Clinical trial results:
Six-month, Randomized, Open-label, Parallel-group Comparison of SAR342434 to Humalog® in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period

Summary

EudraCT number	2013-002945-12
Trial protocol	DE HU ES PL
Global end of trial date	01 July 2016

Results information

Result version number	v1 (current)
This version publication date	14 July 2017
First version publication date	14 July 2017

Trial information

Trial identification

Sponsor protocol code	EFC12619

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02273180
WHO universal trial number (UTN)	U1111-1131-5038
Other trial identifiers	Study Name: SORELLA 1

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	20 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of SAR342434 versus Humalog in terms of change in glycated hemoglobin (HbA1c) from baseline to Week 26 in subjects with Type 1 diabetes mellitus (T1DM) also using insulin glargine (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 was 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 given as the mandatory background basal insulin therapy and was injected once daily (QD) subcutaneously consistent with the local label. Doses of Lantus were adjusted to achieve glycemic target for fasting, pre-prandial plasma glucose (self measured plasma glucose [SMPG]) between 4.4 to 7.2 mmol/L (80 to 130 mg/dL) without hypoglycemia.

Evidence for comparator: -

Actual start date of recruitment	28 October 2014
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	Japan: 61
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	United States: 218
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Hungary: 52
Worldwide total number of subjects	507
EEA total number of subjects	178

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)	463
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 89 centers in 8 countries. A total of 668 subjects were screened between 28 October 2014 and 04 June 2015, of which 161 subjects were screen failures. Screen failures were mainly due to HbA1c <7.0% or >10% at the screening visit.

Pre-assignment

Screening details:

A total of 506 subjects were randomized and treated in the study. Randomization was stratified by HbA1c at the screening visit (<8%, >=8%), prior use of Humalog/Liprolog (Yes, No) and geographical region (Non-Japan, Japan). 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 each meal intake on top of QD Insulin Glargine, up to Week 52.

Arm type	Experimental
Investigational medicinal product name	SAR342434
Investigational medicinal product code	
Other name	Insulin Lispro
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 deep SC injection, immediately (within 5-10 minutes) before any meal intake. Dose adjusted to achieve a 2-hour post prandial plasma 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 each meal intake on top of QD Insulin Glargine, up to Week 52.

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 deep SC injection, immediately (within 5-10 minutes) before any meal 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	254
Treated	252	254
Completed	226	235
Not completed	27	19
Randomized but not treated	1	-
Adverse event	2	2
Other than specified	21	10
Poor compliance to protocol	1	7
Hypoglycemia not reported as serious adverse event	1	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	SAR342434
Reporting group description:	
SAR342434 before each meal intake on top of QD Insulin Glargine, up to Week 52.	
Reporting group title	Humalog
Reporting group description:	
Humalog before each meal intake on top of QD Insulin Glargine, up to Week 52.	

Reporting group values	SAR342434	Humalog	Total
Number of subjects	253	254	507
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	43.3	42.6	
standard deviation	± 14.5	± 13.9	-
Gender categorical			
Units: Subjects			
Female	104	101	205
Male	149	153	302
Previous mealtime insulin type			
Units: Subjects			
Humalog/Liprolog	155	152	307
NovoLog/NovoRapid	95	95	190
Both Humalog/Liprolog and NovoLog/NovoRapid	3	7	10
Randomization Strata of Screening HbA1c			
Units: Subjects			
<8 %	99	99	198
>=8%	154	155	309
Randomization strata of geographical region			
Units: Subjects			
Japan	31	30	61
Non-Japan	222	224	446
Body mass index (BMI)			
Units: kg/m^2			
arithmetic mean	26.2	25.8	
standard deviation	± 4	± 4.1	-
Duration of T1DM			
Units: years			
arithmetic mean	19.53	18.57	
standard deviation	± 12.63	± 11.99	-
Average Daily Basal Insulin Dose			
Data for average daily basal insulin dose is reported for a total of 490 subjects (SAR342434: 245 and			

Humalog: 245).			
Units: Units (U)/kg			
arithmetic mean	0.339	0.33	
standard deviation	± 0.195	± 0.141	-
Average Daily Mealtime Insulin Dose			
Data for average daily mealtime insulin dose is reported for a total of 485 subjects (SAR342434: 241 and Humalog: 244).			
Units: U/kg			
arithmetic mean	0.364	0.355	
standard deviation	± 0.175	± 0.168	-
Average Daily Total Insulin Dose			
Data for average daily total insulin dose is reported for a total of 480 subjects (SAR342434: 239 and Humalog: 241).			
Units: U/kg			
arithmetic mean	0.704	0.685	
standard deviation	± 0.309	± 0.242	-
Glycated Haemoglobin (HbA1c %)			
Units: percentage of hemoglobin			
arithmetic mean	8.07	7.99	
standard deviation	± 0.79	± 0.64	-

End points

End points reporting groups

Reporting group title	SAR342434
Reporting group description:	
SAR342434 before each meal intake on top of QD Insulin Glargine, up to Week 52.	
Reporting group title	Humalog
Reporting group description:	
Humalog before each meal intake on top of QD Insulin Glargine, up to Week 52.	

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 main 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 main 6-month 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	247	249		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.42 (± 0.051)	-0.47 (± 0.05)		

Statistical analyses

Statistical analysis title	SAR342434 vs. Humalog
Statistical analysis description:	
Analysis was performed using a MMRM approach with treatment groups, randomization strata, visits (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	496
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Least square (LS) mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	0.197
Variability estimate	Standard error of the mean
Dispersion value	0.071

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, demonstrated if lower bound of 2-sided 95%CI of difference between SAR342434 & Humalog was >-0.3%.

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

End point title	Percentage of Subjects with HbA1c <7.0% 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	254		
Units: percentage of subjects				
number (not applicable)	22.5	21.7		

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 main 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 main 6-month 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	240	242		
Units: mmol/L				
least squares mean (standard error)	-0.46 (± 0.248)	-0.62 (± 0.248)		

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:

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 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 the main 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 the main 6-month 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	216	207		
Units: mmol/L				
least squares mean (standard error)	-0.23 (± 0.145)	-0.49 (± 0.148)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in Post Prandial Plasma 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 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 main 6-month period and adequate contrasts at Week 26. Analysis was performed on ITT population. Here, 'n' signifies number of subjects with at least one post-baseline data during the main 6-month period for specified categories.

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	254		
Units: mmol/L				
least squares mean (standard error)				
At breakfast (n=205, 198)	-0.46 (± 0.297)	0.19 (± 0.297)		
At lunch (n=207, 193)	0.14 (± 0.298)	-0.26 (± 0.309)		
At dinner (n=208, 190)	0.48 (± 0.308)	0.56 (± 0.324)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hypoglycemia Events (Any Hypoglycemia, Documented Symptomatic Hypoglycemia and Severe Hypoglycemia) Per Subject-Year

End point title	Number of Hypoglycemia Events (Any Hypoglycemia, Documented Symptomatic Hypoglycemia and Severe Hypoglycemia) Per Subject-Year

End point description:

Number of treatment-emergent hypoglycemia per subject-year of exposure 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. 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: 400 days)

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	254		
Units: events per subject-year				
number (not applicable)				
Any hypoglycemia	90.71	92.7		
Severe hypoglycemia	0.73	0.28		
Documented Symptomatic Hypoglycemia (<=3.9 mmol/L)	29.36	31.37		
Documented Symptomatic Hypoglycemia (<3.0 mmol/L)	6.29	6.85		

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.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (maximum treatment exposure: 400 days)

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	254		
Units: percentage of subjects				
number (not applicable)				
Any hypersensitivity reactions	6	6.3		
Any injection site reactions	1.2	1.2		

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 those 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 those with pre-existing AIAs that were boosted to a 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 randomized and exposed to at least 1 dose of IMP (SAR342434 or Humalog) with at least one AIA sample available for analysis during the 12-month 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: 400 days)

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	252		
Units: percentage of subjects				
number (not applicable)	22.6	24.2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Daily Insulin Dose from Baseline to Week 26 and Week 52

End point title	Change in Daily Insulin Dose from Baseline to Week 26 and Week 52

End point description:

Change in daily insulin dose (basal, mealtime and total) was calculated by subtracting baseline value from Week 26 and Week 52 values respectively. Analysis was performed on safety population. Here, 'n' signifies number of subjects with available data for specified categories.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 26, Week 52

End point values	SAR342434	Humalog		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	254		
Units: U/kg				
arithmetic mean (standard deviation)				
Basal insulin dose at Week 26 (n=223,229)	0.03 (± 0.236)	0.014 (± 0.006)		

Mealtime insulin dose at Week 26 (n=217,222)	0.005 (± 0.112)	-0.005 (± 0.089)		
Total insulin dose at Week 26 (n=215,220)	0.019 (± 0.134)	0.01 (± 0.111)		
Basal insulin dose at Week 52 (n=199,209)	0.046 (± 0.364)	0.013 (± 0.066)		
Mealtime insulin dose at Week 52 (n=192, 203)	0.018 (± 0.117)	0.007 (± 0.104)		
Total insulin dose at Week 52 (n=191, 200)	0.039 (± 0.135)	0.019 (± 0.127)		

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 up to the final visit (maximum treatment exposure: 400 days) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment emergent AEs that is AEs that developed/worsened or became serious and deaths that occurred during the 'on treatment period' (time from first injection of IMP up to 1 day after the last injection of IMP). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	SAR342434

Reporting group description:

SAR342434 before each meal intake on top of QD Insulin Glargine, up to Week 52.

Reporting group title	Humalog

Reporting group description:

Humalog before each meal intake on top of QD Insulin Glargine, up to Week 52.

Serious adverse events	SAR342434	Humalog	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 252 (7.94%)	19 / 254 (7.48%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastrectomy			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Threatened			

subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
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			
Cardiac Death			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Social circumstances			
Pregnancy Of Partner			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	3 / 252 (1.19%)	2 / 254 (0.79%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle Fracture			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Injury			

subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius Fracture			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	0 / 252 (0.00%)	2 / 254 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrong Drug Administered			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ventricle Dilatation			

subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Coma			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Seizure			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	6 / 252 (2.38%)	6 / 254 (2.36%)	
occurrences causally related to treatment / all	4 / 6	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis Haemorrhagic			

subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
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			
Osteoarthritis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 252 (0.40%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Viral Infection			

subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 252 (0.40%)	2 / 254 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	3 / 252 (1.19%)	3 / 254 (1.18%)	
occurrences causally related to treatment / all	5 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 254 (0.39%)	
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	46 / 252 (18.25%)	41 / 254 (16.14%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 252 (13.10%)	28 / 254 (11.02%)	
occurrences (all)	45	33	
Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	15 / 252 (5.95%) 15	14 / 254 (5.51%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2014	Following changes were made: • Clarification of Inclusion criteria (frequency of injections with meal time insulin therapy) were added; • Determination of AIA at Week 4 was added; • Monitoring of elevated AIA titers until return to baseline were added in subjects in whom the Allergic Reaction Assessment Committee (ARAC) assessed AIA-mediated hypersensitivity reactions or insulin resistance; • Clarification of procedure related to premature discontinuation of treatment; • Clarification of electronic transfer of patient reported outcome (PRO) (7 point and 3 point SMPG profiles, insulin doses and hypoglycemia); • Option of supplying IMP and non-investigational medicinal product (NIMP) by direct mail was removed; •Changes were done to statistical analysis: if non-inferiority of SAR342434 over Humalog was demonstrated, the inverse non-inferiority of Humalog over SAR342434 was to be tested. Analyses for the description of missing data was added; • Changes to statistical analysis: additional information on treatment group presented in the descriptive analyses: overall (pooling Humalog US and Humalog EU groups) and then by subgroup of Humalog-US (corresponding to US and Japan subjects)/Humalog EU (outside US/Japan); • Changes were done to statistical analysis: addition of an on-treatment sensitivity analysis.
05 February 2016	Following changes were made: •Clarification on ARAC procedure with elevated AIA titers: follow-up by the sponsor of elevated AIA titers until return to baseline value or until ARAC decided that no further follow-up deemed necessary in subjects whom the ARAC assessed an AIA-mediated hypersensitivity reaction or insulin resistance; •Clarification on inclusion criteria and exclusion criteria for use of Liprolog was added; •Clarification of procedure related to premature treatment discontinuation; •Editorial changes; •Change of reporting of asymptomatic overdose: not considered anymore as an adverse event of special interest (AESI).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported