



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/deciliter [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 [\geq] 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 standard deviation | 48.4 ± 14.8 | 47.8 ± 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 standard deviation | 27.45 ± 4.58 | 27.46 ± 4.99 | - |
| Duration of Diabetes Units: years arithmetic mean standard deviation | 19.5 ± 11.9 | 19.4 ± 11.8 | - |
| Glycated Haemoglobin Units: percentage of hemoglobin arithmetic mean standard deviation | 8.00 ± 0.77 | 7.94 ± 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:

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 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 (\leq) 3.9 mmol/L (\leq 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

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|-----------------|--|
| 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