Clinical trial results:
A 12-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	2017-002177-20
Trial protocol	GB LV HU BE DK DE AT RO
Global end of trial date	16 July 2020

Results information

Result version number	v1 (current)
This version publication date	04 August 2021
First version publication date	04 August 2021

Trial information

Trial identification

Sponsor protocol code	RLM-MD-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03426345
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	16 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the safety and efficacy of relamorelin compared to placebo in participants with diabetic gastroparesis. Participants reported daily severity scores of their diabetic gastroparesis symptoms.

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	16 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Mexico: 29
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	United States: 223
Worldwide total number of subjects	311
EEA total number of subjects	11

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)	239
From 65 to 84 years	71
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 311 participants were randomized into one of the two treatment groups: Placebo or Relamorelin 10 µg, out of which 307 participants were included in the Safety Population to receive double-blind study treatment.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following a 2-week placebo run-in, participants received placebo-matching relamorelin injected subcutaneously twice daily for up to 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Relamorelin matching-placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Placebo injected subcutaneously twice daily.

Arm title	Relamorelin 10 µg

Arm description:

Following a 2-week placebo run-in, participants received relamorelin 10 micrograms (µg) injected subcutaneously twice daily for up to 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Relamorelin 10 µg IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Relamorelin 10 µg injected twice daily for 12 weeks.

Number of subjects in period 1	Placebo	Relamorelin 10 µg
Started	155	156
Safety Population	152	155
Completed	137	139
Not completed	18	17
Consent withdrawn by subject	5	6
Adverse event, non-fatal	4	4
Protocol Deviation	3	4
Reason Not Specified	1	2
Missing Completion Status	1	-
Lost to follow-up	3	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Following a 2-week placebo run-in, participants received placebo-matching relamorelin injected subcutaneously twice daily for up to 12 weeks.	
Reporting group title	Relamorelin 10 µg
Reporting group description:	
Following a 2-week placebo run-in, participants received relamorelin 10 micrograms (µg) injected subcutaneously twice daily for up to 12 weeks.	

Reporting group values	Placebo	Relamorelin 10 µg	Total
Number of subjects	155	156	311
Age categorical Units: Subjects			
Adults (18-64 years)	121	118	239
From 65-84 years	34	37	71
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	54.1	55.8	
standard deviation	± 12.13	± 12.07	-
Sex: Female, Male Units: participants			
Female	112	114	226
Male	43	42	85
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	7	11
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	25	17	42
White	123	127	250
More than one race	2	3	5
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic	54	51	105
Not Hispanic	101	105	206
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Following a 2-week placebo run-in, participants received placebo-matching relamorelin injected subcutaneously twice daily for up to 12 weeks.	
Reporting group title	Relamorelin 10 µg
Reporting group description:	
Following a 2-week placebo run-in, participants received relamorelin 10 micrograms (µg) injected subcutaneously twice daily for up to 12 weeks.	

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. Modified Intent-to-treat (mITT) Population included all randomised participants with ≥1 postbaseline assessment of DGSSD.	
End point type	Primary
End point timeframe:	
Baseline (Day-14 to Day-1) to Week 12	
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: Due to early termination of the trial, only a descriptive analyses for the primary and secondary efficacy endpoints were performed.	

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	23.4 (± 5.40)	24.9 (± 6.15)		
Change from Baseline to Week 12	-9.3 (± 10.21)	-10.2 (± 9.24)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Meeting the Vomiting Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point title	Percentage of Participants Meeting the Vomiting Responder

	Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period[2]

End point description:

The number of vomiting episodes in the previous 24 hours were assessed daily by the participant using the DGSSD and were recorded in the e-diary. A Vomiting Responder was defined as a participant with zero weekly vomiting episodes during each of the last 6 weeks of the 12-week Treatment Period. mITT Population included all randomised participants with ≥1 postbaseline assessment of DGSSD.

End point type	Primary

End point timeframe:

Week 6 to Week 12

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: Due to early termination of the trial, only a descriptive analyses for the primary and secondary efficacy endpoints were performed.

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: percentage of participants				
number (not applicable)	19.1	18.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Meeting the Nausea Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point title	Percentage of Participants Meeting the Nausea Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point description:

A Nausea Responder was defined as a participant with improvement (decrease) of at least 2-points in the weekly symptom scores for nausea at each of the last 6 weeks of the 12-week Treatment Period. Nausea was one of the items of the DGSSD assessed daily and recorded in the e-diary by the participant using an 11-point ordinal scale where: 0= no nausea to 10= worst possible nausea. mITT Population included all randomised participants with ≥1 postbaseline assessment of DGSSD.

End point type	Secondary

End point timeframe:

Baseline (Day-14 to Day-1) to (Week 6 to Week 12)

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: percentage of participants				
number (not applicable)	32.9	38.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Meeting the Abdominal Pain Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point title	Percentage of Participants Meeting the Abdominal Pain Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point description:

An Abdominal Pain Responder was defined as a participant with an improvement (decrease) of at least 2-points in the weekly symptom scores for abdominal pain at each of the last 6 weeks of the 12-week Treatment Period. Abdominal pain was one of the items of the DGSSD assessed daily and recorded in the e-diary by the participant using an 11-point ordinal scale where: 0= no abdominal pain to 10= the worst possible abdominal pain and was recorded in an e-diary. mITT Population included all randomised participants with ≥1 postbaseline assessment of DGSSD.

End point type	Secondary

End point timeframe:

Baseline (Day-14 to Day-1) to (Week 6 to Week 12)

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: percentage of participants				
number (not applicable)	27.0	36.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Meeting the Bloating Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point title	Percentage of Participants Meeting the Bloating Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point description:

A Bloating Responder was defined as a participant with an improvement (decrease) of at least 2-points in the weekly symptom scores for bloating at each of the last 6 weeks of the 12-week Treatment Period. Bloating was one of the items of the DGSSD assessed daily and recorded by the participant in the e-diary using an 11-point ordinal scale where: 0= no bloating and 10= the worst possible bloating and was recorded in the e-diary. mITT Population included all randomised participants with ≥1 postbaseline assessment of DGSSD.

End point type	Secondary

End point timeframe:

Baseline (Day-14 to Day-1) to (Week 6 to Week 12)

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: percentage of participants				
number (not applicable)	27.0	31.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Meeting the Postprandial Fullness Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point title	Percentage of Participants Meeting the Postprandial Fullness Responder Criterion During Each of the Last 6 Weeks of the 12-week Treatment Period

End point description:

A Postprandial Fullness Responder was defined as a participant with an improvement (decrease) of at least 2-points in the weekly symptom scores for Postprandial Fullness at each of the last 6 weeks of the 12-week Treatment Period. Postprandial Fullness was one of the items of the DGSSD assessed daily and recorded by the participant in the e-diary using an 11-point ordinal scale where: 0= no feeling of fullness until finishing a meal (best) to 10= feeling full after only a few bites (worst). mITT Population included all randomised participants with ≥1 postbaseline assessment of DGSSD.

End point type	Secondary

End point timeframe:

Baseline (Day-14 to Day-1) to (Week 6 to Week 12)

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: percentage of participants				
number (not applicable)	23.7	27.7		

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

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 double-blind study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 16 weeks

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: participants	75	86		

Statistical analyses

No statistical analyses for this end point

Secondary: 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

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 person 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 double-blind study treatment. n=number analysed is the number of participants with non-PCS Baseline values and at least one post-baseline assessment. Total cholesterol and glucose-chemistry values were analysed in fasting state.Absolute Cell Count=ACC, ULN=upper limit of normal value, LLN=lower limit of normal value, L=liter, fL=femtoliter, RBC=Red Blood Cell, AT=aminotransferase, SGPT=Serum Glutamic Pyruvic Transaminase, U=unit, SGOT=Serum Glutamic Oxaloacetic Transaminase, mmol=millimoles, µmol=micromoles.

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: participants				
Eosinophils ACC [10^9/L]: >3×ULN (n=144,152)	0	1		

Hematocrit (RATIO): >1.1×ULN (n=137,149)	1	0		
Hematocrit (RATIO): <0.9×LLN (n=137,149)	4	4		
Hemoglobin [grams (g)/L]: <0.9×LLN (n=134,148)	2	5		
Lymphocytes ACC (10^9/L): <0.8×LLN (n=141,148)	1	3		
Mean Corpuscular Volume (fL): >1.1×ULN (n=142,151)	1	1		
Neutrophils ACC (10^9/L): >1.5×ULN (n=142,148)	0	1		
Neutrophils ACC (10^9/L): <0.8×LLN (n=142,148)	2	2		
RBC Count (10^12/L): <0.9×LLN (n=139,150)	1	1		
Alanine AT [SGPT] (U/L): >=3×ULN (n=146,151)	1	0		
Albumin (g/L): <0.9×LLN (n=145,152)	0	1		
Alkaline Phosphatase (U/L): >=3×ULN (n=146,152)	1	0		
Aspartate AT [SGOT] (U/L): >=3×ULN (n=146,152)	1	2		
Bicarbonate (HCO3) (mmol/L): >1.1×ULN (n=142,145)	0	1		
Bicarbonate (HCO3) (mmol/L): <0.9×LLN (n=142,145)	1	0		
Blood Urea Nitrogen (mmol/L): >1.2×ULN (n=130,133)	15	3		
Chloride (mmol/L): <0.9×LLN (n=146,152)	2	0		
Cholesterol, Total (mmol/L): >1.6×ULN (n=139,148)	2	1		
Creatinine (µmol/L): >1.3×ULN (n=132,142)	8	7		
Glucose-Chemistry (mmol/L): >2.5×ULN (n=124,132)	11	21		
Glucose-Chemistry (mmol/L): <0.9×LLN (n=124,132)	6	5		
Glycohemoglobin A1C:Increase of >=0.5% (n=146,151)	80	111		
Glycohemoglobin A1C:Increase of >=1% (n=146,151)	80	111		
Phosphorus (mmol/L): >1.1×ULN (n=142,147)	5	5		
Phosphorus (mmol/L): <0.9×LLN (n=142,147)	1	1		
Potassium (mmol/L): <0.9×LLN (n=146,152)	1	0		
Sodium (mmol/L): <0.9×LLN (n=146,152)	1	0		
Triglycerides,Fasting(mmol/L): >=3×ULN (n=137,144)	3	5		
Uric Acid (Urate) (µmol/L): >1.1×ULN (n=125,121)	18	13		
Uric Acid (Urate) (µmol/L): <0.9×LLN (n=125,121)	3	0		

Statistical analyses

No statistical analyses for this end point

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

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

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 double-blind study treatment.

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

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

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

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 double-blind study treatment.

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: participants	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

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 double-blind study treatment. n=number analysed is the number of participants with non-PCS Baseline values and at least one post-baseline assessment.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to 12 weeks

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	151		
Units: participants	80	111		

Statistical analyses

No statistical analyses for this end point

Secondary: 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[3]

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=155 in the Relamorelin 10 µg arm). Anti-relamorelin antibody testing was only done for those participants who received treatment with relamorelin. n=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	Secondary

End point timeframe:

Baseline (Day 1), Day 14, Day 28, Day 84, and End of Treatment (Up to Day 84)

Notes:

[3] - 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: Due to early termination of the trial, only a descriptive analyses for the primary and secondary efficacy endpoints were performed.

End point values	Relamorelin 10 µg			
Subject group type	Reporting group			
Number of subjects analysed	155			
Units: participants				
Negative Screening Test (Baseline) (n=145)	127			
Positive Screening Test (Baseline) (n=145)	18			
Negative Confirmatory Test (Baseline) (n=12)	12			
Positive Confirmatory Test (Baseline) (n=12)	0			
Negative Screening Test (Day 14) (n=133)	115			
Positive Screening Test (Day 14) (n=133)	18			
Negative Confirmatory Test (Day 14) (n=13)	13			
Positive Confirmatory Test (Day 14) (n=13)	0			
Negative Screening Test (Day 28) (n=121)	104			
Positive Screening Test (Day 28) (n=121)	17			
Negative Confirmatory Test (Day 28) (n=12)	12			
Positive Confirmatory Test (Day 28) (n=12)	0			
Negative Screening Test (Day 84) (n=104)	87			
Positive Screening Test (Day 84) (n=104)	17			
Negative Confirmatory Test (Day 84) (n=12)	11			
Positive Confirmatory Test (Day 84) (n=12)	1			
Negative Screening Test (End of Treatment) (n=7)	6			
Positive Screening Test (End of Treatment) (n=7)	1			
Negative Confirmatory Test(End of Treatment) (n=1)	1			
Positive Confirmatory Test(End of Treatment) (n=1)	0			
Negative Screening Test (Unscheduled) (n=6)	6			
Positive Screening Test (Unscheduled) (n=6)	0			
Negative Confirmatory Test (Unscheduled) (n=0)	0			
Positive Confirmatory Test (Unscheduled) (n=0)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 16 weeks

Adverse event reporting additional description:

All-Cause Mortality is reported for all randomised participants. The Safety Population, all participants who received ≥1 administration of double-blind study treatment, was used to determine the number of participants at risk for Serious Adverse Events and Other Adverse Events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Following a 2-week placebo run-in, participants received placebo-matching relamorelin injected subcutaneously twice daily for up to 12 weeks.

Reporting group title	Relamorelin 10 µg

Reporting group description:

Following a 2-week placebo run-in, participants received relamorelin 10 µg injected subcutaneously twice daily for up to 12 weeks.

Serious adverse events	Placebo	Relamorelin 10 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 152 (3.95%)	8 / 155 (5.16%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 152 (0.66%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage	Additional description: Number at risk is based on the female population.		
subjects affected / exposed[1]	0 / 109 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (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			
Muscular weakness			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 152 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper respiratory tract infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 152 (0.66%)	1 / 155 (0.65%)	
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	1 / 152 (0.66%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 152 (0.66%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number of subjects exposed for this adverse event is based on the female population.

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

Non-serious adverse events	Placebo	Relamorelin 10 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 152 (9.21%)	13 / 155 (8.39%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 152 (5.92%)	5 / 155 (3.23%)	
occurrences (all)	9	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 152 (3.29%)	9 / 155 (5.81%)	
occurrences (all)	5	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2018	The following changes were implemented with Amendment 1: Removed glycated albumin from the safety endpoints in Section 1 Synopsis, in Section 4 Objectives and Endpoints, and in the Safety Analyses in Section 10.3.3; Increased the number of sites and participants screened in Sections 1, 5.2 and 12.9; Moved no use of promotility agents and anti-emetics to after Run-in Period in Sections 1 and 5.1; Updated the Schedule of Activities (SOA) to add a new footnote (o) to pharmacokinetic (PK) samples at early termination (ET), to add fasting fingerstick glucose testing at Visit 7 and ET; Updated the SoA footnotes f, i, and q for clarity, added footnote x; Revised Exclusion Criterion #11 (now criterion #12); Revised Exclusion Criterion #15 (now criterion #16); Inserted 2 new exclusion criteria: #6 and #23; Revised Section 7.1 treatments administered for clarity; Revised Section 7.3 method of treatment assignment for clarity; Revised Section 7.6 treatment compliance for clarity; Added text to Section 7.7 concomitant therapy for clarity; Revised Section 7.8; Updated Table 7-2 prohibited medications to clarify the use of anti-emetics, and added an exception to the opioid prohibition; Updated Section 7.7.3 rescue medicine to clarify the use of anti-emetics; Revised Section 8.1.1; Updated Section 9.1.4.1 Patient Global Impression of Status-Diabetic Gastroparesis (PGIS-DG) for clarity; Updated Section 9.2.7.3 major adverse cardiovascular events (MACE) to define the required timing for reporting MACE; Revised Section 9.3; Updated Section 9.4.1 to indicate “clinically significant reactions” at the injection sites; Updated Section 9.5 PK to clarify PK draws at ET; Updated Section 10.3.2.2 - "Hommel test" was changed to "Holm test"; Updated appendix 2: clinical laboratory tests and Table 12-1; Corrected the study title in Section 12.9, and added “by geographic region” to the study design, stratification factor row.
25 March 2018	The following changes were implemented with Amendment 2: Revised SoA footnote[a](to indicate ET Visit was performed soon after decision was made) and footnote(i);Revised footnote(m) to indicate pregnancy testing was performed if required by local regulations; Revised inclusion criterion 3 and 9; Revised exclusion criterion 4 (History of intestinal malabsorption) and 5 (removed functional dyspepsia);Deleted exclusion criterion 7 (anemia);replaced with new exclusion criterion for gastric/duodenal ulcer within 3 months of screening; Revised exclusion criterion 9 (to reduce history of malignancy to 3 years),11 (to shorten exclusion period for promotility agents to 10 days), 12 (urine drug screen results details), 14 (to extend exclusion for use of glucagon-like peptide (GLP)-1 agonists to 6 weeks, and removed pramlintide),20 (removed allowance for gluten-free crackers); Added exclusion criterion 24 for functional dyspepsia diagnosed before diabetes mellitus diagnosis; Revised screen failures (disallowed rescreening after >6 months), Table 7-2 (shortened wash-out period for pro-motility agents, anticholinergics, anti-emetics, amylin analogue, opioids from 2 weeks to 10 days, extended exclusion for GLP-1 agonists use from 2 to 6 weeks prior to the start of Run-in Period), withdrawal from study (indicated ET Visit must be performed soon after decision to discontinue is made), time period for adverse event (AE)/serious adverse event (SAE) collection(included “until 30 days after” final visit); Amended major adverse cardiovascular events (MACE) text to describe planned adjudication process; Added anti-relamorelin antibodies and type 1 diabetes mellitus (T1DM) antibody test to other laboratory assessments in Section 12.2, Table 12-1 Protocol-required safety laboratory assessments; Revised contraception guidance in Section 12.5 and added recommendations for acceptable birth control methods.

05 March 2019	The following changes were implemented with Amendment 3: -Modified definition of primary endpoints, added more details, and replaced definition for responder with Baseline participants -Increased duration of study from 16 weeks to 18 weeks and increased Screening Period from 2 weeks to up to 4 weeks -Removed references to a body mass index (BMI) requirement -Start of Screening Period revised from Day -28 to Day -42 -Added requirement for study population at screening -Increased number of sites and screened participants -Section 2 SOA: Changed number of days for Screening Period from to up to 28 days, Added footnote a, added electrocardiogram (ECG) assessment at Visit 4, Modified footnote j, Added footnote k -Removed assessment of glycated albumin -Reformat section heading: Section 4.1 -Amended inclusion criterion #6, removed BMI criterion #9, inclusion criteria #10: added a reference to Appendix 3 -Amended exclusion criterion #3, exclusion criterion #11: Added 5 hydroxytryptamine (HT) agonists, amended exclusion criteria #12, added exclusion criteria #25, #26 -Added option for sponsor to permit participant with positive urine drug screen at Screening to continue in Screening Period -Deleted option for investigator to contact sponsor if participant could not inject study treatment into abdomen -Replaced breakfast and dinner with morning and evening meals, respectively -Unblinding procedures modified -Made changes to Table 7-2, Section 7.7.1 -Removed 'antihistamines' -Removed: “non-compliance with study treatment”.
05 March 2019	-Added requirement for the investigator to contact the sponsor under specific conditions: 8.1.1 -Defined zero and 10 scores of diabetic gastroparesis (DG) assessments -Specified time period (i.e., from baseline to Week 12) for which the change in Diabetic Gastroparesis Symptom Severity Score (DGSSS) was assessed, deleted few definitions and details -Redefined “exploratory” endpoints as “additional” endpoints; more assessments added in 9.1.3.1, 9.1.3.2, 9.1.3.4 -Specified that medical occurrences beginning before start of study treatment but after obtaining informed consent (IC) was recorded in the AE section of electronic case report form (eCRF) -Added phrase “Inadequate Control of Diabetes” to section title in 9.2.7.2 -Revised sample size determination -Table 10-1, Analysis Populations– specified “double-blind” treatment -Added row in Table 10-2,10.3.1 -Updated primary endpoint and its description: 10.3.2 -Updated how missing data was handled -Replaced language about specific analyses: 10.3.4 -Added a requirement: 10.3.5 -Made un-numbered subsections level 3 headings and reorganized subsections: 12.3 -Additional criteria added for IC process: 12.3.3 -Replaced requirement for records and documents to be retained for 15 years after study completion -Section added: 12.3.9 -Made un-numbered subsections level 3 headings: 12.4 -Revised procedures: 12.4.1. Deleted text, footnote b, updated Pregnancy Testing: 12.5.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported