



Clinical trial results:

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

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC12619 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 July 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of SAR342434 versus Humalog in terms of change in glycated hemoglobin (HbA1c) from baseline to Week 26 in subjects with Type 1 diabetes mellitus (T1DM) also using insulin glargine (Lantus®).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject was participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Insulin glargine 100 U/mL (Lantus) was given as the mandatory background basal insulin therapy and was injected once daily (QD) subcutaneously consistent with the local label. Doses of Lantus were adjusted to achieve glycemic target for fasting, pre-prandial plasma glucose (self measured plasma glucose [SMPG]) between 4.4 to 7.2 mmol/L (80 to 130 mg/dL) without hypoglycemia.

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 28 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Japan: 61 |
| Country: Number of subjects enrolled | Russian Federation: 50 |
| Country: Number of subjects enrolled | United States: 218 |
| Country: Number of subjects enrolled | Poland: 54 |
| Country: Number of subjects enrolled | Spain: 35 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 29 |
| Country: Number of subjects enrolled | Hungary: 52 |
| Worldwide total number of subjects | 507 |
| EEA total number of subjects | 178 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 463 |
| From 65 to 84 years | 44 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

A total of 506 subjects were randomized and treated in the study. Randomization was stratified by HbA1c at the screening visit (<8%, ≥8%), prior use of Humalog/Liprolog (Yes, No) and geographical region (Non-Japan, Japan). Assignment to arms was done centrally using interactive voice/web response system in 1:1 ratio (SAR342434: Humalog).

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

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

Arm description:

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

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

Dosage and administration details:

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

| Number of subjects in period 1 | SAR342434 | Humalog |
|--|-----------|---------|
| Started | 253 | 254 |
| Treated | 252 | 254 |
| Completed | 226 | 235 |
| Not completed | 27 | 19 |
| Randomized but not treated | 1 | - |
| Adverse event | 2 | 2 |
| Other than specified | 21 | 10 |
| Poor compliance to protocol | 1 | 7 |
| Lack of efficacy | 1 | - |
| Hypoglycemia not reported as serious adverse event | 1 | - |

Baseline characteristics

Reporting groups

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

Reporting group description:

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

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

Reporting group description:

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

| Reporting group values | SAR342434 | Humalog | Total |
|------------------------------------|-----------|---------|-------|
| Number of subjects | 253 | 254 | 507 |
| Age categorical Units: Subjects | | | |

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

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

End points

End points reporting groups

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

Primary: Change in HbA1c From Baseline to Week 26

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

| End point values | SAR342434 | Humalog | | |
|-------------------------------------|----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 249 | | |
| Units: percentage of HbA1c | | | | |
| least squares mean (standard error) | -0.42 (\pm 0.051) | -0.47 (\pm 0.05) | | |

Statistical analyses

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

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 496 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.084 |
| upper limit | 0.197 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.071 |

Notes:

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

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

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

| End point values | SAR342434 | Humalog | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 253 | 254 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 22.5 | 21.7 | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Change in Fasting Plasma Glucose (FPG) From Baseline to Week 26 |
| End point description: | |
| Change in FPG was calculated by subtracting baseline value from Week 26 value. Adjusted least squares means and standard errors were obtained from a MMRM approach to account for missing data, using all post-baseline FPG data available during the main 6-month period and adequate contrasts at Week 26. Analysis was performed on ITT population. Here, number of subjects analyzed = subjects with at least one post-baseline FPG assessment during the main 6-month period. | |
| End point type | Secondary |

End point timeframe:

Baseline, Week 26

| | | | | |
|-------------------------------------|----------------------|----------------------|--|--|
| End point values | SAR342434 | Humalog | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 242 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -0.46 (\pm 0.248) | -0.62 (\pm 0.248) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 26

| | | | | |
|-------------------------------------|----------------------|----------------------|--|--|
| End point values | SAR342434 | Humalog | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 207 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -0.23 (\pm 0.145) | -0.49 (\pm 0.148) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 26

| End point values | SAR342434 | Humalog | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 253 | 254 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | | | | |
| At breakfast (n=205, 198) | -0.46 (± 0.297) | 0.19 (± 0.297) | | |
| At lunch (n=207, 193) | 0.14 (± 0.298) | -0.26 (± 0.309) | | |
| At dinner (n=208, 190) | 0.48 (± 0.308) | 0.56 (± 0.324) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of treatment-emergent hypoglycemia per subject-year of exposure were reported. Severe hypoglycemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). Hypoglycemic episodes with plasma glucose of 54 mg/dL (< 3.0 mmol/L) were also analyzed. Analysis was performed on safety population that included all subjects randomized and exposed to at least 1 dose of investigational medicinal product (IMP) (SAR342434 or Humalog), regardless of the amount of treatment administered.

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Percentage of Subjects with Hypersensitivity Reactions and Injection Site Reactions |
| End point description: | |
| Analysis was performed on safety population. | |
| End point type | Secondary |
| End point timeframe: | |
| First dose of study drug up to 1 day after the last dose administration (maximum treatment exposure: 400 days) | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Percentage of Subjects with Treatment Emergent Anti-insulin Antibodies (AIAs) |
| End point description: | |
| Subjects with treatment-emergent AIA (incidence) were reported (as subjects with treatment-boostered or treatment-induced AIAs). Subjects with treatment-induced AIAs were those who developed AIA following IMP administration (subjects with at least one positive AIA sample at any time during on-treatment period, in those subjects without pre-existing AIA or with missing baseline sample). Subjects with treatment-boostered AIAs were those with pre-existing AIAs that were boosted to a significant higher titer following IMP administration (subjects with at least one AIA sample with at least a 4-fold increase in titers compared to baseline value at any time during on-treatment period, in those subjects with pre-existing AIA). Analysis was performed on anti-insulin antibody population that included all subjects randomized and exposed to at least 1 dose of IMP (SAR342434 or Humalog) with at least one AIA sample available for analysis during the 12-month on-treatment period. | |
| End point type | Secondary |
| End point timeframe: | |
| First dose of study drug up to 1 day after the last dose administration (maximum treatment exposure: 400 days) | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Change in Daily Insulin Dose from Baseline to Week 26 and Week 52 |
| End point description: | |
| Change in daily insulin dose (basal, mealtime and total) was calculated by subtracting baseline value from Week 26 and Week 52 values respectively. Analysis was performed on safety population. Here, 'n' signifies number of subjects with available data for specified categories. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Baseline, Week 26, Week 52 | |

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (maximum treatment exposure: 400 days) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

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

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

Reporting group description:

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

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 252 (0.00%) | 1 / 254 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes Mellitus Inadequate Control | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | 1 / 254 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic Ketoacidosis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | 2 / 254 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | 1 / 254 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 3 / 252 (1.19%) | 3 / 254 (1.18%) | |
| occurrences causally related to treatment / all | 5 / 5 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | 1 / 254 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | SAR342434 | Humalog | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 252 (18.25%) | 41 / 254 (16.14%) | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 33 / 252 (13.10%) | 28 / 254 (11.02%) | |
| occurrences (all) | 45 | 33 | |
| Upper Respiratory Tract Infection | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 21 November 2014 | <p>Following changes were made:</p> <ul style="list-style-type: none">• Clarification of Inclusion criteria (frequency of injections with meal time insulin therapy) were added;• Determination of AIA at Week 4 was added;• Monitoring of elevated AIA titers until return to baseline were added in subjects in whom the Allergic Reaction Assessment Committee (ARAC) assessed AIA-mediated hypersensitivity reactions or insulin resistance;• Clarification of procedure related to premature discontinuation of treatment;• Clarification of electronic transfer of patient reported outcome (PRO) (7 point and 3 point SMPG profiles, insulin doses and hypoglycemia);• Option of supplying IMP and non-investigational medicinal product (NIMP) by direct mail was removed;• Changes were done to statistical analysis: if non-inferiority of SAR342434 over Humalog was demonstrated, the inverse non-inferiority of Humalog over SAR342434 was to be tested. Analyses for the description of missing data was added;• Changes to statistical analysis: additional information on treatment group presented in the descriptive analyses: overall (pooling Humalog US and Humalog EU groups) and then by subgroup of Humalog-US (corresponding to US and Japan subjects)/Humalog EU (outside US/Japan);• Changes were done to statistical analysis: addition of an on-treatment sensitivity analysis. |
| 05 February 2016 | <p>Following changes were made:</p> <ul style="list-style-type: none">• Clarification on ARAC procedure with elevated AIA titers: follow-up by the sponsor of elevated AIA titers until return to baseline value or until ARAC decided that no further follow-up deemed necessary in subjects whom the ARAC assessed an AIA-mediated hypersensitivity reaction or insulin resistance;• Clarification on inclusion criteria and exclusion criteria for use of Liprolog was added;• Clarification of procedure related to premature treatment discontinuation;• Editorial changes;• Change of reporting of asymptomatic overdose: not considered anymore as an adverse event of special interest (AESI). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported