



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC13403 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Sanofi aventis recherche & développement |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly--Mazarin, France, 91380 |
| Public contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact- US@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact- US@sanofi.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 April 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

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

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 281 |
| From 65 to 84 years | 222 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | SAR342434 |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | Humalog |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

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

| Reporting group values | SAR342434 | Humalog | Total |
|------------------------------------|-----------|---------|-------|
| Number of subjects | 253 | 252 | 505 |
| Age categorical Units: Subjects | | | |

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

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

End points

End points reporting groups

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

Primary: Change in HbA1c From Baseline to Week 26

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

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

Statistical analyses

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

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

Notes:

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

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

| | |
|--|--|
| End point title | Percentage of Subjects with HbA1c <7.0% and ≤6.5% at Week 26 |
| End point description: | |
| Subjects who had no available assessment for HbA1c at Week 26 were considered as non-responders. Analysis was performed on ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 26 | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Change in Fasting Plasma Glucose (FPG) From Baseline to Week 26 |
| End point description: | |
| Change in FPG was calculated by subtracting baseline value from Week 26 value. Adjusted least squares means and standard errors were obtained from a MMRM approach to account for missing data, using all post-baseline FPG data available during the 6-month period and adequate contrasts at Week 26. | |

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 26 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 26 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, Week 26

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | SAR342434 |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Humalog |
|-----------------------|---------|

Reporting group description:

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events with a frequency $\geq 5\%$ were recorded during the study.

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported