Clinical trial results:
A Phase 2b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of RM-131 Administered to Patients with Vomiting Symptoms and Moderate to Severe Diabetic Gastroparesis

Summary

EudraCT number	2014-005623-27
Trial protocol	SE GB BE
Global end of trial date	09 June 2016

Results information

Result version number	v1 (current)
This version publication date	17 July 2019
First version publication date	17 July 2019

Trial information

Trial identification

Sponsor protocol code	RM-131-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02357420
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Sales, LLC
Sponsor organisation address	5 Giralda Farms, Madison, United States, NJ 07940
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area Head, Allergan plc, 001 862-261-7000, 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	09 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of relamorelin on vomiting episodes in participants with diabetic gastroparesis (DG).

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 January 2015
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: 15
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	United States: 368
Worldwide total number of subjects	393
EEA total number of subjects	21

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)	286
From 65 to 84 years	107

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total 393 participants were randomised and received study treatment, and 334 participants completed the study. Five participants who received study drug but discontinued prematurely were summarised as completing the study because they fulfilled the Visit 8 (Week 12) assessments as per protocol.

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, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo-matching relamorelin was administered subcutaneously (SC) by injection twice daily (BID) for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received placebo SC by injection, BID, in the morning (prior to breakfast) and evening (prior to the evening meal) for 12 weeks.

Arm title	Relamorelin 10 µg

Arm description:

Relamorelin 10 microgram (µg) was administered SC by injection BID for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Relamorelin
Investigational medicinal product code	RM-131
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received relamorelin 10 µg SC by injection, BID, in the morning (prior to breakfast) and evening (prior to the evening meal) for 12 weeks.

Arm title	Relamorelin 30 µg

Arm description:

Relamorelin 30 µg was administered SC by injection BID for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	Relamorelin
Investigational medicinal product code	RM-131
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received relamorelin 30 µg SC by injection, BID, in the morning (prior to breakfast) and evening (prior to the evening meal) for 12 weeks.

Arm title	Relamorelin 100 µg

Arm description:

Relamorelin 100 µg was administered SC by injection BID for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Relamorelin
Investigational medicinal product code	RM-131
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received relamorelin 100 µg SC by injection, BID, in the morning (prior to breakfast) and evening (prior to the evening meal) for 12 weeks.

Number of subjects in period 1	Placebo	Relamorelin 10 µg	Relamorelin 30 µg
Started	104	98	109
Full Analysis Set (FAS)	104	98	109
Completed	92	86	93
Not completed	12	12	16
Adverse Event	3	3	8
Withdrawn Consent	4	8	6
Investigator Decision	1	-	-
Lost to follow-up	3	-	2
Protocol Non-compliance	-	-	-
Prohibited Medication	1	1	-

Number of subjects in period 1	Relamorelin 100 µg
Started	82
Full Analysis Set (FAS)	81
Completed	63
Not completed	19
Adverse Event	9
Withdrawn Consent	6
Investigator Decision	-
Lost to follow-up	3
Protocol Non-compliance	1

Prohibited Medication	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo-matching relamorelin was administered subcutaneously (SC) by injection twice daily (BID) for 12 weeks.	
Reporting group title	Relamorelin 10 µg
Reporting group description:	
Relamorelin 10 microgram (µg) was administered SC by injection BID for 12 weeks.	
Reporting group title	Relamorelin 30 µg
Reporting group description:	
Relamorelin 30 µg was administered SC by injection BID for 12 weeks.	
Reporting group title	Relamorelin 100 µg
Reporting group description:	
Relamorelin 100 µg was administered SC by injection BID for 12 weeks.	

Reporting group values	Placebo	Relamorelin 10 µg	Relamorelin 30 µg
Number of subjects	104	98	109
Age categorical Units: Subjects			
Adults (18-64 years)	79	64	82
Elderly (From 65-84 years)	25	34	27
Age Continuous Units: years			
arithmetic mean	55.7	59.3	56.0
standard deviation	± 11.9	± 10.2	± 11.7
Sex: Female, Male Units: Subjects			
Female	64	59	65
Male	40	39	44

Reporting group values	Relamorelin 100 µg	Total	
Number of subjects	82	393	
Age categorical Units: Subjects			
Adults (18-64 years)	61	286	
Elderly (From 65-84 years)	21	107	
Age Continuous Units: years			
arithmetic mean	57.1		
standard deviation	± 11.0	-	
Sex: Female, Male Units: Subjects			
Female	57	245	
Male	25	148	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo-matching relamorelin was administered subcutaneously (SC) by injection twice daily (BID) for 12 weeks.	
Reporting group title	Relamorelin 10 µg
Reporting group description:	
Relamorelin 10 microgram (µg) was administered SC by injection BID for 12 weeks.	
Reporting group title	Relamorelin 30 µg
Reporting group description:	
Relamorelin 30 µg was administered SC by injection BID for 12 weeks.	
Reporting group title	Relamorelin 100 µg
Reporting group description:	
Relamorelin 100 µg was administered SC by injection BID for 12 weeks.	

Primary: Change from Baseline to Week 12 in Weekly Vomiting Episodes

End point title	Change from Baseline to Week 12 in Weekly Vomiting Episodes
End point description:	
Vomiting episodes were assessed via the Diabetic Gastroparesis Symptoms Severity Diary (DGSSD). The DGSSD is a 7-item, participant-reported daily diary designed to assess the severity of 6 core signs and symptoms of Diabetic Gastroparesis (DG) (nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety) and the frequency of vomiting episodes. Each day, the participant recorded the number of vomiting episodes in the past 24 hours in the diary. Higher scores indicate more vomiting episodes. Weekly scores were averaged across the 12 weeks period. A negative change from Baseline indicates improvement. Full Analysis Set (FAS) included all randomised participants who received at least 1 dose of study treatment and provided at least 1 postbaseline primary efficacy measurement (DGSSD). 'n' is the number of participants with data available at the given time-point.	
End point type	Primary
End point timeframe:	
7 days prior to Day 1 for Baseline to 7 days prior to Week 12	

End point values	Placebo	Relamorelin 10 µg	Relamorelin 30 µg	Relamorelin 100 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	98	109	81
Units: vomiting episodes per week				
arithmetic mean (standard deviation)				
Baseline (n=85,81,86,56)	5.7 (± 6.0)	7.7 (± 17.2)	6.9 (± 10.3)	4.8 (± 5.2)
Change from Baseline to Week 12 (n=85,81,86,56)	-2.9 (± 5.8)	-3.7 (± 12.5)	-3.8 (± 7.6)	-1.1 (± 13.5)

Statistical analyses

Statistical analysis title	Relamorelin 10 µg vs Placebo
Comparison groups	Placebo v Relamorelin 10 µg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36 [1]
Method	MMRM

Notes:

[1] - Measures mixed effects model (MMRM) analysis included treatment, week, treatment-by-week interaction as fixed factors and baseline values as the covariates with unstructured variance-covariance correlation matrix.

Statistical analysis title	Relamorelin 30 µg vs Placebo
Comparison groups	Placebo v Relamorelin 30 µg
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [2]
Method	MMRM

Notes:

[2] - MMRM analysis included treatment, week, treatment-by-week interaction as fixed factors and baseline values as the covariates with unstructured variance-covariance correlation matrix.

Statistical analysis title	Relamorelin 100 µg vs Placebo
Comparison groups	Placebo v Relamorelin 100 µg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59 [3]
Method	MMRM

Notes:

[3] - MMRM analysis included treatment, week, treatment-by-week interaction as fixed factors and baseline values as the covariates with unstructured variance-covariance correlation matrix.

Secondary: Change from Baseline to Week 12 in Weekly DGSSD 4-symptom Composite Score (Nausea, Bloating, Early Satiety, Abdominal Pain)

End point title	Change from Baseline to Week 12 in Weekly DGSSD 4-symptom Composite Score (Nausea, Bloating, Early Satiety, Abdominal Pain)

End point description:

The DGSSD is a 7-item, participant-reported daily diary designed to assess the severity of 6 core signs and symptoms of DG (nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety) and frequency of vomiting episodes. Severity of nausea, bloating and abdominal pain, were assessed on a numerical rating scale of 0 to 10, with 0="no" (symptom) and 10="worst possible" (symptom). Early satiety was assessed on a 5-item scale with 1="Only 1 or 2 bites" and 5="All of a normal-sized meal"; symptom severity scores for this item were reversed and normalized to a range 0 to 10 for the development of the DGSSD 4-symptom Composite Score. The DGSSD 4-symptom Composite Score (Nausea, Bloating, Early Satiety, Abdominal pain) range is 0 to 40. Higher scores indicate worse condition. Weekly scores were averaged across 12 weeks period. A negative change from Baseline indicates improvement. FAS population. 'n' is the number of participants with data available at the timepoint.

End point type	Secondary

End point timeframe:

7 days prior to Day 1 for Baseline to 7 days prior to Week 12

End point values	Placebo	Relamorelin 10 µg	Relamorelin 30 µg	Relamorelin 100 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	98	109	81
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=88,86,91,63)	21.4 (± 6.7)	21.8 (± 6.9)	21.1 (± 6.0)	22.3 (± 6.2)
Change from Baseline to Week 12 (n=88,86,91,63)	-5.4 (± 8.1)	-7.7 (± 7.8)	-7.5 (± 7.4)	-8.9 (± 8.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 for Gastric Emptying (GE) as Measured by the Gastric Emptying Breath Test (GEBT) Half-time

End point title	Change from Baseline to Week 12 for Gastric Emptying (GE) as Measured by the Gastric Emptying Breath Test (GEBT) Half-time

End point description:

GE was measured via the GEBT and was reported as a time to half (t1/2) of the theoretical total GE. GEBT is a non-radioactive stable isotope breath test intended for measurement of GE of solids in participants. A negative change from Baseline indicates improvement. FAS included all randomised participants who received at least 1 dose of study treatment and provided at least 1 postbaseline primary efficacy measurement (DGSSD). 'n' is the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 12

End point values	Placebo	Relamorelin 10 µg	Relamorelin 30 µg	Relamorelin 100 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	98	109	81
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (n=89,83,92,63)	127.1 (± 36.5)	126.8 (± 37.6)	128.6 (± 35.9)	133.6 (± 35.4)
Change from Baseline to Week 12 (n=88,82,92,61)	0.0 (± 38.5)	-12.7 (± 38.1)	-12.8 (± 36.5)	-13.6 (± 40.5)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 98 days

Adverse event reporting additional description:

Safety set included all the participants who were randomised and received at least 1 dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo-matching relamorelin was administered subcutaneously (SC) by injection twice daily (BID) for 12 weeks.

Reporting group title	Relamorelin 10 µg

Reporting group description:

Relamorelin 10 microgram (µg) was administered SC by injection BID for 12 weeks.

Reporting group title	Relamorelin 30 µg

Reporting group description:

Relamorelin 30 µg was administered SC by injection BID for 12 weeks.

Reporting group title	Relamorelin 100 µg

Reporting group description:

Relamorelin 100 µg was administered SC by injection BID for 12 weeks.

Serious adverse events	Placebo	Relamorelin 10 µg	Relamorelin 30 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 104 (7.69%)	7 / 98 (7.14%)	10 / 109 (9.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Median nerve injury			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic hematoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	2 / 104 (1.92%)	1 / 98 (1.02%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			

subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary tract disorder			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 98 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Relamorelin 100 µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 82 (7.32%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnea			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Median nerve injury			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Traumatic hematoma			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Syncope			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroduodenitis			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary tract disorder			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			

subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Relamorelin 10 µg	Relamorelin 30 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 104 (12.50%)	21 / 98 (21.43%)	30 / 109 (27.52%)
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 104 (0.96%)	3 / 98 (3.06%)	4 / 109 (3.67%)
occurrences (all)	1	4	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	1 / 109 (0.92%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	3 / 104 (2.88%)	4 / 98 (4.08%)	6 / 109 (5.50%)
occurrences (all)	3	4	7
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0	4 / 98 (4.08%) 4	7 / 109 (6.42%) 7
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	7 / 104 (6.73%) 9	7 / 98 (7.14%) 8	8 / 109 (7.34%) 9
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 104 (1.92%) 2	5 / 98 (5.10%) 6	10 / 109 (9.17%) 11

Non-serious adverse events	Relamorelin 100 µg		
Total subjects affected by non-serious adverse events subjects affected / exposed	28 / 82 (34.15%)		
Investigations Blood glucose increased subjects affected / exposed occurrences (all)	6 / 82 (7.32%) 7		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	5 / 82 (6.10%) 5 2 / 82 (2.44%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	6 / 82 (7.32%) 7		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	6 / 82 (7.32%) 6		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	10 / 82 (12.20%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2014	The protocol was updated throughout to add Relamorelin 100 µg treatment arm to confirm the dose range and provide assurance that maximal efficacy has been achieved. Inclusion/exclusion criteria were updated for safety and clarification. Safety monitoring and clinical laboratory assessments were modified for participant safety. Pharmacokinetic time points were added for Day 84 measurements. Participant contacts during the study were detailed and clarified for safety and to encourage compliance with study procedures. Statistical methodology and Schedule of Assessments were updated. Study Procedures by Visit was updated to reflect the changes in procedures and/or timing. Symptom and Global Assessments was updated to present the specific assessments that were to be conducted at Visits 4 and 8, separately.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported