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

Summary

EudraCT number	2017-002144-33
Trial protocol	GB HU FR BE BG DK AT LV ES IT
Global end of trial date	05 November 2020

Results information

Result version number	v1 (current)
This version publication date	20 October 2021
First version publication date	20 October 2021

Trial information

Trial identification

Sponsor protocol code	RLM-MD-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03383146
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Therapeutic Area, Head, Allergan, 001 714-246-4500, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area, Head, Allergan, 001 714-246-4500, IR-CTRegistration@Allergan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to compare the efficacy of relamorelin with that of placebo in participants with diabetic gastroparesis (DG) with respect to the core signs and symptoms of diabetic gastroparesis.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Argentina: 19
Country: Number of subjects enrolled	Brazil: 16
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Philippines: 1
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Ukraine: 14
Country: Number of subjects enrolled	United States: 331
Worldwide total number of subjects	450
EEA total number of subjects	13

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	316
From 65 to 84 years	133
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who completed the placebo run-in of relamorelin studies: RLM-MD-01 [NCT03285308] and RLM-MD-02 [NCT03426345] were eligible to rollover to this study. De novo (New) participants, who had not participated in the previous studies, were also eligible for enrollment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.

Arm type	Placebo
Investigational medicinal product name	Placebo-matching relamorelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo injected subcutaneously twice daily.

Arm title	Relamorelin 10 µg

Arm description:

Relamorelin 10 micrograms (µg) injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.

Arm type	Experimental
Investigational medicinal product name	Relamorelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Relamorelin 10 micrograms (µg) injected subcutaneously twice daily.

Number of subjects in period 1	Placebo	Relamorelin 10 µg
Started	148	302
Safety Population	145	299
Run-in Period	91	207
Completed	63	118
Not completed	85	184
Physician decision	-	1
Screen Failure	1	-
Adverse Event	6	18
Protocol Deviation	1	8
Death	-	2
Withdrawal by Subject	20	36
Study Terminated by the Sponsor	48	95
Lost to follow-up	5	15
Reason not Specified	4	6
Lack of efficacy	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.	
Reporting group title	Relamorelin 10 µg
Reporting group description:	
Relamorelin 10 micrograms (µg) injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.	

Reporting group values	Placebo	Relamorelin 10 µg	Total
Number of subjects	148	302	450
Age categorical Units: Subjects			
Adults (<65 years)	107	209	316
From >= 65 years	41	93	134
Age Continuous Units: years			
arithmetic mean	57.0	57.9	
standard deviation	± 12.37	± 11.57	-
Sex: Female, Male Units: participants			
Female	102	224	326
Male	46	78	124
Race Units: Subjects			
American Indian or Alaska Native	7	11	18
Asian	0	9	9
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	27	53	80
White	109	218	327
More than one race	4	11	15
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	50	82	132
Not Hispanic or Latino	98	220	318
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.

Reporting group title	Relamorelin 10 µg

Reporting group description:

Relamorelin 10 micrograms (µg) injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.

Primary: Change from Baseline to Week 12 in the Weekly Diabetic Gastroparesis Symptom Severity Score (DGSSS)

End point title	Change from Baseline to Week 12 in the Weekly Diabetic Gastroparesis Symptom Severity Score (DGSSS)[1]

End point description:

Participants assessed the severity of diabetic gastroparesis symptoms daily using the Diabetic Gastroparesis Symptom Severity Diary (DGSSD), recorded in an electronic diary (e-diary). The DGSSS was derived as the sum of the weekly averages of the 4 DGSSD items: nausea, abdominal pain, postprandial fullness and bloating. Each symptom was scored using an 11-point ordinal scale where: 0=no or not at all uncomfortable to 10=worst possible or most uncomfortable for a total possible DGSSS of 0 (best) to 40 (worst). A negative change from Baseline indicates improvement. Baseline was defined as the average of the 2 weekly DGSSS from the run-in period of the previous study or the run-in period of this study for new participants. Modified-intent-to-treat (mITT) Population included all randomised participants with ≥1 postbaseline assessment of DGSSD. 'n' indicates number analysed is the number of participants with data available at the given time-point.

End point type	Primary

End point timeframe:

Baseline (14-day Run-in Period of the previous relamorelin study RLM-MD-01 or RLM-MD-02 for rollover participants or Day -14 to Day -1 for new participants) to Week 12 of this study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	295		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=147, 295)	20.3 (± 6.70)	19.7 (± 6.39)		
Change from Baseline to Week 12 (n=133, 247)	-7.1 (± 8.82)	-6.5 (± 7.80)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline to Week 52 in the Weekly Average DGSSS

End point title	Change from Baseline to Week 52 in the Weekly Average DGSSS[2]

End point description:

Participants assessed the severity of diabetic gastroparesis symptoms daily using the DGSSD, recorded in an electronic diary (e-diary). The DGSSS was derived as the sum of the weekly averages of the 4 DGSSD items: nausea, abdominal pain, postprandial fullness and bloating. Each symptom was scored using an 11-point ordinal scale where: 0=no or not at all uncomfortable to 10=worst possible or most uncomfortable for a total possible DGSSS of 0 (best) to 40 (worst). The average weekly scores at Week 52 were the average of the DGSSS scores from Week 49 to Week 52. A negative change from Baseline indicates improvement. Baseline was defined as the average of the 2 weekly DGSSS from the run-in period of the previous study or the run-in period of this study for new participants. mITT Population included all randomised participants with ≥1 postbaseline assessment of DGSSD. 'n' indicates number analysed is the number of participants with data available at the given time-point.

End point type	Primary

End point timeframe:

Baseline (14-day Run-in Period of the previous relamorelin study RLM-MD-01 or RLM-MD-02 for rollover participants or Day -14 to Day -1 for new participants) to Week 52 of this study

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	295		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=147, 295)	20.3 (± 6.70)	19.7 (± 6.39)		
Change from Baseline to Week 52 (n=65, 129)	-10.7 (± 8.93)	-8.6 (± 8.92)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Experienced One or More Treatment-Emergent Adverse Events (TEAE)

End point title	Number of Participants who Experienced One or More Treatment-Emergent Adverse Events (TEAE)[3]

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. 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. A TEAE is an AE that begins or worsens after receiving study drug. Safety Population included all participants who received ≥1 administration of study treatment.

End point type	Primary

End point timeframe:

First dose of study drug to within 30 days of the last dose of study drug (Up to approximately 56 weeks)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	299		
Units: participants	105	221		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Potential Clinically Significant (PCS) Clinical Laboratory Results

End point title	Number of Participants with Potential Clinically Significant (PCS) Clinical Laboratory Results[4]

End point description:

Clinical Laboratory tests included Hematology, Chemistry and Urinalysis tests. The investigator determined if the results were clinically significant. Only those categories where at least 1 participant had a non-PCS value at Baseline and met the PCS criterion at least once during postbaseline are reported. Safety Population included all participants who received ≥1 administration of study treatment. 'n' indicates number analysed is the number of participants with non-PCS Baseline values and at least one post-baseline assessment. Upper limit of normal value (ULN), lower limit of normal value (LLN), gram (g), liter(L), femtoliter (fL), millimoles(mmol/L), micromoles(µmol/L), absolute cell count (ACC), red blood cell (RBC), white blood cell (WBC), alanine aminotransferase (ALT), serum glutamate-pyruvate transaminase (SGPT), aspartate aminotransferase, serum glutamic-oxaloacetic transaminase (SGOT) unit (U), fasting (F), glycohemoglobin A1C (HbA1c).

End point type	Primary

End point timeframe:

Up to 52 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	299		
Units: participants				
Hematocrit (RATIO): >1.1×ULN (n=139, 289)	0	1		
Hematocrit (RATIO): <0.9×LLN (n=139, 289)	5	14		
Hemoglobin (g)/L): <0.9×LLN (n=137, 288)	10	20		
Lymphocytes ACC(10^9/(L): >1.5×ULN (n=141, 287)	1	5		
Lymphocytes ACC (10^9/L): <0.8×LLN (n=141, 287)	2	9		
Mean Corpuscular Volume (fL):>1.1×ULN (n=140, 284)	2	2		
Neutrophils ACC (10^9/L): >1.5×ULN (n=143, 288)	2	0		
Neutrophils ACC (10^9/L): <0.8×LLN (n= 143, 288)	7	3		
RBC (10^12/L):<0.9×LLN (n=141, 290)	2	10		
WBC (10^9/L): <0.7×LLN (n=144, 291)	2	0		

ALT (SGPT) (U)/L): ≥3.0×ULN (n=144, 291)	0	6		
Albumin (g/L): <0.9×LLN (n=143, 292)	0	1		
Alkaline Phosphatase (U/L): ≥3.0×ULN (n=144, 292)	0	1		
AST (SGOT) (U/L): ≥3.0×ULN (n=144, 291)	2	3		
Bicarbonate (HCO3) (mmol)/L):>1.1×ULN (n=138, 290)	3	2		
Bicarbonate (HCO3) (mmol)/L):>1.1×LLN (n=138, 290)	3	2		
Bicarbonate (HCO3) (mmol)/L):<0.9×LLN (n=138, 290)	6	6		
Bilirubin, Total (umol/L): >1.5×ULN (n=144, 292)	0	1		
Blood Urea Nitrogen (mmol/L):>1.2×ULN (n=125, 272)	14	27		
Calcium (mmol/L): >1.1×ULN (n=144, 292)	0	1		
Chloride (mmol/L): <0.9×LLN (n=144, 292)	1	1		
Cholesterol, Total, F(mmol/L):>1.6×ULN(n=142, 284)	2	5		
Creatinine (umol/L): >1.3×ULN (n=134, 275)	15	20		
Glucose-Chemistry, F(mmol/L):>2.5×ULN (n=132, 269)	22	52		
Glucose-Chemistry, F(mmol/L):<0.9×LLN (n=132, 269)	4	14		
HbA1C: Increase of ≥0.5% (n=144, 292)	95	247		
HbA1C: Increase of ≥1% (n=144, 292)	94	246		
Phosphorus (mmol/L): >1.1×ULN (n=142, 287)	13	5		
Phosphorus (mmol/L): <0.9×LLN (n=142, 287)	1	4		
Potassium (mmol/L): <0.9×LLN (n=144, 292)	1	0		
Protein, Total (g)/L): >1.1×ULN (n=143, 291)	1	0		
Triglycerides, F (mmol/L): ≥3.0×ULN (n=140, 280)	8	9		
Uric Acid (Urate) (umol/L): >1.1×ULN (n=114, 233)	17	37		
Uric Acid (Urate) (umol/L): <0.9×LLN (n=114, 233)	1	9		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Clinically Meaningful Trends for Vital Signs

End point title	Number of Participants with Clinically Meaningful Trends for Vital Signs[5]

End point description:

Vital Signs included assessments of heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. The investigator determined if the abnormal results were clinically significant.

Safety Population included all participants who received ≥1 administration of study treatment.

End point type	Primary

End point timeframe:

Up to 52 weeks

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	299		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Clinically Significant Abnormal Electrocardiogram (ECG) Results

End point title	Number of Participants with Clinically Significant Abnormal Electrocardiogram (ECG) Results[6]

End point description:

A standard 12-lead ECG was performed. The investigator determined if the abnormal results were clinically significant. Safety Population included all participants who received ≥1 administration of study treatment.

End point type	Primary

End point timeframe:

Up to 52 weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	299		
Units: participants	2	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with a ≥1% Increase in Glycosylated Hemoglobin A1c (HbA1c)

End point title	Number of Participants with a ≥1% Increase in Glycosylated Hemoglobin A1c (HbA1c)[7]

End point description:

HbA1c is also known as glycosylated hemoglobin. It is the concentration of glucose bound to hemoglobin as a percentage of the absolute maximum that can be bound. Safety Population included all participants who received ≥1 administration of study treatment.

End point type	Primary

End point timeframe:

Up to 52 weeks

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	299		
Units: participants	94	246		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Anti-relamorelin Antibody Testing Results by Visit

End point title	Number of Participants with Anti-relamorelin Antibody Testing Results by Visit[8][9]

End point description:

A blood sample was collected that was sent to a laboratory for an anti-relamorelin antibody screening test. A positive screening test was confirmed by an immunodepletion assay. The number of participants in each of the following categories are reported: Negative Screening Test, Positive Screening Test, Negative Confirmatory Test, and Positive Confirmatory Test at each time point. Safety Population included all participants who received ≥1 administration of double-blind study treatment (N=299 in the Relamorelin 10 µg arm). Anti-relamorelin antibody testing was only done for those participants who received treatment with relamorelin. 'n' indicates number analysed is the number of participants with data available at the given timepoint. Due to a laboratory issue not all positive screening tests were confirmed.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 84, Day 364, and End of Treatment (Up to Day 364)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses are reported for this endpoint.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all Baseline arms are applicable to this endpoint.

End point values	Relamorelin 10 µg			
Subject group type	Reporting group			
Number of subjects analysed	299			
Units: participants				
Screening Test (Baseline) Negative (n=166)	127			

Screening Test (Baseline) Positive (n=166)	39			
Confirmatory Test (Baseline) Negative (n=5)	5			
Confirmatory Test (Baseline) Positive (n=5)	0			
Screening Test (Day 84) Negative (n=96)	73			
Screening Test (Day 84) Positive (n=96)	23			
Confirmatory Test (Day 84) Negative (n=7)	6			
Confirmatory Test (Day 84) Positive (n=7)	1			
Screening Test (Day 364) Negative (n=14)	10			
Screening Test (Day 364) Positive (n=14)	4			
Confirmatory Test (Day 364) Negative (n=0)	0			
Confirmatory Test (Day 364) Positive (n=0)	0			
Screening Test (End of Treatment) Negative (n=26)	20			
Screening Test (End of Treatment) Positive (n=26)	6			
Confirmatory Test (EOT) Negative (n=1)	1			
Confirmatory Test (EOT) Positive (n=1)	0			
Screening Test (Unscheduled) Negative (n=3)	2			
Screening Test (Unscheduled) Positive (n=3)	1			
Confirmatory Test (Unscheduled) Negative (n=1)	1			
Confirmatory Test (Unscheduled) Positive (n=1)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to within 30 days of the last dose of study drug (Up to approximately 56 weeks)

Adverse event reporting additional description:

All-Cause Mortality included all randomised participants. Adverse Events: Safety Population included all participants who received ≥1 administration of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Relamorelin 10 µg

Reporting group description:

Relamorelin 10 µg injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.

Reporting group title	Placebo

Reporting group description:

Placebo injected subcutaneously twice daily for up to 52 weeks. De novo (New) participants, who did not participate in the previous relamorelin studies, began the study with a 2-week placebo run-in.

Serious adverse events	Relamorelin 10 µg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 299 (14.38%)	21 / 145 (14.48%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytoma			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical deconditioning			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 299 (1.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose decreased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 299 (1.00%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			

subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute left ventricular failure			
subjects affected / exposed	1 / 299 (0.33%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery occlusion			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			

subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 299 (0.33%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			

subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			

subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 299 (0.33%)	2 / 145 (1.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			

subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 299 (0.33%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 299 (0.67%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Relamorelin 10 µg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 299 (27.42%)	37 / 145 (25.52%)	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 299 (5.02%)	7 / 145 (4.83%)	
occurrences (all)	16	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 299 (7.02%)	14 / 145 (9.66%)	
occurrences (all)	24	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 299 (6.02%)	11 / 145 (7.59%)	
occurrences (all)	20	13	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	28 / 299 (9.36%)	9 / 145 (6.21%)	
occurrences (all)	29	9	
Metabolism and nutrition disorders			

Hyperglycaemia subjects affected / exposed occurrences (all)	15 / 299 (5.02%) 21	8 / 145 (5.52%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2017	The following changes were implemented with Amendment 1: -Added Screening and Run-in Periods to the protocol to allow participants to enter the study as de novo participants -Supplemented and revised the study schematic -Revised and supplemented the objectives and endpoints -Revised the number of participants and the description of the study population -Updated the Schedule of Activities (SoA) to add columns for Screening and Run-in, renumbered visits, and updated the footnotes -Deleted endpoint definitions -Revised the clinical hypotheses to present 2 new hypotheses in place of the original 4 hypotheses -Revised the number of participants -Updated the inclusion and exclusion criteria in to allow for participants who enrolled directly into RLM-MD-04; added 2 additional exclusion criteria -Updated the rational for the inclusion and exclusion criteria -Updated treatments administered -Updated treatment compliance -Updated concomitant therapy to alert the investigator that concomitant therapies should be held stable during the study, and to insert an exception to the prohibition for opioid use -Updated rescue medicine -Updated treatment after the end of the study -Updated temporary discontinuation -Updated study assessments and procedures -Updated primary efficacy assessments -Deleted secondary efficacy assessments -Added 2 new sections to include participants Global Impression of Status (PGIS-DG), and Patient Global Impression of Change (PGIC-DG).
20 December 2017	-Added treatment continuation -Revised time period and frequency for collecting adverse event (AE) and serious adverse event (SAE) information -Updated major adverse cardiovascular events -Updated treatment of overdose -Updated physical examination -Updated self-monitoring of blood glucose -added resource utilization assessment -Updated analysis populations -Updated statistical analyses -Updated efficacy analyses -Updated key endpoints -Updated missing data -Updated other screening tests -Updated tabular summary.
29 March 2018	The following changes were implemented with Amendment 2: -Updated SoA footnote (b) to indicate the early termination visit was performed as soon as possible after the decision has been made -Updated SoA (f) footnote to include evaluation of injection sites -Updated SoA footnote (j) to clarify the details of urine drug screen results -Updated SoA footnote (l) to indicate pregnancy testing can be performed if required by local regulations -Updated the SoA to add a new footnote (u) to inspect injection sites for clinically significant reactions -Revised inclusion criterion to remove the treatment requirement "for at least 3 months" for participants being treated with medications for diabetes mellitus type I (T1DM) or diabetes mellitus type II (T2DM) -Revised inclusion criterion to remove the upper limit for body mass index (BMI) -Revised exclusion criterion (History of intestinal malabsorption) for clarification that celiac disease even if well-controlled on gluten-free diet is exclusionary, and to add history of non-celiac gluten sensitivity as exclusionary -Revised exclusion criterion to remove functional dyspepsia -Deleted exclusion criterion which addresses anemia; in its place added exclusion criterion for gastric or duodenal ulcer within 3 months of screening -Revised exclusion criterion to reduce history of malignancy from 5 to 3 years -Revised exclusion criterion to shorten the exclusion period for promotility agents from 2 weeks to 10 days -Revised exclusion criterion which addresses positive drug screen results -Revised exclusion criterion to extend the exclusion for use of glucagon-like peptide-1 (GLP-1) agonists to 6 weeks, and remove pramlintide -Revised exclusion criterion to remove the allowance for gluten-free crackers -Added exclusion criterion for functional dyspepsia diagnosed before the diagnosis of diabetes mellitus.

29 March 2018	-Revised screen failures to disallow rescreening after greater than 6 months -Shortened the wash-out period for pro-motility agents, anticholinergics, anti-emetics, amylin analogue, and opioids from 2 weeks to 10 days; to extend the exclusion for use of GLP-1 agonists from 2 to 6 weeks prior to the start of the Run-in Period -Revised withdrawal from the study to indicate the early termination visit was performed as soon as possible after the decision to discontinue was made -Amended study assessments and procedures to increase the maximum amount of blood collected from 73.0 mL to 74.5 mL -Revised the time period for AE/SAE Collection to include "until 30 days after" the final visit -Amended the major adverse cardiovascular events (MACE) text for clarity and to describe the planned adjudication process -Amended physical examinations to add text about injection site inspection -Added anti-relamorelin antibodies test to other laboratory assessments -Revised the contraception guidance and added recommendations for acceptable birth control methods.
29 April 2019	The following changes were implemented with Amendment 3: -Replaced "Potential Hy's Law" with "Hy's Law" -Removed responder endpoints from list of key endpoints -Updated key objectives -Addition of other objectives and corresponding "Other Endpoints" -Schematic updated to show screening starting at Week -6 instead of Week -4 -Increased number of screening participants from 4000 to 5000 -Added requirements for "de novo" participants to have had a history of nausea and/or at most a single episode of vomiting in 2 weeks prior to screening added at screening Visit (Visit -2) -Deleted requirement for BMI -Increased number of sites from 400 to 700 -Deleted criterion for BMI > 18.5 kg/m2 -Beginning of Screening Period changed from Day -28 to Day -42; changed from "Up to 14 Days" to "Up to 28 Days" -Statement added to footnote (a) that results from assessments done at screening that might result in exclusion from the study are to be obtained prior to the endoscopy if done at the start of the Run-in Period -Added electrocardiogram (ECG) assessment at Visit 2 -Modified footnote (j) referencing to specify certain prescribed drugs (ie, barbiturates, benzodiazepines, amphetamines, but not opioids and cannabinoids) should not be exclusionary -Footnote "k" added for fasting glucose to be serum for all visits except Visits 4 and 6 (plasma) -Modified hypotheses -Changed requirement for delayed gastric emptying breath test (GEBT) from occurring at Screening to occurring during the Run-in Period -Modified inclusion criteria to add option to use upper GI series with contrast to document absence of obstructing lesion; revised time of performance from some time prior to Screening to some time prior to the Run-in Period -Section added for 2 new exclusion criteria applicable to both sets of participants including specific ECG results, allergy/hypersensitivity to study treatment.
29 April 2019	-Amended exclusion criteria to allow a participant with a positive urine drug screen at Screening to continue in the study while confirmatory testing is done on an aliquot of the original sample -Added reference to screen failures -Added exclusion criteria (hypersensitivity to study treatments and their excipients) and (ECG results obtained at baseline that would exclude a participant) -Added option for the sponsor to permit a participant with a positive urine drug screen at Screening to continue in the Screening Period while confirmatory urine drug screen testing by a more specific method is carried on an aliquot of the original sample -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 minutes before the evening meal -Deleted option for investigator to contact sponsor if the participant could not inject study treatment into abdomen -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 -Sodium-glucose co-transporter-1 (SLGT-1) added to same rules for sodium-glucose co-transporter-2 (SGLT-2), Addition of details to the requirement of prohibiting SGLT-1 and SGLT-2 inhibitors -Amended information regarding SGLT-2 inhibitors as noted above and by adding SLGT-1 to same drug class/treatment as SGLT-2, rearranged rows by washout period, added tramadol as an example of opioid.

29 April 2019	-Added washout requirements for de novo participants -pro-motility agents, anticholinergics, anti-emetics, amyline analogue, 5 hydroxy tryptamine 4 (5HT4) agonists, and glucagon-like peptide-1 -Updated description of antiemetics -Added row for 5HT4 agonists -Amended washout period for opioids from "10 days prior to the start of the Run-in Period" to Not applicable since use of opioids is not allowed and referenced exclusion criteria -Specified that the day prior to and day of clinic visits are "during the Treatment Period" -Deleted antihistamines as an example of an anti-emetic drug -Revised to require investigator to contact (i.e., "should contact) sponsor if participant requires anti-emetic more than 1 day/week or once weekly repeatedly instead of making it optional for investigator to contact (i.e., "should consider contacting) -Deleted "non-compliance with study treatment" as a criterion -Additional criteria added for when the investigator should contact the sponsor -Added statement detailing when participants would be reporting their symptoms in the DGSSD -Deleted description on vomiting frequency and how vomiting was calculated -Changed title from "Other Patient-reported Outcomes (PRO) Assessments – Exploratory Endpoints to "Additional Assessments'' -Added a subsection (i.e., Section 9.1.2.1) for description and calculation of vomiting frequency and renumbered all subsequent subsections accordingly -Specified that medical occurrences that begin before the start of study treatment but after obtaining informed consent was recorded in the AE section of the eCRF and was considered pretreatment AEs (instead of being recorded on the Medical History/Current Medical Conditions section of the eCRF) -Clarified reporting procedures for Hy's Law cases -Added the phrase "Inadequate Control of Diabetes" to section title -Specified 10 µg twice a day (BID) or 20 µg/day as the maximum recommended dose.
29 April 2019	-Deleted statement referencing a dose of greater than 150 µg BID to be considered an overdose -Specified that the mITT Population is a subset of all randomised participants -Replaced Responder analysis with Change from Baseline (CFB) mixed model for repeated measures (MMRM) methodology and description -Deleted CFB ANCOVA methodology and description -Updated to only include CFB to Week 12 in weekly DGSSS and CFB to Week 52 in weekly average DGSSS -Deleted original text in section Section 10.3.2.2 Missing Data and replaced with reference to statistical analysis plan (SAP) -Added statement that data analyses for additional endpoints was specified in the SAP -Deleted language that PRO and HEOR measures was presented separately from CSR -Replaced the "Non-applicable" statement with a description of a DSMB process that was used to review interim safety data -Footnote added for fasting blood glucose to be serum at all visits except for Visits 4 & 6 -Headings added for subsections -Statement added that written documentation was obtained in accordance with relevant country and local privacy requirements -Revised from requirement of investigator retaining records for 15 years after study completion to retaining "as stated in the clinical trial agreement" -Added statement that the results of the study may be published or presented at scientific meetings -Updated procedures for reporting adverse events of special interest (AESIs) -Identified specific AESIs -Specified that DG symptoms were captured in the DGSSS and not the CRF -Moved acceptable methods of contraception from text to table -Deleted footnote "b" regarding hormonal contraception's susceptible interactions with study intervention -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 -Removed criteria for noncompliance -Changed trial length from 52 to 54 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

05 November 2020	The study was prematurely terminated on 05 November 2020 as the sponsor decided not to develop the investigational product further. The study termination was not due to any safety concerns. As a result, only descriptive primary and secondary efficacy analyses and selected key safety analyses were conducted.	-

Notes:

Limitations and caveats

None reported