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	2017-002136-16
Trial protocol	FR BG ES IT
Global end of trial date	08 July 2020

Results information

Result version number	v1 (current)
This version publication date	26 July 2021
First version publication date	26 July 2021

Trial information

Trial identification

Sponsor protocol code	RLM-MD-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03285308
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	08 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to evaluate the safety and efficacy of relamorelin compared to placebo in participants with diabetic gastroparesis. Participants will report 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	29 September 2017
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	Poland: 9
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	India: 46
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	United States: 236
Worldwide total number of subjects	336
EEA total number of subjects	12

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	259
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with a diagnosis of diabetic gastroparesis entered a screening period of up to 4 weeks, a 2-week run-in period, and a 12-week treatment period. The participants were randomised in 1:1 ratio to blinded treatment period with relamorelin 10 µg or placebo.

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	Investigator, Subject

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	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:

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

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	167	169
Safety Population	163	163
Completed	147	146
Not completed	20	23
Consent withdrawn by subject	8	9
Adverse event, non-fatal	3	7
Protocol Deviation	6	5
Lost to follow-up	3	1
Reason not Specified	-	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 µg injected subcutaneously twice daily for up to 12 weeks.	

Reporting group values	Placebo	Relamorelin 10 µg	Total
Number of subjects	167	169	336
Age categorical Units: Subjects			
Adults (<65 years)	130	129	259
From >= 65 years	37	40	77
Age Continuous Units: years			
arithmetic mean	55.4	56.3	
standard deviation	± 10.78	± 11.47	-
Sex: Female, Male Units: participants			
Female	107	115	222
Male	60	54	114
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	26	24	50
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	25	19	44
White	116	125	241
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	51	53	104
Not Hispanic or Latino	116	116	232
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 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. '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 (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	163	165		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=163, 165)	25.1 (± 5.53)	24.5 (± 5.99)		
Change from Baseline to Week 12 (n=142, 141)	-10.0 (± 8.89)	-9.3 (± 8.17)		

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	164	165		
Units: percentage of participants				
number (not applicable)	19.5	21.8		

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	164	165		
Units: percentage of participants				
number (not applicable)	34.1	29.7		

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	164	165		
Units: percentage of participants				
number (not applicable)	28.0	27.9		

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	164	165		
Units: percentage of participants				
number (not applicable)	26.2	27.9		

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	164	165		
Units: percentage of participants				
number (not applicable)	22.6	25.5		

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 approximately to 16 weeks

End point values	Placebo	Relamorelin 10 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	163		
Units: participants	68	70		

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' 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), liter(L), femtoliter (fL), millimoles(mmol/L), micromoles(µmol/L), absolute cell count (ACC), platelet count (Thrombocytes), red blood cell (RBC), white blood cell (WBC), non-fasting (NF), fasting (F), glycohemoglobin A1C (HbA1c).

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	163	163		
Units: participants				
Eosinophils ACC [10^9/L]: >3×ULN (n=152,158)	0	1		
Hematocrit (RATIO): <0.9×LLN (n=145,157)	2	2		

Hemoglobin (g/L): <0.9×LLN (n=147,153)	10	4		
Lymphocytes ACC (10^9/L): >1.5×ULN (n=151,158)	1	0		
Lymphocytes ACC (10^9/L): <0.8×LLN (n=151,158)	2	1		
Mean Corpuscular Volume (fL): >1.1×ULN (n=151,158)	2	0		
Neutrophils ACC (10^9/L): >1.5×ULN (n=150,156)	0	1		
Neutrophils ACC (10^9/L): <0.8×LLN (n=150,156)	2	3		
Thrombocytes (10^9/L): >1.5×ULN (n=152,158)	0	1		
RBC Count (10^12/L): >1.1×ULN (n=151,159)	0	1		
RBC Count (10^12/L): <0.9×LLN (n=151,159)	1	1		
WBC Count (10^9/L): >1.5×ULN (n=152,159)	1	1		
Bicarbonate (HCO3) (mmol/L): >1.1×ULN (n=152,156)	3	1		
Bicarbonate (HCO3) (mmol/L): >0.9×LLN (n=152,156)	3	1		
Blood Urea Nitrogen (mmol/L): >1.2×ULN (n=137,153)	11	11		
Calcium (mmol/L): <0.9×LLN (n=153,160)	0	1		
Cholesterol, Total, NF (mmol/L) (n=151,158)	0	1		
Creatinine [µmol/L]: >1.3×ULN (n=141,149)	7	8		
Glucose-Chemistry, F (mmol/L): >2.5×ULN(n=141,148)	10	21		
Glucose-Chemistry, F (mmol/L):<0.9×LLN(n=141,148)	3	1		
HbA1C: Increase of >=0.5% (n=155,160)	91	125		
HbA1C: Increase of >=1% (n=155,160)	91	124		
Phosphorus (mmol/L): >1.1×ULN (n=147,156)	2	5		
Phosphorus (mmol/L): <0.9×LLN (n=147,156)	0	1		
Triglycerides, F (mmol/L): >=3×ULN (n=149,154)	5	5		
Uric Acid (Urate) (µmol/L): >1.1×ULN (n=123,130)	10	18		
Uric Acid (Urate) (µmol/L): <0.9×LLN (n=123,130)	1	3		

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 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	163	163		
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	163	163		
Units: participants	4	3		

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' indicates 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	163	163		
Units: participants				
Glycohemoglobin A1C: Increase of >=0.5%(n=155,160)	91	125		
Glycohemoglobin A1C: Increase of >=1% (n=155,160)	91	124		

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 and Positive Confirmatory Test at each time point. Safety Population included all participants who received ≥ 1 administration of double-blind study treatment (N=163 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	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	163			
Units: participants				
Screening Test (Baseline) Negative (n=149)	133			

Screening Test (Baseline) Positive (n=149)	16			
Confirmatory Test (Baseline) Negative (n=15)	13			
Confirmatory Test (Baseline) Positive (n=15)	2			
Screening Test (Day 14) Negative (n=137)	124			
Screening Test (Day 14) Positive (n=137)	13			
Confirmatory Test (Day 14) Negative (n=13)	13			
Confirmatory Test (Day 14) Positive (n=13)	0			
Screening Test (Day 28) Negative (n=131)	115			
Screening Test (Day 28) Positive (n=131)	16			
Confirmatory Test (Day 28) Negative (n=16)	15			
Confirmatory Test (Day 28) Positive (n=16)	1			
Screening Test (Day 84) Negative (n=111)	95			
Screening Test (Day 84) Positive (n=111)	16			
Confirmatory Test (Day 84) Negative (n=15)	14			
Confirmatory Test (Day 84) Positive (n=15)	1			
Screening Test (End of Treatment) Negative (n=15)	13			
Screening Test (End of Treatment) Positive (n=15)	2			
Confirmatory Test (EOT) Negative (n=2)	2			
Confirmatory Test (EOT) Positive (n=2)	0			
Screening Test (Unscheduled) Negative (n=4)	2			
Screening Test (Unscheduled) Positive (n=4)	2			
Confirmatory Test (Unscheduled) Negative (n=2)	1			
Confirmatory Test (Unscheduled) Positive (n=2)	1			

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 based on the Intent-to-treat (ITT) Population. 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	15 / 163 (9.20%)	16 / 163 (9.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (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	2 / 163 (1.23%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			

subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 163 (0.61%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 163 (0.61%)	1 / 163 (0.61%)	
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	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 163 (0.61%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
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	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (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			
Acute respiratory failure			
subjects affected / exposed	2 / 163 (1.23%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (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	2 / 163 (1.23%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (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			
Arthralgia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vertebral wedging			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (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			
Pneumonia			
subjects affected / exposed	3 / 163 (1.84%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 163 (0.00%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 163 (1.23%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 163 (1.23%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (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			

Hypoglycaemia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (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 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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	9 / 163 (5.52%)	9 / 163 (5.52%)	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	9 / 163 (5.52%)	9 / 163 (5.52%)	
occurrences (all)	10	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2017	The following changes were implemented with Amendment 1: -Changed the definition of the diabetic gastroparesis symptom severity diary (DGSSS) score for responder (the primary endpoint) from ≥8 point improvement to a ≥10 point improvement -Added GE by gastric emptying breath test (GEBTs) to Visit 7 and the early termination Visit, and to adjust the schedule of assessment (SoA) footnote l to add GEBT to assessments performed on a subset of participants at a subset of sites -Revised the wording of inclusion criteria -Revised the order of the inclusion and exclusion criteria -Added an exclusion criterion for hepatic disease -Removed the exclusion for treatment with a sodium-glucose co-transporter 2 (SGLT-2) -Reordered the objectives and endpoints -Corrected the maximum volumes of blood drawn for the scheduled labs and for the pharmacokinetic (PK) and hormone subset -Moved the questions for Patient Global Impression of Status and Impression of Change -Added information on the GEBT analysis -Revised the washout requirements for SGLT-2 inhibitors from 2 weeks prior to the start of the Run-in Period to 3 days prior to the GEBT done at the start of Run-in Period -Revised the sample size determination -Updated the definition of the PK population -Updated the statistical methodology to remove unused methodologies and descriptions -Removed the Multiple Comparisons Procedures for the United States and European Union, and added sections on multiple comparisons procedure and missing data -Added a new section on major adverse cardiovascular events -Clarified Hy’s Law and adverse events of special interest (AESI) reporting.
18 January 2018	The following changes were implemented with Amendment 2: -Removed glycated albumin from the safety endpoints and objectives and endpoints, and in the safety analyses -Increased the number of sites and participants screened -Moved no use of promotility agents and anti-emetics to after Run-in Period -Updated the SoA to add a new footnote (o) to PK samples at end of treatment (ET), to add fasting fingerstick glucose testing at Visit 7 and ET -Updated the SoA footnotes (f), (i). and (q) for clarity -Updated the SoA to add a new footnote (x) to inspect injection sites -Revised exclusion criterion -Inserted 2 new exclusion criteria -Revised treatments administered for clarity -Revised treatment compliance for clarity -Added text to concomitant therapy for clarity -Updated prohibited medications to clarify the use of anti-emetics, and to add an exception from the opioid prohibition -Updated rescue medicine to clarify the use of anti-emetics -Updated Patient Global Impression of Change-Diabetic Gastroparesis (PGIS-DG) for clarity -Updated major adverse cardiovascular events to define the required timing for reporting major adverse cardiovascular events (MACE) -Revised treatment of overdose for accuracy -Revise physical examinations for clarity -Updated PK to clarify PK draws at ET -Updated "Hommel test" was changed to "Holm test" -Updated clinical laboratory tests -Corrected the study title.

25 March 2018	The following changes were implemented with Amendment 3: -Revised SoA footnote (a) to indicate early termination visit must be performed as soon as possible after decision has been made -Revised SoA footnote (i) to clarify details of urine drug screen results -Revised SoA footnote (m) to indicate pregnancy testing can be performed if required by local regulations -Revised inclusion criterion 3 to remove 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 upper limit for body mass index (BMI) -Revised exclusion criterion to clarify 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 5 to remove functional dyspepsia -Deleted exclusion criterion which addresses anemia, replacing it with a new exclusion criterion for gastric or duodenal ulcer within 3 months of screening -Revised exclusion criterion 9 to reduce history of malignancy from 5 to 3 years -Revised exclusion criterion to shorten exclusion period for promotility agents from 2 weeks to 10 days -Revised exclusion criterion to clarify details of urine drug screen results -Revised exclusion criterion to extend exclusion for use of glucagon-like peptide-1 (GLP-1) agonists to 6 weeks, and remove pramlintide.
25 March 2018	-Revised exclusion criterion to remove the allowance for gluten-free crackers -Added exclusion criterion for functional dyspepsia diagnosed before diagnosis of diabetes mellitus -Revised screen failures to disallow rescreening after greater than 6 months -Revised Table 7-2 to shorten wash-out period for pro-motility agents, anticholinergics, anti-emetics, amylin analogue, and opioids from 2 weeks to 10 days prior to the start of Run-in Period; to extend exclusion for use of GLP-1 agonists from 2 to 6 weeks -Revised withdrawal from study to indicate ET Visit must be performed as soon as possible after the decision to discontinue has been made -Amended MACE text for clarity and to describe planned adjudication process -Added anti-relamorelin antibodies to other laboratory assessments in protocol-required safety laboratory assessments -Revised contraception guidance to add recommendations for acceptable birth control methods.
08 February 2019	The following changes were implemented with Amendment 4: - Modified definition of primary endpoints - Increased number of sites from approximately 200 to approximately 350 Increased number of participants screened from 2000 to 2500 -Added requirement for study population at screening to have had a history of at least 2 vomiting episodes and to have had at least 1 vomiting episode during Run-in Period - Removed body mass index (BMI) information - Start of screening period was revised from Day -28 to Day -42 -Increased duration of Screening Visit from 14 days to 28 days. Updated study schematic to reflect change in length of Screening Visit -Increased duration of study from 16 weeks to 18 weeks and increased screening period from 2 weeks to up to 4 weeks -Added footnote (a) for screening Visit -Added electrocardiogram (ECG) obtained at Visit 4 -Amended footnote (j) -Removed assessment of glycated albumin from SOA and all related text -Added footnote for fasting blood glucose: Serum for all visits except for Visit 4 and 6 (plasma) -Removed year in all references to the relamorelin investigator brochure -Amended clinical hypotheses -Amended inclusion #6 to allow for a GI series with contrast as an assessment tool for documenting absence of an obstructing lesion and adjust timing of assessments from some time before screening (Visit 1) to sometime before the Run-in Period (Visit 2) -Removed BMI criterion #9 -Inclusion #10: added a reference to Appendix 3 -Amended exclusion #3 to specify that participants with active eating disorders at the time of screening are to be excluded, as opposed to those with a history of eating disorders -exclusion #11: Added 5HT agonists as exclusionary drug -Amended exclusion #12 to allow a participant with a positive urine drug screen at Screening to continue in study while confirmatory testing is done on an aliquot of original sample; specified that opioids are not drugs for which investigator may choose not to consider exclusionary.

08 February 2019	-Added exclusion criteria for hypersensitivity to the study treatments and their excipients (Exclusion #25) and for specific corrected ECG results (Exclusion #26) -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 within 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 -Removed: "non-compliance with study treatment" -Defined zero and 10 scores of the DG assessments -Changed Section 9.1.1.1 from diabetic gastroparesis symptom severity score (DGSSS) responder definition to Change from Baseline to Week 12 in the Weekly DGSSS -Revised assessment of DGSSS Weekly Scores -More assessments added in order to evaluate the additional endpoints -More assessments added in order to evaluate the additional endpoints -Added a row to describe Change from Baseline (CFB) -Updated primary endpoint and its description -Clarifications made to Hypothesis H1; reference made to SAP for other efficacy analyses -Added a requirement for a DSMB to review interim safety data at defined intervals throughout the study -Revised procedures for reporting AESIs; specified that specific DG manifestations will be captured in the DGSSS and not in the eCRF as a complication of the disease, as originally specified -Provided AESIs that have been identified for relamorelin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported