Clinical trial results:
Six-month, Randomized, Open-label, Parallel-group Comparison of the Insulin Analog SAR342434 to Humalog® in Adult Patients With Type 2 Diabetes Mellitus also Using Insulin Glargine

Summary

EudraCT number	2014-002844-42
Trial protocol	HU DE IT ES
Global end of trial date	16 February 2016

Results information

Result version number	v1 (current)
This version publication date	02 March 2017
First version publication date	02 March 2017

Trial information

Trial identification

Sponsor protocol code	EFC13403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02294474
WHO universal trial number (UTN)	U1111-1156-4296
Other trial identifiers	Study Name: SORELLA 2

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	11 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of SAR342434 versus Humalog in terms of changes in glycated hemoglobin (HbA1c) from baseline to Week 26 in subjects with type 2 diabetes mellitus also using Lantus.

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:

Insulin Glargine 100 U/ml (Lantus) was used as the mandatory background basal insulin therapy. Doses were adjusted to achieve fasting, pre-breakfast self-measured plasma glucose (SMPG) of 4.4 to 7.2 mmol/l (80 to 130 mg/dL). Non-insulin antihyperglycemic background therapy (except injectable peptides) taken at a stable dose for at least 3 months prior to the screening visit may be continued during the study. Doses were to be kept stable throughout the study unless there was a specific safety issue related to these treatments.

Evidence for comparator: -

Actual start date of recruitment	14 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 40
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Argentina: 37
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Turkey: 10

Country: Number of subjects enrolled	United States: 242
Worldwide total number of subjects	505
EEA total number of subjects	154

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)	281
From 65 to 84 years	222
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 103 centers in 12 countries. A total of 707 subjects were screened between 14 January 2015 and 24 July 2015, of which 202 were screen failures. Screen failures were mainly due to glycated hemoglobin (HbA1c) <6.5% or >10% at screening visit.

Pre-assignment

Screening details:

A total of 505 subjects were randomized and treated in the study. Randomization was stratified by HbA1c at the screening visit (<8%, ≥8%) and prior use of Humalog (Yes, No). Assignment to arms was done centrally using interactive voice/web response system in 1:1 ratio (SAR342434: Humalog).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SAR342434

Arm description:

SAR342434 before meals intake on top of once daily (QD) Insulin Glargine, up to Week 26.

Arm type	Experimental
Investigational medicinal product name	SAR342434
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SAR342434 100 U/mL (dose range of 1 Unit to 80 Units) self-administered by subcutaneous (SC) injection, immediately (within 5-10 minutes) before meals intake. Dose adjusted to achieve a 2-hour post prandial glucose (PPG) in range of 6.7 to 8.9 mmol/L (120 to 160 mg/dL) while avoiding hypoglycemia.

Arm title	Humalog

Arm description:

Humalog before meals intake on top of QD Insulin Glargine, up to Week 26.

Arm type	Active comparator
Investigational medicinal product name	Humalog
Investigational medicinal product code	
Other name	Insulin Lispro
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Humalog 100 U/ml (dose range of 1 unit to 60 units) self-administered by SC injection, immediately (within 5-10 minutes) before meals intake. Dose adjusted to achieve a 2-hour PPG in range of 6.7 to 8.9 mmol/L (120 to 160 mg/dL) while avoiding hypoglycemia.

Number of subjects in period 1	SAR342434	Humalog
Started	253	252
Completed	228	230
Not completed	25	22
Other than specified above	12	12
Adverse event	7	7
Poor compliance to protocol	4	2
Lack of efficacy	2	1

Baseline characteristics

Reporting groups	
Reporting group title	SAR342434
Reporting group description:	
SAR342434 before meals intake on top of once daily (QD) Insulin Glargine, up to Week 26.	
Reporting group title	Humalog
Reporting group description:	
Humalog before meals intake on top of QD Insulin Glargine, up to Week 26.	

Reporting group values	SAR342434	Humalog	Total
Number of subjects	253	252	505
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.1	62.8	
standard deviation	± 9.4	± 8.9	-
Gender categorical Units: Subjects			
Female	117	120	237
Male	136	132	268
Previous meal time insulin Units: Subjects			
Humalog/Liprolog	133	126	259
NovoLog/NovoRapid	119	124	243
Both Humalog/Liprolog and NovoLog/NovoRapid	1	1	2
None of the above	0	1	1
Randomization Strata of Screening HbA1c Units: Subjects			
<8 %	105	104	209
≥8 %	148	148	296
Body mass index (BMI) Units: kg/m^2			
arithmetic mean	32.3	32.1	
standard deviation	± 4.8	± 4.8	-
Duration of type 2 diabetes mellitus (T2DM) Units: years			
arithmetic mean	16.6	17.52	
standard deviation	± 7.93	± 8.67	-
Glycated Haemoglobin (HbA1c %) Units: percentage of hemoglobin			
arithmetic mean	8	8.03	
standard deviation	± 0.86	± 0.91	-
Average Daily Basal Insulin Dose			
Data for average daily basal insulin dose is reported for 476 subjects.			

Units: Units (U)/kg			
arithmetic mean	0.477	0.458	
standard deviation	± 0.265	± 0.239	-
Average Daily Mealtime Insulin Dose			
Data for average daily mealtime insulin dose is reported for 474 subjects.			
Units: U/kg			
arithmetic mean	0.449	0.433	
standard deviation	± 0.294	± 0.315	-
Average Daily Total Insulin Dose			
Data for average daily total insulin dose is reported for 472 subjects.			
Units: U/kg			
arithmetic mean	0.927	0.888	
standard deviation	± 0.47	± 0.449	-

End points

End points reporting groups

Reporting group title	SAR342434
Reporting group description:	
SAR342434 before meals intake on top of once daily (QD) Insulin Glargine, up to Week 26.	
Reporting group title	Humalog
Reporting group description:	
Humalog before meals intake on top of QD Insulin Glargine, up to Week 26.	

Primary: Change in HbA1c From Baseline to Week 26

End point title	Change in HbA1c From Baseline to Week 26
End point description:	
Change in HbA1c was calculated by subtracting baseline value from Week 26 value. Adjusted least square means and standard errors were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data, using all post-baseline HbA1c data available during the 6-month period and adequate contrasts at Week 26. Analysis was performed on intent-to-treat (ITT) population that included all randomized subjects, irrespective of compliance with the study protocol and procedures. Here, number of subjects analyzed = subjects with at least one post-baseline HbA1c assessment during the 6-month study period.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	246		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.92 (± 0.051)	-0.85 (± 0.051)		

Statistical analyses

Statistical analysis title	SAR342434 vs. Humalog
Statistical analysis description:	
Analysis was performed using a MMRM approach with treatment groups, randomization strata, visit (Week 12, Week 26) and treatment-by-visit interaction as fixed categorical effects and baseline HbA1c value and baseline HbA1c value-by-visit interaction as continuous fixed covariates. An unstructured correlation matrix was used to model within-subject errors.	
Comparison groups	SAR342434 v Humalog

Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.215
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.072

Notes:

[1] - Non-inferiority of SAR342434 over Humalog was demonstrated if upper bound of 2-sided 95% confidence interval(CI) of difference between SAR342434 & Humalog was <0.3%.Inverse non-inferiority of Humalog over SAR342434 was tested using hierarchical step-down testing procedure: if non-inferiority of SAR342434 over Humalog was demonstrated,then inverse non-inferiority of Humalog over SAR342434 was tested and demonstrated if lower bound of 2-sided 95% CI of difference between SAR342434 & Humalog >-03%.

Secondary: Percentage of Subjects with HbA1c <7.0% and ≤6.5% at Week 26

End point title	Percentage of Subjects with HbA1c <7.0% and ≤6.5% at Week 26

End point description:

Subjects who had no available assessment for HbA1c at Week 26 were considered as non-responders. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 26

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	252		
Units: percentage of subject				
number (not applicable)				
HbA1c <7.0%	42.3	40.5		
HbA1c ≤6.5%	27.3	24.2		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change in FPG was calculated by subtracting baseline value from Week 26 value. Adjusted least squares means and standard errors were obtained from a MMRM approach to account for missing data, using all post-baseline FPG data available during the 6-month period and adequate contrasts at Week 26.

Analysis was performed on ITT population. Here, number of subjects analyzed = subjects with at least one post-baseline FPG assessment during the 6-months study period.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	235		
Units: mmol/L				
least squares mean (standard error)	-0.62 (± 0.176)	-0.67 (± 0.176)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Mean 24-Hour Plasma Glucose Concentration from Baseline to Week 26

End point title	Change in Mean 24-Hour Plasma Glucose Concentration from Baseline to Week 26

End point description:

The mean 24-hour plasma glucose concentration was calculated based on 7-point self-measured plasma glucose (SMPG) profiles with plasma glucose measurements before and 2-hours after each main meal and at bedtime. 7-point SMPGs were performed at least two times in a week before baseline, before visit Week 12 and before visit Week 26. Mean 24-hour plasma glucose concentration was calculated for each profile and then averaged across profiles performed in the week before a visit. Change in mean 24-hour plasma glucose concentration was calculated by subtracting baseline value from Week 26 value. Adjusted least squares means and standard errors were obtained from a MMRM to account for missing data, using all post-baseline data available during 6-month period and adequate contrasts at Week 26. Analysis was performed on ITT population. Here, number of subjects analyzed=subjects with at least one post-baseline mean 24-hour plasma glucose concentration assessment during 6-month study period.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	210		
Units: mmol/L				
least squares mean (standard error)	-1 (± 0.137)	-0.91 (± 0.133)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Post Prandial Glucose (PPG) Excursion From Baseline to Week 26

End point title	Change in Post Prandial Glucose (PPG) Excursion From Baseline to Week 26

End point description:

Plasma glucose excursions were calculated at breakfast, lunch and dinner for each 7-point SMPG profile, as 2-hour postprandial glucose (PPG) minus plasma glucose value obtained 30 minutes prior to start of the meal. Values of plasma glucose excursions at each visit were then calculated as average across the profiles performed in the week before the visit. Change in PPG excursions was calculated by subtracting baseline value from Week 26 value. Adjusted least squares means and standard errors were obtained from a MMRM to account for missing data, using all post-baseline data available during the 6-month period and adequate contrasts at Week 26. Analysis was performed on ITT population. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	252		
Units: mmol/L				
least squares mean (standard error)				
At breakfast (n=194, 204)	-0.72 (± 0.236)	-0.23 (± 0.228)		
At lunch (n=195, 200)	0.06 (± 0.255)	0.11 (± 0.25)		
At dinner (n=190, 193)	0.11 (± 0.264)	-0.1 (± 0.264)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia and Severe Hypoglycemia)

End point title	Percentage of Subjects with Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia and Severe Hypoglycemia)

End point description:

Percentage of subjects with at least one treatment emergent hypoglycemia reported at any time of the day were reported. Severe hypoglycemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration, if no plasma glucose measurement was available. Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L). Hypoglycemic episodes with plasma glucose of 54 mg/dL (<3.0 mmol/L) were also analyzed. Analysis was performed on safety population that included all subjects randomized and exposed to at least 1 dose of investigational medicinal product (IMP) (SAR342434 or Humalog), regardless of the amount of treatment administered.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (maximum treatment exposure: 210 days)

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	252		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	68.4	74.6		
Severe hypoglycemia	2.4	1.6		
Documented Symptomatic Hypoglycemia (≤3.9mmol/L)	60.1	66.3		
Documented Symptomatic Hypoglycemia (<3.0mmol/L)	28.9	27.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Hypersensitivity Reactions and Injection Site Reactions

End point title	Percentage of Subjects with Hypersensitivity Reactions and Injection Site Reactions

End point description:

Analysis was performed on safety population that included all subjects randomized and exposed to at least 1 dose of IMP (SAR342434 or Humalog), regardless of the amount of treatment administered.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (maximum treatment exposure: 210 days)

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	252		
Units: percentage of subjects				
number (not applicable)				
Any hypersensitivity reactions	4	3.6		
Any injection site reactions	0.4	1.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-emergent Anti-insulin Antibodies (AIAs)

End point title	Percentage of Subjects with Treatment-emergent Anti-insulin Antibodies (AIAs)

End point description:

Subjects with treatment-emergent AIA (incidence) were reported (as subjects with treatment-boosted or treatment-induced AIAs). Subjects with treatment-induced AIAs were subjects who developed AIA following IMP administration (subjects with at least one positive AIA sample at any time during on-treatment period, in those subjects without pre-existing AIA or with missing baseline sample). Subjects with treatment-boosted AIAs were subjects with pre-existing AIAs that were boosted significant higher titer following IMP administration (subjects with at least one AIA sample with at least a 4-fold increase in titers compared to baseline value at any time during on-treatment period, in those subjects with pre-existing AIA). Analysis was performed on anti-insulin antibody population that included all subjects from the safety population with at least one AIA sample available for analysis during the 6-months on-treatment period.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (maximum treatment exposure: 210 days)

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	248		
Units: percentage of subjects				
number (not applicable)	18.8	14.5		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Daily Insulin Dose from Baseline to Week 26

End point title	Change in Daily Insulin Dose from Baseline to Week 26

End point description:

Change in daily insulin dose (basal, mealtime and total) was calculated by subtracting baseline value from Week 26 value. Analysis was performed on safety population. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 26

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	252		
Units: U/kg				
arithmetic mean (standard deviation)				
Basal insulin (n=196, 218)	0.082 (± 0.133)	0.071 (± 0.122)		
Mealtime insulin (n=197, 218)	0.087 (± 0.209)	0.08 (± 0.248)		
Total insulin (n=196, 216)	0.172 (± 0.296)	0.151 (± 0.297)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Day 183) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed, worsened or became serious during the 'on treatment period' (time from first injection of IMP up to 1 day after the last injection of IMP).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	SAR342434

Reporting group description:

SAR342434 before meals intake on top of QD Insulin Glargine, up to Week 26.

Reporting group title	Humalog

Reporting group description:

Humalog before meals intake on top of QD Insulin Glargine, up to Week 26.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events with a frequency ≥5% were recorded during the study.

Serious adverse events	SAR342434	Humalog	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 253 (5.53%)	27 / 252 (10.71%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Carcinoma Of The Bladder			

subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic Carcinoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			

subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 253 (0.00%)	3 / 252 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 253 (0.00%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle Branch Block Left			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 253 (0.40%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary Failure			

subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary Artery Disease			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Cardiomyopathy			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Bradycardia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gliosis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			

subjects affected / exposed	2 / 253 (0.79%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous Haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis Erosive			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 253 (0.79%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Spinal Stenosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 253 (0.79%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 253 (0.00%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SAR342434	Humalog	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 253 (0.00%)	0 / 252 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2015	Clarified the following points: -appropriateness of measurements referring to efficacy and safety endpoints; -procedures of notification in case of changes of the pre-defined injection area; -criteria for permanent discontinuation due to subject's request; -procedures and consequences of subject withdrawal from the study; -addition of pregnancy, symptomatic overdose and alanine transaminase (ALT) value increase as adverse events of special interests (AESIs) to be reported to health authorities; -Definition of hypoglycemia: asymptomatic and relative hypoglycemia have been added; -Procedures of notification of ALT increases respect to baselines values.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported