# Clinical trial results:
# A 26-Week Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Phase 2 Study to Assess the Safety and Efficacy of SAR425899 in Patients with Type 2 Diabetes Mellitus

## Summary

| | |
|---|---|
| EudraCT number | 2016-001328-77 |
| Trial protocol | ES DE CZ HU |
| Global end of trial date | 27 December 2017 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 06 January 2019 |
| First version publication date | 06 January 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | DRI13940 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02973321 |
| WHO universal trial number (UTN) | U1111-1179-4786 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Sanofi aventis recherche & développement |
| Sponsor organisation address | 1 avenue Pierre Brossolette , Chilly-Mazarin, France, 91380 |
| Public contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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 February 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the dose-response relationship of SAR425899 versus placebo in terms of glycemic control as measured by the change in glycosylated hemoglobin (HbA1c) from baseline to Week 26.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Metformin was orally administered at a stable dose of at least 1500 mg per day or at the maximal tolerated dose depending on the dose regimen which the subject was following prior to screening, unless a safety issue related to this medication occurred. Lifestyle and diet therapy followed before the screening were continued during the study, if applicable.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 02 December 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 31 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | Germany: 11 |
| Country: Number of subjects enrolled | Hungary: 38 |
| Country: Number of subjects enrolled | Canada: 19 |
| Country: Number of subjects enrolled | Mexico: 42 |
| Country: Number of subjects enrolled | Russian Federation: 33 |
| Country: Number of subjects enrolled | United States: 108 |
| Worldwide total number of subjects | 296 |
| EEA total number of subjects | 94 |

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) | 238 |
| From 65 to 84 years | 58 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 59 centers in 8 countries. A total of 539 subjects were screened between 2 December 2016 and 2 June 2017, of whom, 245 subjects were screen failures. Screen failures were mainly due to exclusion criteria met. The study was double-blind for SAR425899 vs placebo and open-label for active comparator liraglutide.

### Pre-assignment

Screening details:

A total of 296 subjects were randomized and treated in the study. Randomization was stratified by HbA1c at the screening visit (<8% vs >=8%) and body mass index (BMI) (<35.0 kg/m^2 vs >=35.0 kg/m^2) at Day 1 (start of investigational medicinal product [IMP] administration).

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Placebo (for SAR425899) subcutaneous (SC) injection once daily (QD) from Week 1 to Week 26, matching 3 SAR425899 dose levels of 0.12 mg, 0.16 mg and 0.20 mg.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo (for SAR425899) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo self-administered by SC injection.

| | |
|---|---|
| **Arm title** | SAR425899 0.12 mg |

Arm description:

SAR425899 SC injection QD at maintenance dose of 0.12 mg for 25 weeks (Week 2 to Week 26) following 1 week dose increase step (0.06 mg at Week 1).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | SAR425899 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

SAR425899 self-administered by SC injection.

| | |
|---|---|
| **Arm title** | SAR425899 0.16 mg |

Arm description:

SAR425899 SC injection QD at maintenance dose of 0.16 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase step (0.06 mg at Week 1 and 0.12 mg at Week 2).

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | SAR425899 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

SAR425899 self-administered by SC injection.

| | |
|---|---|
| **Arm title** | SAR425899 0.20 mg |

Arm description:

SAR425899 SC injection QD at maintenance dose of 0.20 mg for 23 weeks (Week 4 to Week 26) following 3 weeks dose increase step (0.06 mg at Week 1, 0.12 mg at Week 2 and 0.16 mg at Week 3).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | SAR425899 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

SAR425899 self-administered by SC injection.

| | |
|---|---|
| **Arm title** | Liraglutide |

Arm description:

Liraglutide SC injection QD at maintenance dose of 1.8 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase steps (0.6 mg daily at Week 1 and by 1.2 mg daily at Week 2).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Liraglutide self-administered by SC injection using a prefilled multidose pen.

| **Number of subjects in period 1** | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg |
|---|---|---|---|
| Started | 33 | 66 | 66 |
| Completed | 32 | 51 | 52 |
| Not completed | 1 | 15 | 14 |
| Adverse Event | 1 | 10 | 11 |
| Other than specified | - | 5 | 3 |
| Lack of efficacy | - | - | - |

| **Number of subjects in period 1** | SAR425899 0.20 mg | Liraglutide |
|---|---|---|
| Started | 64 | 67 |
| Completed | 48 | 62 |
| Not completed | 16 | 5 |
| Adverse Event | 13 | 3 |
| Other than specified | 3 | 1 |

| | | |
|---|---|---|
| Lack of efficacy | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo (for SAR425899) subcutaneous (SC) injection once daily (QD) from Week 1 to Week 26, matching 3 SAR425899 dose levels of 0.12 mg, 0.16 mg and 0.20 mg. | |
| Reporting group title | SAR425899 0.12 mg |
| Reporting group description: | |
| SAR425899 SC injection QD at maintenance dose of 0.12 mg for 25 weeks (Week 2 to Week 26) following 1 week dose increase step (0.06 mg at Week 1). | |
| Reporting group title | SAR425899 0.16 mg |
| Reporting group description: | |
| SAR425899 SC injection QD at maintenance dose of 0.16 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase step (0.06 mg at Week 1 and 0.12 mg at Week 2). | |
| Reporting group title | SAR425899 0.20 mg |
| Reporting group description: | |
| SAR425899 SC injection QD at maintenance dose of 0.20 mg for 23 weeks (Week 4 to Week 26) following 3 weeks dose increase step (0.06 mg at Week 1, 0.12 mg at Week 2 and 0.16 mg at Week 3). | |
| Reporting group title | Liraglutide |
| Reporting group description: | |
| Liraglutide SC injection QD at maintenance dose of 1.8 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase steps (0.6 mg daily at Week 1 and by 1.2 mg daily at Week 2). | |

| Reporting group values | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg |
|---|---|---|---|
| Number of subjects | 33 | 66 | 66 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 56.2 | 56.8 | 54.5 |
| standard deviation | ± 9.3 | ± 9.0 | ± 10.1 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 15 | 29 | 35 |
| Male | 18 | 37 | 31 |
| BMI<br>Units: kg/m^2 | | | |
| arithmetic mean | 32.07 | 33.67 | 34.23 |
| standard deviation | ± 4.41 | ± 5.37 | ± 4.68 |
| Baseline HbA1c<br>Units: Percentage of HbA1c | | | |
| arithmetic mean | 8.04 | 7.97 | 7.99 |
| standard deviation | ± 0.86 | ± 0.88 | ± 0.85 |

| Reporting group values | SAR425899 0.20 mg | Liraglutide | Total |
|---|---|---|---|
| Number of subjects | 64 | 67 | 296 |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 55.0 | 56.1 | |
| standard deviation | ± 10.4 | ± 11.4 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 28 | 36 | 143 |
| Male | 36 | 31 | 153 |
| BMI<br>Units: kg/m^2 | | | |
| arithmetic mean | 33.63 | 34.23 | |
| standard deviation | ± 4.35 | ± 5.51 | - |
| Baseline HbA1c<br>Units: Percentage of HbA1c | | | |
| arithmetic mean | 8.14 | 8.11 | |
| standard deviation | ± 0.94 | ± 0.86 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo (for SAR425899) subcutaneous (SC) injection once daily (QD) from Week 1 to Week 26, matching 3 SAR425899 dose levels of 0.12 mg, 0.16 mg and 0.20 mg. | |
| Reporting group title | SAR425899 0.12 mg |
| Reporting group description: | |
| SAR425899 SC injection QD at maintenance dose of 0.12 mg for 25 weeks (Week 2 to Week 26) following 1 week dose increase step (0.06 mg at Week 1). | |
| Reporting group title | SAR425899 0.16 mg |
| Reporting group description: | |
| SAR425899 SC injection QD at maintenance dose of 0.16 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase step (0.06 mg at Week 1 and 0.12 mg at Week 2). | |
| Reporting group title | SAR425899 0.20 mg |
| Reporting group description: | |
| SAR425899 SC injection QD at maintenance dose of 0.20 mg for 23 weeks (Week 4 to Week 26) following 3 weeks dose increase step (0.06 mg at Week 1, 0.12 mg at Week 2 and 0.16 mg at Week 3). | |
| Reporting group title | Liraglutide |
| Reporting group description: | |
| Liraglutide SC injection QD at maintenance dose of 1.8 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase steps (0.6 mg daily at Week 1 and by 1.2 mg daily at Week 2). | |
| Subject analysis set title | SAR425899 0.06 mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Subjects received SAR425899 SC injection QD at dose of 0.06 for 26 weeks: 0.06 mg from Week 1 to Week 26 (for 26 weeks). | |

### Primary: Change From Baseline in HbA1c to Week 26

| | |
|---|---|
| End point title | Change From Baseline in HbA1c to Week 26 |
| End point description: | |
| Change in HbA1c was calculated by subtracting baseline value from Week 26 value. Missing post-baseline values were imputed by placebo control-based multiple imputation (MI) method under the missing not at random framework. Analysis was performed on Intent-to-treat (ITT) population which included all randomized subjects, irrespective of compliance with the study protocol and procedures. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 26 | |

| End point values | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: percentage of HbA1c | | | | |
| least squares mean (standard error) | -0.663 (± 0.169) | -1.517 (± 0.137) | -1.618 (± 0.133) | -1.562 (± 0.131) |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: percentage of HbA1c | | | | |
| least squares mean (standard error) | -1.312 (± 0.118) | | | |

## Statistical analyses

| Statistical analysis title | 1st trend test:SAR425899 0.20,0.16,0.12 mg,placebo |
|---|---|

Statistical analysis description:

Analysis was performed using analysis of covariance (ANCOVA) model with treatment groups, randomization strata of screening HbA1c value (<8, >=8 %), randomization strata of Visit 4 (Day 1) BMI (<35.0 kg/m^2, >=35.0 kg/m^2), and country as fixed effects and baseline HbA1c as a covariate. Overall 1st trend test based on a contrast with coefficients of +3, +1, -1, -3 and 0 for SAR425899 0.20 mg, 0.16 mg, 0.12 mg, placebo and liraglutide. Here it is test 1 of testing order.

| Comparison groups | SAR425899 0.12 mg v SAR425899 0.16 mg v SAR425899 0.20 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | < 0.0001 [2] |
| Method | ANCOVA |

Notes:

[1] - The overall Type 1 error for multiple comparisons of the HbA1c and body weight was controlled by a Hierarchical testing procedure. Testing was performed in following sequence: 1. 1st trend test for HbA1c, 2. 1st trend test for body weight, 3. 2nd trend test for HbA1c, 4. 2nd trend test for body weight, 5. 3rd trend test for HbA1c, 6. 3rd trend test for body weight.

[2] - Hierarchical testing procedure continued only, if the previous comparison was statistically significant. Threshold for significance at 0.05 level.

| Statistical analysis title | 2nd Trend Test: SAR425899 0.16 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using ANCOVA model with treatment groups, randomization strata of screening HbA1c value (<8, >=8 %), randomization strata of Visit 4 (Day 1) BMI (<35.0 kg/m^2, >=35.0 kg/m^2), and country as fixed effects and baseline HbA1c as a covariate. Second Trend test based on a contrast with coefficients of 0, +1, 0, -1 and 0 for SAR425899 0.20 mg, 0.16 mg, 0.12 mg, placebo and liraglutide, respectively. Here, it is test no. 3 of hierarchical testing sequence.

| Comparison groups | SAR425899 0.16 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| P-value | < 0.0001 [4] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -0.956 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.359 |
| upper limit | -0.552 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.206 |

Notes:

[3] - Hierarchical testing procedure continued only, if the previous comparison was statistically significant.
[4] - Threshold for significance at 0.05 level.

| **Statistical analysis title** | 3rd Trend Test: SAR425899 0.12 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using ANCOVA model with treatment groups, randomization strata of screening HbA1c value (<8, >=8 %), randomization strata of Visit 4 (Day 1) BMI (<35.0 kg/m^2, >=35.0 kg/m^2), and country as fixed effects and baseline HbA1c as a covariate. Third Trend test based on a contrast with coefficients of 0, 0, +1, -1 and 0 for SAR425899 0.20 mg, 0.16 mg, 0.12 mg, placebo and liraglutide, respectively. Here, it is test no. 5 of hierarchical testing sequence.

| | |
|---|---|
| Comparison groups | SAR425899 0.12 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other[5] |
| P-value | < 0.0001 [6] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -0.854 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.264 |
| upper limit | -0.444 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.209 |

Notes:

[5] - Hierarchical testing procedure continued only, if the previous comparison was statistically significant.
[6] - Threshold for significance at 0.05 level.

## Secondary: Mean Change From Baseline in Body Weight to Week 26

| End point title | Mean Change From Baseline in Body Weight to Week 26 |
|---|---|

End point description:

Change in body weight was calculated by subtracting baseline value from Week 26 value. Missing post-baseline values were imputed by placebo control-based MI method under the missing not at random framework. Analysis was performed on ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 26

| **End point values** | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: kg | | | | |
| least squares mean (standard error) | -1.759 (± 0.734) | -4.276 (± 0.564) | -5.330 (± 0.549) | -4.407 (± 0.559) |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: kg | | | | |
| least squares mean (standard error) | -4.590 (± 0.521) | | | |

## Statistical analyses

| Statistical analysis title | 1st trend test:SAR425899 0.20,0.16,0.12 mg,placebo |
|---|---|

Statistical analysis description:

Analysis was performed using ANCOVA model with treatment groups, randomization strata of screening HbA1c value (<8, >=8 %), randomization strata of Day 1 BMI (<35.0 kg/m^2, >=35.0 kg/m^2), and country as fixed effects and baseline body weight as a covariate. Here, it is test no. 2 of hierarchical testing sequence.

| Comparison groups | SAR425899 0.12 mg v SAR425899 0.16 mg v SAR425899 0.20 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | = 0.0012 [8] |
| Method | ANCOVA |

Notes:

[7] - Hierarchical testing procedure continued only, if the previous comparison was statistically significant.
[8] - Threshold for significance at 0.05 level.

| Statistical analysis title | 2nd Trend Test: SAR425899 0.16 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using ANCOVA model with treatment groups, randomization strata of screening HbA1c value (<8, >=8 %), randomization strata of Day 1 BMI (<35.0 kg/m^2, >=35.0 kg/m^2), and country as fixed effects and baseline body weight as a covariate. Here, it is test no. 4 of hierarchical testing sequence.

| Comparison groups | SAR425899 0.16 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other[9] |
| P-value | < 0.0001 [10] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -3.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.309 |
| upper limit | -1.832 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.887 |

Notes:

[9] - Hierarchical testing procedure continued only, if the previous comparison was statistically significant

[10] - Threshold for significance at 0.05 level.

| **Statistical analysis title** | 3rd Trend Test: SAR425899 0.12 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using ANCOVA model with treatment groups, randomization strata of screening HbA1c value (<8, >=8 %), randomization strata of Day 1 BMI (<35.0 kg/m^2, >=35.0 kg/m^2), and country as fixed effects and baseline body weight as a covariate. Here, it is test no. 6 of hierarchical testing sequence.

| | |
|---|---|
| Comparison groups | SAR425899 0.12 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other[11] |
| P-value | = 0.0047 [12] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -2.517 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.264 |
| upper limit | -0.77 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.891 |

Notes:

[11] - Hierarchical testing procedure continued only, if the previous comparison was statistically significant.
[12] - Threshold for significance at 0.05 level.

## Secondary: Percentage of Subjects reached HbA1c Target of <6.5% or <7% at Week 26

| End point title | Percentage of Subjects reached HbA1c Target of <6.5% or <7% at Week 26 |
|---|---|

End point description:

The analysis included assessment collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. Subjects with no measurement at Week 26 were treated as non-responders. Analysis was performed on ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 26

| **End point values** | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Subjects with HbA1c Target of <6.5% | 12.1 | 47.0 | 51.5 | 48.4 |
| Subjects with HbA1c Target of <7% | 36.4 | 66.7 | 68.2 | 65.6 |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Subjects with HbA1c Target of <6.5% | 44.8 | | | |
| Subjects with HbA1c Target of <7% | 67.2 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving >=5% or >=10% Body Weight Loss at Week 26

| End point title | Percentage of Subjects Achieving >=5% or >=10% Body Weight Loss at Week 26 |
|---|---|

End point description:

The analysis included assessment collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. Subjects with no measurement at Week 26 were treated as non-responders. Analysis was performed on ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 26

| End point values | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Subjects Achieving >=5% Body Weight Loss | 3.0 | 33.3 | 45.5 | 35.9 |
| Subjects Achieving >=10% Body Weight Loss | 0.0 | 12.1 | 13.6 | 15.6 |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Subjects Achieving >=5% Body Weight Loss | 40.3 | | | |

| | | | | |
|---|---|---|---|---|
| Subjects Achieving >=10% Body Weight Loss | 9.0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) to Week 26

| | |
|---|---|
| End point title | Change From Baseline in Fasting Plasma Glucose (FPG) to Week 26 |

End point description:

Change in FPG was calculated by subtracting baseline value from Week 26 value. Missing post-baseline values were imputed by placebo control-based MI method under the missing not at random framework. Analysis was performed on ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline, Week 26

| End point values | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -0.931 (± 0.394) | -2.408 (± 0.308) | -2.548 (± 0.301) | -2.318 (± 0.312) |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -2.124 (± 0.280) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Average 7 Point Self-Monitoring Plasma Glucose (SMPG) to Week 26

| | |
|---|---|
| End point title | Change From Baseline in Average 7 Point Self-Monitoring Plasma Glucose (SMPG) to Week 26 |

End point description:

Change in 7-point SMPG profile from baseline to Week 26 was assessed by summary statistics. Analysis was performed on ITT population. Analysis was performed on ITT population. Overall number of subjects analysed= subjects with at least 1 baseline & 1 post-baseline SMPG assessment during 26 week treatment period.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 26

| **End point values** | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 40 | 43 | 44 |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -1.82 (± 3.11) | -2.86 (± 2.62) | -2.63 (± 2.70) | -2.49 (± 3.18) |

| **End point values** | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -2.21 (± 2.33) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Requiring Rescue Therapy

| End point title | Percentage of Subjects Requiring Rescue Therapy |
|---|---|

End point description:

Rescue medication was introduced in case FPG or HbA1c values were above pre-defined thresholds, and if no reasons were found for insufficient glucose control, and appropriate action failed to decrease FPG / HbA1c under the threshold values (from baseline to Week 8: FPG >270 mg/dL 15.0 mmol/L, from Week 8 to Week 14: FPG >13.3 mmol/L, and from Week 14 to Week 26: FPG >11.1 mmol/L or HbA1c>8%). The choice of rescue therapy was at the Investigator’s discretion with the exception of using glucagon-like peptide-1 receptor (GLP-1R) agonists or dipeptidyl peptidase 4 (DPP4) inhibitors. Analysis was performed on ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to 26 weeks

| End point values | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 18.2 | 0.0 | 1.5 | 3.1 |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 6.0 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in β-Cell Function to Week 26

| End point title | Change From Baseline in β-Cell Function to Week 26 |
|---|---|

End point description:

Beta-cell function was assessed by homeostatic model assessment (HOMA)-beta, derived from FPG and fasting plasma insulin (FPI). Analysis was performed on ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 26

| End point values | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: HOMA-β | | | | |
| least squares mean (standard error) | 15.025 (± 19.785) | 26.768 (± 15.833) | 31.122 (± 16.467) | 17.932 (± 14.397) |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: HOMA-β | | | | |
| least squares mean (standard error) | 27.263 (± 13.234) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Insulin Resistance to Week 26

| End point title | Change From Baseline in Insulin Resistance to Week 26 |
|---|---|

End point description:

Insulin Resistance was assessed by homeostasis model assessment for insulin resistance (HOMA-IR), derived from FPG and FPI. Analysis was performed on ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 26

| End point values | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: HOMA-IR | | | | |
| least squares mean (standard error) | -1.315 (± 0.865) | -1.244 (± 0.670) | -2.233 (± 0.664) | -2.324 (± 0.649) |

| End point values | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: HOMA-IR | | | | |
| least squares mean (standard error) | -1.405 (± 0.613) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Pharmacodynamic Biomarkers to Week 26 - Waist and Hip Circumferences

| End point title | Change From Baseline in Pharmacodynamic Biomarkers to Week 26 - Waist and Hip Circumferences |
|---|---|

End point description:

Waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape providing a constant 100 g tension. Hip

circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. Each measurement was repeated twice; if the measurements were within 1 cm of one another, the average was calculated, and if the difference exceeded 1 cm, the measurements were repeated. Analysis was performed on ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 26

| **End point values** | Placebo | SAR425899 0.12 mg | SAR425899 0.16 mg | SAR425899 0.20 mg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 66 | 66 | 64 |
| Units: cm | | | | |
| arithmetic mean (standard error) | | | | |
| Waist Circumference | -2.0 (± 0.75) | -5.3 (± 1.34) | -2.3 (± 1.61) | -3.2 (± 0.66) |
| Hip Circumference | -1.42 (± 0.781) | -4.46 (± 1.378) | -1.97 (± 1.572) | -4.09 (± 0.945) |

| **End point values** | Liraglutide | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 67 | | | |
| Units: cm | | | | |
| arithmetic mean (standard error) | | | | |
| Waist Circumference | -4.0 (± 2.03) | | | |
| Hip Circumference | -2.56 (± 1.513) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form until 3 days after last treatment administration (Day 185).

Adverse event reporting additional description:

Reported AEs were treatment-emergent AEs that is AEs that developed/worsened or became serious during the 26-week 'treatment period' (Treatment period was defined as time from the first injection of IMP up to last injection of IMP + 3 days). Safety Analysis set.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Placebo (for SAR425899) subcutaneous (SC) injection once daily (QD) from Week 1 to Week 26, matching 3 SAR425899 dose levels of 0.12 mg, 0.16 mg and 0.20 mg.

| | |
|---|---|
| Reporting group title | SAR425899 0.06 mg |

Reporting group description:

Subjects received SAR425899 SC injection QD at dose of 0.06 for 26 weeks: 0.06 mg from Week 1 to Week 26 (for 26 weeks).

| | |
|---|---|
| Reporting group title | SAR425899 0.12 mg |

Reporting group description:

SAR425899 SC injection QD at maintenance dose of 0.12 mg for 25 weeks (Week 2 to Week 26) following 1 week dose increase step (0.06 mg at Week 1).

| | |
|---|---|
| Reporting group title | SAR425899 0.16 mg |

Reporting group description:

SAR425899 SC injection QD at maintenance dose of 0.16 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase step (0.06 mg at Week 1 and 0.12 mg at Week 2).

| | |
|---|---|
| Reporting group title | SAR425899 0.20 mg |

Reporting group description:

SAR425899 SC injection QD at maintenance dose of 0.20 mg for 23 weeks (Week 4 to Week 26) following 3 weeks dose increase step (0.06 mg at Week 1, 0.12 mg at Week 2 and 0.16 mg at Week 3).

| | |
|---|---|
| Reporting group title | Liraglutide |

Reporting group description:

Liraglutide SC injection QD at maintenance dose of 1.8 mg for 24 weeks (Week 3 to Week 26) following 2 weeks dose increase steps (0.6 mg daily at Week 1 and by 1.2 mg daily at Week 2).

| Serious adverse events | Placebo | SAR425899 0.06 mg | SAR425899 0.12 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 18 (11.11%) | 3 / 72 (4.17%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases To Adrenals | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 0 / 72 (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 |
| Pancreatic Carcinoma | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Rectal Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 0 / 72 (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 |
| Vascular disorders | | | |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 1 / 72 (1.39%) |
| 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 | | | |
| Sinus Tachycardia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 0 / 72 (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 |
| Nervous system disorders | | | |
| Hypoglycaemic Unconsciousness | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 0 / 72 (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 |
| Loss Of Consciousness | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 0 / 72 (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 |
| Gastrointestinal disorders | | | |
| Pancreatic Cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (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 |
| Pancreatitis Chronic | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (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 | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (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 |
| Infections and infestations | | | |
| Cellulitis Staphylococcal | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 0 / 72 (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 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 18 (0.00%) | 0 / 72 (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** | SAR425899 0.16 mg | SAR425899 0.20 mg | Liraglutide |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 47 (4.26%) | 2 / 67 (2.99%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases To Adrenals | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic Carcinoma | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (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 |
| Rectal Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (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 |
| Cardiac disorders | | | |
| Sinus Tachycardia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 1 / 67 (1.49%) |
| 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 | | | |
| Hypoglycaemic Unconsciousness | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss Of Consciousness | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 47 (0.00%) | 0 / 67 (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 | | | |
| Pancreatic Cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (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 |
| Pancreatitis Chronic | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (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 |
| Infections and infestations | | | |
| Cellulitis Staphylococcal | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (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 / 59 (0.00%) | 1 / 47 (2.13%) | 0 / 67 (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 / 59 (0.00%) | 1 / 47 (2.13%) | 0 / 67 (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 |

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

| **Non-serious adverse events** | Placebo | SAR425899 0.06 mg | SAR425899 0.12 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 33 (30.30%) | 18 / 18 (100.00%) | 49 / 72 (68.06%) |
| Vascular disorders | | | |
| Aortic Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Hot Flush | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 1 / 72 (1.39%) |
| occurrences (all) | 0 | 1 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 18 (5.56%) | 1 / 72 (1.39%) |
| occurrences (all) | 1 | 1 | 1 |
| Injection Site Pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injection Site Reaction | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 1 / 72 (1.39%) |
| occurrences (all) | 0 | 1 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood Creatinine Increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lipase Increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 1 / 72 (1.39%) |
| occurrences (all) | 0 | 1 | 2 |
| Weight Decreased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| Ligament Sprain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Arteriosclerosis Coronary Artery | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac Failure Chronic | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 18 (0.00%) | 4 / 72 (5.56%) |
| occurrences (all) | 2 | 0 | 4 |
| Headache | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 18 (16.67%) | 5 / 72 (6.94%) |
| occurrences (all) | 1 | 4 | 5 |
| Blood and lymphatic system disorders | | | |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal Discomfort | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 1 / 72 (1.39%) |
| occurrences (all) | 0 | 1 | 1 |
| Abdominal Distension | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 18 (11.11%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Abdominal Pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 18 (5.56%) | 1 / 72 (1.39%) |
| occurrences (all) | 2 | 1 | 1 |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 3 / 72 (4.17%) |
| occurrences (all) | 0 | 1 | 3 |
| Chronic Gastritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 18 (0.00%) | 5 / 72 (6.94%) |
| occurrences (all) | 1 | 0 | 5 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 7 / 18 (38.89%) | 15 / 72 (20.83%) |
| occurrences (all) | 2 | 10 | 23 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 6 / 18 (33.33%) | 13 / 72 (18.06%) |
| occurrences (all) | 0 | 8 | 14 |
| Eructation | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 18 (11.11%) | 1 / 72 (1.39%) |
| occurrences (all) | 0 | 3 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 4 / 72 (5.56%) |
| occurrences (all) | 0 | 1 | 4 |
| Gastrooesophageal Reflux Disease | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 18 (16.67%) | 2 / 72 (2.78%) |
| occurrences (all) | 0 | 3 | 2 |
| Gingival Pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Irritable Bowel Syndrome | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 13 / 18 (72.22%) | 33 / 72 (45.83%) |
| occurrences (all) | 8 | 22 | 45 |
| Pyloric Sphincter Insufficiency | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 33 (6.06%) | 10 / 18 (55.56%) | 21 / 72 (29.17%) |
| occurrences (all) | 2 | 17 | 32 |
| Hepatobiliary disorders | | | |
| Hepatic Steatosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Neck Pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Herpes Zoster | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 18 (11.11%) | 4 / 72 (5.56%) |
| occurrences (all) | 1 | 3 | 4 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 18 (5.56%) | 0 / 72 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| **Non-serious adverse events** | SAR425899 0.16 mg | SAR425899 0.20 mg | Liraglutide |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 59 (76.27%) | 34 / 47 (72.34%) | 34 / 67 (50.75%) |
| Vascular disorders | | | |
| Aortic Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hot Flush | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 47 (2.13%) | 1 / 67 (1.49%) |
| occurrences (all) | 1 | 1 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 5 / 47 (10.64%) | 3 / 67 (4.48%) |
| occurrences (all) | 2 | 6 | 3 |
| Injection Site Pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection Site Reaction | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 47 (2.13%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 1 | 1 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood Creatinine Increased | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lipase Increased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 47 (6.38%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 4 | 1 |
| Weight Decreased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Ligament Sprain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Cardiac disorders | | | |
| Arteriosclerosis Coronary Artery | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac Failure Chronic | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 1 / 47 (2.13%) | 2 / 67 (2.99%) |
| occurrences (all) | 3 | 1 | 2 |
| Headache | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 47 (2.13%) | 3 / 67 (4.48%) |
| occurrences (all) | 1 | 2 | 3 |
| Blood and lymphatic system disorders | | | |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal Discomfort | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 0 / 47 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 2 | 0 | 1 |
| Abdominal Distension | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | 1 / 47 (2.13%) | 1 / 67 (1.49%) |
| occurrences (all) | 7 | 1 | 2 |
| Abdominal Pain | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 5 / 47 (10.64%) | 2 / 67 (2.99%) |
| occurrences (all) | 3 | 6 | 2 |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 2 / 47 (4.26%) | 1 / 67 (1.49%) |
| occurrences (all) | 5 | 2 | 1 |
| Chronic Gastritis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 6 / 59 (10.17%) | 3 / 47 (6.38%) | 2 / 67 (2.99%) |
| occurrences (all) | 6 | 3 | 2 |

| | | | |
|---|---|---|---|
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 59 (18.64%) | 9 / 47 (19.15%) | 8 / 67 (11.94%) |
| occurrences (all) | 16 | 14 | 10 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 3 / 47 (6.38%) | 5 / 67 (7.46%) |
| occurrences (all) | 4 | 4 | 5 |
| Eructation | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 1 / 47 (2.13%) | 0 / 67 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 1 / 47 (2.13%) | 3 / 67 (4.48%) |
| occurrences (all) | 2 | 1 | 3 |
| Gastrooesophageal Reflux Disease | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 47 (4.26%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 2 | 1 |
| Gingival Pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Irritable Bowel Syndrome | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 33 / 59 (55.93%) | 26 / 47 (55.32%) | 21 / 67 (31.34%) |
| occurrences (all) | 41 | 36 | 25 |
| Pyloric Sphincter Insufficiency | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 14 / 59 (23.73%) | 17 / 47 (36.17%) | 1 / 67 (1.49%) |
| occurrences (all) | 23 | 24 | 1 |
| Hepatobiliary disorders | | | |
| Hepatic Steatosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 47 (2.13%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Neck Pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Herpes Zoster | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | 4 / 47 (8.51%) | 3 / 67 (4.48%) |
| occurrences (all) | 5 | 4 | 3 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 47 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 January 2017 | - To add urinary free-cortisol and creatinine measured in 24 hours urines at baseline and in Visit 12 (Week 26, End of treatment).<br>- To make a change to the exclusion criteria (add a clarification on methods of contraception).<br>- To add metabolic acidosis as a new adverse event of special interest.<br>- To add amylase/lipase assessment in Visits 9 and 11. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported