.

No efficacy endpoints were specified for this study. Safety assessments include adverse events (AEs), clinical laboratory values, vital signs and electrocardiograms (ECGs).

6.0 PARTICPANT FOR ANALYSES

For this open-label safety extension study, the analysis populations will consist of participants as defined in Table 6–1.

Table 6–1 Analysis population

Population	Definition
Enrolled	All participants who sign informed consent (IC).
Safety	All participants who received ≥ 1 administration of study intervention. The Safety population will be used for all safety analyses.

If the lead-in study is RLM-MD-03, the treatment sequences in this open-label study will be presented as RLM/RLM/RLM for participants who received Relamorelin in 40-week placebo-controlled treatment period and Relamorelin in 6-week randomized withdraw period in the lead-in study, RLM/Placebo/RLM for participants who received Relamorelin in 40-week placebo-controlled treatment period and Placebo in 6-week randomized withdraw period in the lead-in study, Placebo/RLM/RLM for participants who received Placebo in 40-week placebo-controlled treatment period and Relamorelin in 6-week randomized withdraw period in the lead-in study.

If the lead-in study is RLM-MD-04, the treatment sequences in this open-label study will be presented as RLM/RLM for participants who received Relamorelin in double-blind treatment period in the lead-in study, Placebo/RLM for participants who received Placebo in double-blind treatment period in the lead-in study.

All the summary statistics in this analysis plan will be described by the treatment sequences and overall, unless stated otherwise.

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants will be presented for enrolled population. .

The number and percentage of participants who complete the open-label study (ie, the participant has completed a final visit) and of participants who prematurely discontinue during the open-label treatment period will be presented for the Safety Population. The reasons for premature discontinuation from the study as recorded on the termination pages of the electronic case report forms (eCRF) will be summarized (number and percentage) for the Safety Population. All participants who prematurely discontinue during the study will be listed by discontinuation reason for the Safety Population.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demography will be rolled over from Studies RLM-MD-03 or RLM-MD-04.

Demographic parameters (age; race; ethnicity; sex) will be summarized descriptively for the Safety populations. Continuous variables will be summarized by number of participants and mean, standard deviation (SD), Q1, Q3, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants. For all participants in 3071-305-020, demographics from the lead-in studies (Study RLM-MD-03 or Study RLM-MD-04) will be used.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Due to early termination of the study and sCSR requirement, this section is not applicable.

10.0 EFFICACY ANALYSES

No efficacy assessments are planned for this open-label safety extension study.

11.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include AEs, vital signs, clinical laboratory tests, and ECG values.

The safety baseline in lead-in studies RLM-MD-03 and RLM-MD-04 will be used as the baseline for all analyses of that safety parameter. Categorical variables will be summarized by number and percentage of participants.

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 22.0 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 double-blinded dose of the lead-in study treatment. However, an AE that occurs more than 30 days after the last dose of study treatment in this study 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 study treatment and within 30 days of the last dose of study treatment. Only TEAEs that started on or after the date of first dose of open-label study treatment will be summarized.

An AE will be considered a treatment-emergent SAE (TESAE) if it is a TEAE that also an SAE. The number and percent of participants with TEAEs, TEAEs leading to study intervention discontinuation, Deaths, and TESAEs will be presented.

The number and percentage of participants reporting TEAEs will be tabulated 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 in the Safety Population who have TEAEs leading to premature discontinuation of the study treatment will be summarized by SOC/ preferred term.

The number and percentage of participants who have TESAE will be summarized by SOC/preferred term.

Listing of all AE, death, TESAEs, and TEAEs leading to study intervention discontinuation by participant will be presented.

AEs of Special Interest

Study site personnel must record and report every participant who meets the criteria for potential Hy's law as SAEs. Potential Hy's law cases are considered AESIs.

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3x ULN, along with total bilirubin (TBL) ≥ 2x ULN and alkaline phosphatase (ALP) < 2x ULN, all based on blood draws collected within a 24 hour period.

Potential Hy's Law criteria without time window (e-DISH) is defined by maximum of post baseline elevation of ALT or AST ≥ 3x ULN, along with maximum of post baseline elevation of TBL ≥ 2x ULN and alkaline phosphatase (ALP) < 2x ULN.

Listing of all participants who meet the potential Hy's law criteria will be presented.

11.2 CLINICAL LABORATORY PARAMETERS

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11-1. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated for the open-label treatment 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 the treatment period. [redacted]

Table 11-1 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
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

Table 11-1 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	***SI Unit***	***Lower Limit***	***Higher Limit***
Platelet Count	10^9/L	< 0.5 * LLN	> 1.5 * ULN
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 correction.

12.0 HEALTH OUTCOMES ANALYSES

Not Applicable.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this open-label safety extension study.

14.0 DETERMINATION OF SAMPLE SIZE

There was no sample size calculation performed for this open-label safety extension study.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS.

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

No analysis window is defined for this study. The eCRF visit will be used.

16.2 DERIVED VARIABLES

Not applicable.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a participant in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

16.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

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

16.6 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

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

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, 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, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

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

16.8 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 16–1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16–1 Examples for Coding of Special Character Values for Clinical Laboratory Parameters

Laboratory Test (Unit)	***Possible Lab Results (in SI units)***	***Coded Value for Analysis***
Chemistry: ALT	< 5	0
Chemistry: AST	< 5	0
Chemistry: Bilirubin, Total	< 2	0
Urinalysis: Glucose	= OR > 55, >= 55, > 0	Positive
	<= 0, Negative	Negative
Urinalysis: Ketones	= OR > 8.0, >=8.0, > 0	Positive
	<= 0, Negative	Negative
Urinalysis: pH	> 8.0, >= 8.0	8.0
	>= 8.5,	8.5
Urinalysis: Protein	= OR > 3.0, >=3.0, > 0	Positive
	<= 0	Negative

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None.

18.0 REFERENCES

Study RLM-MD-01 and Study RLM-MD-02 SAP: A 12-week, randomized, double-blind, placebo-controlled, phase 3 study to evaluate the safety and efficacy of relamorelin in patients with diabetic gastroparesis. Madison, NJ: Allergan, Inc; 2018 Dec 06.

Study RLM-MD-03 SAP: 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. Madison, NJ: Allergan, Inc; 2020 September 28.

Study RLM-MD-04 SAP: A 52-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis. Madison, NJ: Allergan, Inc; 2020 September 28.

Electronic Signatures

User	Date	Justification
[redacted]	07-Oct-2020 19:59:20 (GMT)	Document Originator Approval
[redacted]	07-Oct-2020 20:04:17 (GMT)	Manager Approval
[redacted]	08-Oct-2020 19:41:35 (GMT)	Subject Matter Expert Approval
[redacted]	09-Oct-2020 13:00:06 (GMT)	Subject Matter Expert Approval
[redacted]	07-Oct-2020 20:02:38 (GMT)	Subject Matter Expert Approval