



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 |
|-----------------|---|

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 μ g | | |
|-----------------------------------|-----------------|------------------------|--|--|
| 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 |
|-----------------|--|

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 [$10^9/\text{L}$]: $>3 \times \text{ULN}$ (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 (HCO ₃) (mmol/L): >1.1×ULN (n=142,145) | 0 | 1 | | |
| Bicarbonate (HCO ₃) (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 μ g | | |
|-----------------------------|-----------------|------------------------|--|--|
| 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 μ g | | |
|-----------------------------|-----------------|------------------------|--|--|
| 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 $\geq 1\%$ Increase in Glycosylated Hemoglobin A1c (HBA1c)

| | |
|-----------------|--|
| End point title | Number of Participants with a $\geq 1\%$ 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