Clinical trial results:
Six-month, Randomized, Open-label, Parallel-group Comparison of SAR341402 to NovoLog®/NovoRapid® in Adult Patients With Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period

Summary

EudraCT number	2017-000091-28
Trial protocol	HU FI DE PL
Global end of trial date	12 January 2019

Results information

Result version number	v1
This version publication date	22 January 2020
First version publication date	22 January 2020

Trial information

Trial identification

Sponsor protocol code	EFC15081

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03211858
WHO universal trial number (UTN)	U1111-1191-5775
Other trial identifiers	Study name: Gemelli 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	24 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of SAR341402 versus NovoLog/NovoRapid in glycated hemoglobin A1c (HbA1c) change from baseline to Week 26 in subjects with type 1 or type 2 diabetes mellitus (T1DM or T2DM) 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 units per millilitre (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 between 4.4 to 7.2 millimoles per litre (mmol/L) (80 to 130 milligram/deciLitre [mg/dL]) without hypoglycemia.

Evidence for comparator: -

Actual start date of recruitment	02 August 2017
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	Poland: 56
Country: Number of subjects enrolled	Finland: 23
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hungary: 73
Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	United States: 335
Worldwide total number of subjects	597
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)	498
From 65 to 84 years	98
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 82 centres in 7 countries. A total of 846 subjects were screened between 02 August 2017 and 29 December 2017, of which 249 subjects were screen failures. Screen failures were mainly due to HbA1c level less than (<) 7.0 percent (%) or greater than (>) 10% at the screening visit.

Pre-assignment

Screening details:

Randomisation was stratified by HbA1c at screening visit (<8%, greater than or equal to [>=] 8%), prior use of NovoLog/NovoRapid (Yes, No), geographical region (Europe, United States [US], Japan) and type 1 or 2 of diabetes mellitus (T1DM/T2DM [US only]). Assigned to arms in 1:1 ratio (SAR341402: NovoLog/NovoRapid).

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	SAR341402

Arm description:

SAR341402 100 U/mL subcutaneous (SC) injection, before meals intake on top of QD Insulin Glargine, up to Week 52.

Arm type	Experimental
Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	SAR341402
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SAR341402 100 U/mL (dose range of 1 unit to 80 units), once daily self-administered SC injection in 3 mL pre-filled disposable SoloSTAR® pens. Dose adjusted to achieve a 2-hour postprandial plasma glucose of <10mmol/L (<180mg/dL).

Arm title	NovoLog/NovoRapid

Arm description:

NovoLog/NovoRapid 100 U/mL SC injection, before meals intake on top of QD Insulin Glargine, up to Week 52.

Arm type	Active comparator
Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	
Other name	Novolog/Novorapid
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NovoLog/NovoRapid 100 U/mL (dose range of 1 unit to 60 units), once daily self-administered SC injection in 3 mL pre-filled disposable FlexPens. Dose adjusted to achieve a 2-hour postprandial plasma glucose of <10mmol/L (<180mg/dL) while avoiding hypoglycemia.

Number of subjects in period 1	SAR341402	NovoLog/NovoRapid
Started	301	296
Treated	301	296
Completed	264	263
Not completed	37	33
Adverse Event	8	6
Non-serious Hypoglycemia	1	-
Other than specified	22	21
Poor compliance to protocol	6	2
Lack of efficacy	-	4

Baseline characteristics

Reporting groups	
Reporting group title	SAR341402
Reporting group description:	
SAR341402 100 U/mL subcutaneous (SC) injection, before meals intake on top of QD Insulin Glargine, up to Week 52.	
Reporting group title	NovoLog/NovoRapid
Reporting group description:	
NovoLog/NovoRapid 100 U/mL SC injection, before meals intake on top of QD Insulin Glargine, up to Week 52.	

Reporting group values	SAR341402	NovoLog/NovoRapid	Total
Number of subjects	301	296	597
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	48.4	47.8	
standard deviation	± 14.8	± 15.4	-
Gender categorical Units: Subjects			
Female	122	119	241
Male	179	177	356
Race Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	37	37	74
Native Hawaiian or Other Pacific Islander	3	0	3
Black or African American	11	8	19
White	248	242	490
More than one race	0	3	3
Unknown or Not Reported	2	4	6
Baseline Body Mass Index (BMI) Units: kilogram/metre square^2 (kg/m^2)			
arithmetic mean	27.45	27.46	
standard deviation	± 4.58	± 4.99	-
Duration of Diabetes Units: years			
arithmetic mean	19.5	19.4	
standard deviation	± 11.9	± 11.8	-
Glycated Haemoglobin Units: percentage of hemoglobin			
arithmetic mean	8.00	7.94	
standard deviation	± 0.77	± 0.70	-

End points

End points reporting groups

Reporting group title	SAR341402
Reporting group description:	
SAR341402 100 U/mL subcutaneous (SC) injection, before meals intake on top of QD Insulin Glargine, up to Week 52.	
Reporting group title	NovoLog/NovoRapid
Reporting group description:	
NovoLog/NovoRapid 100 U/mL SC injection, before meals intake on top of QD Insulin Glargine, up to Week 52.	

Primary: Change in Glycated Hemoglobin A1c (HbA1c) From Baseline to Week 26

End point title	Change in Glycated Hemoglobin A1c (HbA1c) From Baseline to Week 26
End point description:	
All values up to Week 26 were taken into account in the analysis, regardless of adherence to treatment. Change in HbA1c was calculated by subtracting baseline value from Week 26 value. Missing changes at Week 26 were imputed using a retrieved dropout multiple imputation method (separately for subjects who prematurely discontinued or completed treatment). Adjusted least square (LS) means and standard errors (SE) were obtained using an analysis of covariance (ANCOVA) model on data obtained from the multiple imputations (results were combined using Rubin's formulae). Analysis was performed on intent-to-treat (ITT) population, which included all randomised subjects, irrespective of compliance with the study protocol and procedures.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.38 (± 0.042)	-0.30 (± 0.041)		

Statistical analyses

Statistical analysis title	SAR341402 Versus NovoLog/NovoRapid
Statistical analysis description:	
Analysis was performed using ANCOVA with treatment group (SAR341402, NovoLog/NovoRapid), the randomisation strata of geographical region, type of diabetes and prior use of NovoLog/NovoRapid as fixed categorical effects, as well as the continuous fixed covariate of baseline HbA1c value.	
Comparison groups	SAR341402 v NovoLog/NovoRapid

Number of subjects included in analysis	597
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	LS Mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.192
upper limit	0.039
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[1] - Non-inferiority of SAR341402 over NovoLog/NovoRapid was demonstrated if upper bound of the 2-sided 95% confidence interval (CI) of the difference between SAR341402 and NovoLog/NovoRapid was <0.3%. If non-inferiority was demonstrated, using a hierarchical step down testing procedure, the inverse non-inferiority of NovoLog/NovoRapid over SAR341402 was tested and was demonstrated if lower bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid was > -0.3%.

Secondary: Change in HbA1c From Baseline to Week 52

End point title	Change in HbA1c From Baseline to Week 52

End point description:

All values up to Week 52 were taken into account in the analysis, regardless of adherence to treatment. Change in HbA1c was calculated by subtracting baseline value from Week 52 value. Missing changes at Week 52 were imputed using a retrieved dropout multiple imputation method (separately for subjects who prematurely discontinued or completed treatment). Adjusted LS means and SE were obtained using ANCOVA model on data obtained from the multiple imputations (results were combined using Rubin's formulae). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.25 (± 0.057)	-0.26 (± 0.059)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c <7% at Week 26 and Week 52

End point title	Percentage of Subjects With HbA1c <7% at Week 26 and Week 52

End point description:

Subjects who had no available assessment at Week 26 and Week 52 were considered as non-responders. Analysis was performed on ITT population.

End point type	Secondary
End point timeframe: Week 26 and Week 52	

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: percentage of subjects				
number (not applicable)				
At Week 26	16.6	14.5		
At Week 52	19.6	18.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fasting Plasma Glucose (FPG) From Baseline to Week 26 and Week 52

End point title	Change in Fasting Plasma Glucose (FPG) From Baseline to Week 26 and Week 52

End point description:

All values up to Week 26 and Week 52 were taken into account in the analysis, regardless of adherence to treatment. Change in FPG at Weeks 26 and 52 was calculated by subtracting baseline value from Week 26 and Week 52 values, respectively. Missing changes at Week 26 and Week 52 were imputed using a retrieved dropout multiple imputation method (separately for subjects who prematurely discontinued or completed treatment). Adjusted LS means and SE were obtained using ANCOVA analysis on data obtained from the multiple imputations (results were combined using Rubin's formulae). Analysis was performed on ITT population.

End point type	Secondary
End point timeframe: Baseline, Week 26 and Week 52	

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: millimoles per liter (mmol/L)				
least squares mean (standard error)				
At Week 26	-0.49 (± 0.249)	-0.17 (± 0.245)		
At Week 52	-0.10 (± 0.366)	-0.34 (± 0.359)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Mean 24-hour Plasma Glucose (PG) Concentration From Baseline to Week 26 and Week 52

End point title	Change in the Mean 24-hour Plasma Glucose (PG) Concentration From Baseline to Week 26 and Week 52

End point description:

Mean 24-hour PG concentration was calculated by 7-point self-measured plasma glucose (SMPG) profiles with PG measurements before and 2-hours after each main meal and at bedtime. Mean 24-hour PG concentration was calculated for each profile and then averaged across profiles performed in week before a visit. All calculated values up to Week 26 and Week 52 were taken for analysis, regardless of adherence to treatment. Change in mean 24-hour PG concentration was calculated by subtracting baseline value from Week 26 and Week 52 values. Missing changes at Week 26 and Week 52 were imputed using return-to-baseline multiple imputation method (values imputed as subject baseline plus an error). Adjusted LS means and SE were obtained using ANCOVA analysis on data obtained from multiple imputations (results were combined using Rubin's formulae). Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with a baseline for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 26 and Week 52

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	295		
Units: mmol/L				
least squares mean (standard error)				
At Week 26	-0.34 (± 0.120)	-0.53 (± 0.121)		
At Week 52	0.12 (± 0.144)	-0.18 (± 0.147)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Postprandial Plasma Glucose (PPG) Excursion From Baseline to Week 26 and Week 52

End point title	Change in Postprandial Plasma Glucose (PPG) Excursion From Baseline to Week 26 and Week 52

End point description:

Plasmsa 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 meal. Values of PG excursions at each visit were then calculated as average across profiles performed in week before visit. All calculated values up to Week 26 and Week 52 were taken into account in the analysis, regardless of adherence to treatment. Change in PPG excursions at Weeks 26 and 52 was calculated by subtracting baseline value from Week 26 and Week 52 values, respectively. Missing changes at Week 26 and Week 52 were imputed using a return-to-baseline multiple imputation method (values imputed as subject baseline plus an error).Adjusted LS means and SE were obtained using ANCOVA analysis on data obtained from the multiple imputations (results were combined using Rubin's formulae). Analysis was performed on ITT population. Here, 'n'= number of subjects with a baseline for each specified category.

End point type	Secondary
End point timeframe: Baseline, Week 26, and Week 52	

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: mmol/L				
least squares mean (standard error)				
Week 26: At Breakfast (n = 288, 288)	0.50 (± 0.232)	0.65 (± 0.233)		
Week 26: At Lunch (n = 290, 291)	0.18 (± 0.230)	0.12 (± 0.228)		
Week 26: At Dinner (n = 290, 292)	0.36 (± 0.243)	0.66 (± 0.243)		
Week 52: At Breakfast (n = 288, 288)	0.73 (± 0.253)	0.91 (± 0.255)		
Week 52: At Lunch (n = 290, 291)	0.43 (± 0.252)	0.34 (± 0.251)		
Week 52: At Dinner (n = 290, 292)	0.26 (± 0.255)	0.51 (± 0.254)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 7-Point SMPG Profiles From Baseline to Week 26 and Week 52 Per Time Point

End point title	Change in 7-Point SMPG Profiles From Baseline to Week 26 and Week 52 Per Time Point

End point description:

7-point SMPG profiles were measured at the following 7 points at each visit (Baseline, Week 26, and Week 52): before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, 2 hours after dinner, and bedtime. For each time point, the value at each visit was calculated as the average of values obtained for the same time point across profiles performed in the week before the visit. Analysis was performed on ITT population. Here, 'n' = number of subjects with available data for at baseline, Week 26/Week 52 for the specified 7-point SMPG time point.

End point type	Secondary
End point timeframe: Baseline, Week 26 and Week 52	

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: mmol/L				
arithmetic mean (standard deviation)				
Week 26: Before Breakfast (n = 254, 253)	-0.62 (± 4.48)	-0.50 (± 3.98)		
Week 26: 2 Hours After Breakfast (n = 236, 229)	-0.39 (± 4.97)	-0.30 (± 4.12)		
Week 26: Before Lunch (n = 250, 253)	-0.60 (± 4.14)	-0.60 (± 4.25)		

Week 26: 2 Hours After Lunch (n = 246, 251)	-0.61 (± 4.54)	-0.62 (± 4.65)		
Week 26: Before Dinner (n = 256, 251)	-0.04 (± 4.87)	-0.78 (± 4.12)		
Week 26: 2 Hours After Dinner (n = 240, 245)	-0.36 (± 4.71)	-0.25 (± 4.14)		
Week 26: Bedtime (n = 239, 238)	-0.71 (± 5.13)	-0.54 (± 4.03)		
Week 52: Before Breakfast (n = 240, 229)	-0.54 (± 4.80)	-0.31 (± 4.37)		
Week 52: 2 Hours After Breakfast (n = 226, 214)	-0.21 (± 4.30)	0.05 (± 4.31)		
Week 52: Before Lunch (n = 233, 230)	0.24 (± 4.64)	-0.13 (± 4.24)		
Week 52: 2 Hours After Lunch (n = 231, 227)	0.05 (± 5.01)	-0.37 (± 4.64)		
Week 52: Before Dinner (n = 238, 231)	0.75 (± 5.59)	-0.06 (± 4.26)		
Week 52: 2 Hours After Dinner (n = 227, 227)	0.16 (± 4.60)	-0.17 (± 4.63)		
Week 52: Bedtime (n = 220, 215)	-0.11 (± 4.98)	0.10 (± 4.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With at Least One Hypoglycemic Event

End point title	Number of Subjects With at Least One Hypoglycemic Event

End point description:

Severe hypoglycemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, because the subject was not capable of helping self. Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of less than or equal to (<=) 3.9 mmol/L (<=70 mg/dL) or plasma glucose level of <3.0 mmol/L (54 mg/dL). Percentage of subjects with at least one hypoglycemia event (any, severe and documented [both thresholds]) were reported. Analysis was performed on safety population that included all randomised subjects who received at least one dose of IMP, analysed according to the treatment actually received.

End point type	Secondary

End point timeframe:

From first injection of investigational medicinal product (IMP) up to Week 26 or up to 1 day after last injection of IMP, whichever comes earlier, for Week 26 analysis, and from first injection of IMP up to 1 day after last injection of IMP for Week 52

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: subjects				
number (not applicable)				
Week 26: Any hypoglycemia	291	285		
Week 26: Severe hypoglycemia	12	10		
Week 26: Documented symptomatic <=3.9 mmol/L	264	251		
Week 26: Documented symptomatic < 3.0 mmol/L	207	193		
Week 52: Any hypoglycemia	295	290		

Week 52: Severe hypoglycemia	18	14		
Week 52: Documented symptomatic <=3.9 mmol/L	274	267		
Week 52:Documented symptomatic < 3.0 mmol/L	223	220		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hypoglycemia Events Per Subject-Year

End point title	Number of Hypoglycemia Events Per Subject-Year

End point description:

Number of hypoglycemia events (any, severe and documented [both thresholds]) 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, because the subject was not capable of helping self. Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <=3.9 mmol/L (<=70 mg/dL) or plasma glucose level of <3.0 mmol/L (54 mg/dL). Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

From first injection of IMP up to Week 26 or up to 1 day after last injection of IMP, whichever comes earlier, for Week 26 analysis, and from first injection of IMP up to 1 day after last injection of IMP for Week 52

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: events per subject-year				
number (not applicable)				
Week 26: Any hypoglycemia	73.33	69.71		
Week 26: Severe hypoglycemia	0.14	0.10		
Week 26: Documented symptomatic <=3.9 mmol/L	40.36	36.37		
Week 26: Documented symptomatic <3.0 mmol/L	11.18	9.81		
Week 52: Any hypoglycemia	66.00	64.46		
Week 52: Severe hypoglycemia	0.12	0.08		
Week 52: Documented symptomatic <=3.9 mmol/L	35.68	33.73		
Week 52: Documented symptomatic <3.0 mmol/L	9.37	8.91		

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:

Subjects with at least one treatment-emergent adverse event linked to hypersensitivity reaction and injection site reaction regardless of relationship to IMP during the main 6-month and the 12-month on-treatment periods was assessed and reported. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

From first injection of IMP up to Week 26 or up to 1 day after last injection of IMP, whichever comes earlier, for Week 26 analysis, and from first injection of IMP up to 1 day after last injection of IMP for Week 52

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: percentage of subjects				
number (not applicable)				
Week 26: Hypersensitivity Reactions	3.7	3.7		
Week 26: Injection site reactions	0.7	1.4		
Week 52: Hypersensitivity Reactions	5.6	7.1		
Week 52: Injection site reactions	0.7	1.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With at Least One Positive Anti-Insulin Aspart Antibodies (AIAs) Sample

End point title	Percentage of Subjects With at Least One Positive Anti-Insulin Aspart Antibodies (AIAs) Sample

End point description:

Subjects with at least one positive AIA sample at baseline or at any time during the on-treatment period (Prevalence). Analysis was performed on AIA population, which included all subjects who received at least one dose of IMP and had at least one AIA sample available for analysis during the on-treatment period, analysed according to the treatment actually received. Here, 'n' = number of subjects included in the AIA population at Week 26 and Week 52.

End point type	Secondary

End point timeframe:

From first injection of IMP up to Week 26 or up to 1 day after last injection of IMP, whichever comes earlier, for Week 26 analysis, and from first injection of IMP up to 1 day after last injection of IMP for Week 52

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: percentage of subjects				
number (not applicable)				
At Week 26 (n = 296, 292)	48.0	52.4		
At Week 52 (n = 298, 292)	54.7	58.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Induced, Treatment-Boosted and Treatment-Emergent Anti-insulin Aspart Antibodies

End point title	Percentage of Subjects With Treatment Induced, Treatment-Boosted and Treatment-Emergent Anti-insulin Aspart Antibodies

End point description:

AIA incidence were categorised as follows 1) 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). 2) 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). 3) Subjects with treatment-emergent AIA were defined as subjects with treatment-induced, or treatment-boosted AIAs. Analysis was performed on AIA population. Here, 'n' = number of subjects included in the AIA population at Week 26 and Week 52 and with negative or missing AIA status at baseline (for treatment-induced AIA) or with positive AIA status at baseline (for treatment-boosted AIA).

End point type	Secondary

End point timeframe:

From first injection of IMP up to Week 26 or up to 1 day after last injection of IMP, whichever comes earlier, for Week 26 analysis, and from first injection of IMP up to 1 day after last injection of IMP for Week 52

End point values	SAR341402	NovoLog/Novo Rapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: percentage of subjects				
number (not applicable)				
Week 26: Treatment-Induced AIA (n = 200, 194)	23.0	28.4		
Week 26: Treatment-Boosted AIA (n = 96, 98)	4.2	5.1		
Week 26: Treatment-Emergent AIA (n = 296, 292)	16.9	20.5		
Week 52: Treatment-Induced AIA (n = 202, 194)	33.2	37.1		
Week 52: Treatment-Boosted AIA (n = 96, 98)	9.4	13.3		
Week 52: Treatment-Emergent AIA (n = 298, 292)	25.5	29.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) weeks were collected from signature of the informed consent form up to the study completion (up to 52 Weeks) 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 '12-month on-treatment period' (time from the first injection of IMP 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	21.1

Reporting groups

Reporting group title	SAR341402

Reporting group description:

SAR341402 100 U/mL subcutaneous (SC) injection, before meals intake on top of QD Insulin Glargine, up to Week 52.

Reporting group title	NovoLog/NovoRapid

Reporting group description:

NovoLog/NovoRapid 100 U/mL SC injection, before meals intake on top of QD Insulin Glargine, up to Week 52.

Serious adverse events	SAR341402	NovoLog/NovoRapid	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 301 (11.96%)	29 / 296 (9.80%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon Adenoma			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolymphocytic Leukaemia			

subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
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			
Asthenia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax Spontaneous			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
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	4 / 301 (1.33%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	9 / 9	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Use Error			
subjects affected / exposed	2 / 301 (0.66%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Pain			

subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna Fracture			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Pseudoaneurysm			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac Failure Congestive			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Left Ventricular Failure			

subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic Unconsciousness			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Coma			
subjects affected / exposed	1 / 301 (0.33%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Seizure			
subjects affected / exposed	3 / 301 (1.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	10 / 301 (3.32%)	4 / 296 (1.35%)	
occurrences causally related to treatment / all	8 / 13	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			

subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 301 (0.33%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis Ischaemic			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic Ulcer Haemorrhage			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Haemorrhage			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Biliary Dyskinesia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic Foot			
subjects affected / exposed	2 / 301 (0.66%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Intercapillary Glomerulosclerosis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial Nephritis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
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			
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator Cuff Syndrome			

subjects affected / exposed	2 / 301 (0.66%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Bacterial			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 301 (0.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Foot Infection			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis Chronic			

subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 301 (0.33%)	0 / 296 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 301 (0.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	0 / 301 (0.00%)	1 / 296 (0.34%)	
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	4 / 301 (1.33%)	1 / 296 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemia			
subjects affected / exposed	3 / 301 (1.00%)	2 / 296 (0.68%)	
occurrences causally related to treatment / all	7 / 9	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SAR341402	NovoLog/NovoRapid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 301 (23.26%)	66 / 296 (22.30%)	
Infections and infestations			
Influenza			
subjects affected / exposed	15 / 301 (4.98%)	12 / 296 (4.05%)	
occurrences (all)	15	13	
Nasopharyngitis			
subjects affected / exposed	34 / 301 (11.30%)	29 / 296 (9.80%)	
occurrences (all)	45	39	
Upper Respiratory Tract Infection			
subjects affected / exposed	22 / 301 (7.31%)	28 / 296 (9.46%)	
occurrences (all)	28	31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2017	Following changes were made: Change to the inclusion/exclusion criteria; Clarified criteria for permanent treatment discontinuation; Clarified frequency of SMPG to assist insulin titration after reaching target ranges for plasma glucose; Simplified hypoglycemia events analysis by the time of the day; Changes in planned presentation of subject disposition and in time periods of interest for extent of investigational medicinal product exposure; Removal of analysis of hypoglycemia events by treatment period. Inserted "approximately" throughout the document for number of subjects.
13 December 2017	Following changes were made: Inclusion of additional exploratory statistical analyses of AIAs; Increase of the number of subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported