



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
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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/m² vs ≥35.0 kg/m²) 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
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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
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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
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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
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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			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	56.2	56.8	54.5
standard deviation	± 9.3	± 9.0	± 10.1
Gender categorical			
Units: Subjects			
Female	15	29	35
Male	18	37	31
BMI			
Units: kg/m ²			
arithmetic mean	32.07	33.67	34.23
standard deviation	± 4.41	± 5.37	± 4.68
Baseline HbA1c			
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 Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	55.0 ± 10.4	56.1 ± 11.4	-
Gender categorical Units: Subjects			
Female	28	36	143
Male	36	31	153
BMI Units: kg/m ² arithmetic mean standard deviation	33.63 ± 4.35	34.23 ± 5.51	-
Baseline HbA1c Units: Percentage of HbA1c arithmetic mean standard deviation	8.14 ± 0.94	8.11 ± 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 (\pm 0.118)			

Statistical analyses

Statistical analysis title	1st trend test:SAR425899 0.20,0.16,0.12 mg,placebo
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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/m², ≥ 35.0 kg/m²), 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
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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/m², ≥ 35.0 kg/m²), 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
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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/m², >=35.0 kg/m²), 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
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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
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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 (\pm 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

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 $\geq 5\%$ or $\geq 10\%$ Body Weight Loss at Week 26

End point title	Percentage of Subjects Achieving $\geq 5\%$ or $\geq 10\%$ Body Weight Loss at Week 26
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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
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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 $\geq 5\%$ Body Weight Loss	3.0	33.3	45.5	35.9
Subjects Achieving $\geq 10\%$ 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 $\geq 5\%$ Body Weight Loss	40.3			

Subjects Achieving $\geq 10\%$ Body Weight Loss	9.0			
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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 (\pm 0.394)	-2.408 (\pm 0.308)	-2.548 (\pm 0.301)	-2.318 (\pm 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 (\pm 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
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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
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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
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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
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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 (\pm 19.785)	26.768 (\pm 15.833)	31.122 (\pm 16.467)	17.932 (\pm 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 (\pm 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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

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

Injury, poisoning and procedural complications Ligament Sprain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	0 / 72 (0.00%) 0
Cardiac disorders Arteriosclerosis Coronary Artery subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	0 / 72 (0.00%) 0
Cardiac Failure Chronic subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	0 / 72 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 18 (0.00%) 0	4 / 72 (5.56%) 4
Headache subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 18 (16.67%) 4	5 / 72 (6.94%) 5
Blood and lymphatic system disorders Splenomegaly subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	0 / 72 (0.00%) 0
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	1 / 72 (1.39%) 1
Abdominal Distension subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 18 (11.11%) 2	0 / 72 (0.00%) 0
Abdominal Pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2	1 / 18 (5.56%) 1	1 / 72 (1.39%) 1
Abdominal Pain Upper subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	3 / 72 (4.17%) 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 occurrences (all)	2 / 33 (6.06%) 2	10 / 18 (55.56%) 17	21 / 72 (29.17%) 32
Hepatobiliary disorders Hepatic Steatosis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	0 / 72 (0.00%) 0
Musculoskeletal and connective tissue disorders Neck Pain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 18 (5.56%) 1	0 / 72 (0.00%) 0
Infections and infestations Herpes Zoster subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0 2 / 33 (6.06%) 2	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1	0 / 72 (0.00%) 0 0 / 72 (0.00%) 0
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 0 / 33 (0.00%) 0	2 / 18 (11.11%) 3 1 / 18 (5.56%) 1	4 / 72 (5.56%) 4 0 / 72 (0.00%) 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 occurrences (all) Hot Flush subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0 0 / 59 (0.00%) 0	0 / 47 (0.00%) 0 0 / 47 (0.00%) 0	0 / 67 (0.00%) 0 0 / 67 (0.00%) 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 occurrences (all)	0 / 59 (0.00%) 0	1 / 47 (2.13%) 1	0 / 67 (0.00%) 0
Musculoskeletal and connective tissue disorders Neck Pain subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	0 / 47 (0.00%) 0	0 / 67 (0.00%) 0
Infections and infestations Herpes Zoster subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0 2 / 59 (3.39%) 2	0 / 47 (0.00%) 0 0 / 47 (0.00%) 0	0 / 67 (0.00%) 0 0 / 67 (0.00%) 0
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 5 0 / 59 (0.00%) 0	4 / 47 (8.51%) 4 0 / 47 (0.00%) 0	3 / 67 (4.48%) 3 0 / 67 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2017	<ul style="list-style-type: none">- To add urinary free-cortisol and creatinine measured in 24 hours urines at baseline and in Visit 12 (Week 26, End of treatment).- To make a change to the exclusion criteria (add a clarification on methods of contraception).- To add metabolic acidosis as a new adverse event of special interest.- 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