# Clinical trial results:
# The efficacy and safety of liraglutide as adjunct therapy to insulin in the treatment of type 1 diabetes.
# A 52-week randomised, treat-to-target, placebo-controlled, double-blinded, parallelgroup, multinational, multi-centre trial

## Summary

| | |
|---|---|
| EudraCT number | 2012-003580-21 |
| Trial protocol | SE FI IE NL GB NO PL BE |
| Global end of trial date | 04 June 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 June 2016 |
| First version publication date | 08 June 2016 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | NN9211-3919 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01836523 |
| WHO universal trial number (UTN) | U1111-1133-0590 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Novo Nordisk A/S |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880 |
| Public contact | Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact | Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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 | 10 December 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 June 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To confirm the efficacy of liraglutide as adjunct to insulin treatment on glycaemic control, and to confirm the superiority of liraglutide treatment compared to placebo, both adjunct to insulin treatment, with regard to reduction in total daily insulin dose and body weight loss, after 52 weeks of treatment in subjects with established type 1 diabetes with inadequate glycaemic control.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza. 1 Oct 2013. 2013) and ICH Good Clinical Practice (International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. 01-May-1996) and 21 CFR 312.120 (Food and Drug Administration. FDA Code Federal Regulations. 21 CFR 312.120. Foreign clinical studies not conducted under an IND. 4 Jan 2008).

Background therapy:

Subjects' pre-trial insulin treatment was considered background medication.

Evidence for comparator:

Not applicable

| | |
|---|---|
| Actual start date of recruitment | 25 November 2013 |
| 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 | Australia: 51 |
| Country: Number of subjects enrolled | Argentina: 73 |
| Country: Number of subjects enrolled | Belgium: 33 |
| Country: Number of subjects enrolled | Canada: 99 |
| Country: Number of subjects enrolled | Finland: 49 |
| Country: Number of subjects enrolled | France: 102 |
| Country: Number of subjects enrolled | Germany: 88 |
| Country: Number of subjects enrolled | Ireland: 31 |
| Country: Number of subjects enrolled | Israel: 52 |
| Country: Number of subjects enrolled | Netherlands: 37 |
| Country: Number of subjects enrolled | Norway: 30 |
| Country: Number of subjects enrolled | Poland: 60 |
| Country: Number of subjects enrolled | Sweden: 42 |
| Country: Number of subjects enrolled | Ukraine: 41 |
| Country: Number of subjects enrolled | United Kingdom: 85 |

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 473 |
| Country: Number of subjects enrolled | Russian Federation: 52 |
| Worldwide total number of subjects | 1398 |
| EEA total number of subjects | 557 |

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) | 1321 |
| From 65 to 84 years | 77 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 177 sites in 17 countries:
Argentina: 6, Australia: 5, Belgium: 4, Canada: 14, Germany: 8, Finland: 6, France: 13, United Kingdom: 10, Ireland: 5, Israel: 6, Netherlands: 6, Norway: 5, Poland: 5, Russia: 5, Sweden: 4, Ukraine: 5, United States: 70.

### Pre-assignment

Screening details:

Eligible subjects were randomised in a 3:3:3:1:1:1 manner to receive liraglutide (0.6 mg, 1.2 mg or 1.8 mg) or placebo (0.1 mL, 0.2 mL or 0.3 mL), both adjunct to insulin treatment.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Blinding implementation details:

Treatment allocation was blinded to all subjects, investigators and Novo Nordisk. The evaluations performed by the independent EAC and CMC committees were also based on blinded data.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Liraglutide 0.6 mg |

Arm description:

Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza® |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Liraglutide 0.6 mg, to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

| | |
|---|---|
| **Arm title** | Liraglutide 1.2 mg |

Arm description:

Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza® |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Liraglutide 1.2 mg, to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

| | |
|---|---|
| **Arm title** | Liraglutide 1.8 mg |

Arm description:

Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza® |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Liraglutide 1.8 mg, to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously as an add-on to their pre-trial insulin treatment.
Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks.
Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52.
Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52.
All the 3 placebo doses were pooled for data analysis.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo (0.1 mL, 02 mL or 0.3 mL), to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

| **Number of subjects in period 1** | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|---|---|---|---|
| Started | 351 | 350 | 349 |
| Exposed | 350 | 348 | 347 |
| Completed | 300 | 265 | 258 |
| Not completed | 51 | 85 | 91 |
| Adverse event, non-fatal | 15 | 41 | 49 |
| Unclassified | 17 | 28 | 19 |
| Protocol deviation | 6 | 3 | 2 |
| Met Withdrawal Criteria | 13 | 13 | 21 |

| **Number of subjects in period 1** | Placebo |
|---|---|
| Started | 348 |
| Exposed | 348 |

| | |
|---|---|
| Completed | 274 |
| Not completed | 74 |
| Adverse event, non-fatal | 14 |
| Unclassified | 29 |
| Protocol deviation | 4 |
| Met Withdrawal Criteria | 27 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Liraglutide 0.6 mg |
| Reporting group description: | |
| Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment. | |
| Reporting group title | Liraglutide 1.2 mg |
| Reporting group description: | |
| Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment. | |
| Reporting group title | Liraglutide 1.8 mg |
| Reporting group description: | |
| Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously as an add-on to their pre-trial insulin treatment.<br>Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks.<br>Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52.<br>Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52.<br>All the 3 placebo doses were pooled for data analysis. | |

| Reporting group values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|---|---|---|---|
| Number of subjects | 351 | 350 | 349 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous | | | |
| Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo). | | | |
| Units: years | | | |
| arithmetic mean | 43.6 | 43.9 | 43.7 |
| standard deviation | ± 12.78 | ± 13.06 | ± 13.33 |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 186 | 179 | 181 |
| Male | 164 | 167 | 165 |
| Data not used for this summary | 1 | 4 | 3 |
| Glycosylated haemoglobin (HbA1c) | | | |
| Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo). | | | |
| Units: percentage of glycosylated haemoglobin | | | |
| arithmetic mean | 8.18 | 8.16 | 8.14 |
| standard deviation | ± 0.738 | ± 0.779 | ± 0.74 |
| Body weight | | | |
| Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 | | | |

| | | | |
|---|---|---|---|
| (liraglutide 1.8 mg) and 347 (placebo). | | | |
| Units: kg | | | |
| arithmetic mean | 86.54 | 85.39 | 86.27 |
| standard deviation | ± 17.338 | ± 17.21 | ± 17.321 |
| Total daily actual insulin dose - continuous subcutaneous insulin infusion | | | |
| Total insulin daily dose of subjects who were on continuous subcutaneous insulin infusion treatment. Number of subjects analysed=69 (liraglutide 0.6 mg), 99 (liraglutide 1.2 mg), 113 (liraglutide 1.8 mg), 95 (Placebo). | | | |
| Units: units | | | |
| geometric mean | 52.97 | 50.73 | 50.46 |
| full range (min-max) | 13.8 to 137.1 | 19.7 to 160.5 | 8.7 to 150.2 |
| Total daily actual insulin dose - multiple daily injections | | | |
| Total insulin daily dose of subjects who were on multiple daily insulin injection treatment. Number of subjects analysed=277 (liraglutide 0.6 mg), 242 (liraglutide 1.2 mg), 227 (liraglutide 1.8 mg), 250 (Placebo). | | | |
| Units: units | | | |
| geometric mean | 59.54 | 59.61 | 62.52 |
| full range (min-max) | 22.9 to 181.6 | 16 to 282.5 | 16.4 to 271.3 |

| **Reporting group values** | Placebo | Total | |
|---|---|---|---|
| Number of subjects | 348 | 1398 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous | | | |
| Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo). | | | |
| Units: years | | | |
| arithmetic mean | 43.4 | | |
| standard deviation | ± 12.57 | - | |
| Gender, Male/Female | | | |
| Units: Subjects | | | |
| Female | 180 | 726 | |
| Male | 167 | 663 | |
| Data not used for this summary | 1 | 9 | |
| Glycosylated haemoglobin (HbA1c) | | | |
| Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo). | | | |
| Units: percentage of glycosylated haemoglobin | | | |
| arithmetic mean | 8.15 | | |
| standard deviation | ± 0.728 | - | |
| Body weight | | | |
| Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo). | | | |
| Units: kg | | | |
| arithmetic mean | 86.41 | | |
| standard deviation | ± 17.768 | - | |
| Total daily actual insulin dose - continuous subcutaneous insulin infusion | | | |
| Total insulin daily dose of subjects who were on continuous subcutaneous insulin infusion treatment. Number of subjects analysed=69 (liraglutide 0.6 mg), 99 (liraglutide 1.2 mg), 113 (liraglutide 1.8 mg), | | | |

| | | | |
|---|---|---|---|
| 95 (Placebo). | | | |
| Units: units<br>geometric mean<br>full range (min-max) | <br>49.18<br>3.9 to 176.1 | <br><br>- | <br><br> |
| Total daily actual insulin dose - multiple daily injections | | | |
| Total insulin daily dose of subjects who were on multiple daily insulin injection treatment. Number of subjects analysed=277 (liraglutide 0.6 mg), 242 (liraglutide 1.2 mg), 227 (liraglutide 1.8 mg), 250 (Placebo). | | | |
| Units: units<br>geometric mean<br>full range (min-max) | <br>62.42<br>20.3 to 230 | <br><br>- | <br><br> |

## End points

### End points reporting groups

| Reporting group title | Liraglutide 0.6 mg |
|---|---|
| Reporting group description: | |
| Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment. | |
| Reporting group title | Liraglutide 1.2 mg |
| Reporting group description: | |
| Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment. | |
| Reporting group title | Liraglutide 1.8 mg |
| Reporting group description: | |
| Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously as an add-on to their pre-trial insulin treatment.<br>Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks.<br>Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52.<br>Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52.<br>All the 3 placebo doses were pooled for data analysis. | |

### Primary: Change from baseline in HbA1c

| End point title | Change from baseline in HbA1c |
|---|---|
| End point description: | |
| Change from baseline in HbA1C at week 52. Missing values were handled by using a mixed model for repeated measurements (MMRM). Full analysis set (FAS) included all randomised subjects who received at least one dose and had any post-randomisation data. Five subjects, who started the study, were excluded because of no exposure to study drug and 4 subjects were excluded because of non-availability of post-baseline data. Number of subjects analysed=subjects with any post-baseline HbA1c data. | |
| End point type | Primary |
| End point timeframe: | |
| After 52 weeks of treatment | |

| End point values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 334 | 312 | 305 | 324 |
| Units: percentage of glycosylated haemoglobin | | | | |
| arithmetic mean (standard deviation) | -0.45 (± 0.741) | -0.5 (± 0.767) | -0.54 (± 0.729) | -0.34 (± 0.707) |

## Statistical analyses

| **Statistical analysis title** | Liraglutide 1.8 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

| | |
|---|---|
| Comparison groups | Liraglutide 1.8 mg v Placebo |
| Number of subjects included in analysis | 629 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | -0.07 |

Notes:

[1] - Non-inferiority was concluded if the upper bound of 95% confidence interval was <0.3.

| **Statistical analysis title** | Liraglutide 1.2 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

| | |
|---|---|
| Comparison groups | Liraglutide 1.2 mg v Placebo |
| Number of subjects included in analysis | 636 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | -0.03 |

Notes:

[2] - Non-inferiority was concluded if the upper bound of 95% confidence interval was <0.3.

| Statistical analysis title | Liraglutide 0.6 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

| | |
|---|---|
| Comparison groups | Liraglutide 0.6 mg v Placebo |
| Number of subjects included in analysis | 658 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[3] |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | 0.03 |

Notes:

[3] - Non-inferiority was concluded if the upper bound of 95% confidence interval was <0.3.

## Primary: Change from baseline in body weight

| End point title | Change from baseline in body weight |
|---|---|

End point description:

Change from baseline in body weight at week 52. Missing values were handled by using a MMRM. Analysis was performed on full analysis set. Number of subjects analysed=subjects with any post-baseline body weight data.

| End point type | Primary |
|---|---|

End point timeframe:

After 52 weeks of treatment

| End point values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 324 | 300 | 298 | 311 |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | -1.34 (± 4.183) | -2.73 (± 4.524) | -4.02 (± 4.873) | 0.94 (± 3.828) |

## Statistical analyses

| Statistical analysis title | Liraglutide 1.8 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

| | |
|---|---|
| Comparison groups | Liraglutide 1.8 mg v Placebo |
| Number of subjects included in analysis | 609 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -4.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.65 |
| upper limit | -4.16 |

| **Statistical analysis title** | Liraglutide 1.2 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 7 days after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

| | |
|---|---|
| Comparison groups | Liraglutide 1.2 mg v Placebo |
| Number of subjects included in analysis | 611 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -3.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.29 |
| upper limit | -2.81 |

| **Statistical analysis title** | Liraglutide 0.6 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 7 days after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

| | |
|---|---|
| Comparison groups | Liraglutide 0.6 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 635 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -2.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.91 |
| upper limit | -1.47 |

## Primary: Change from baseline in total daily insulin dose

| | |
|---|---|
| End point title | Change from baseline in total daily insulin dose |

End point description:

Change from baseline in total daily insulin dose at week 52. Change from baseline was represented in terms of ratio to baseline for insulin dose i.e. Total daily insulin dose at week 52/total daily insulin dose at baseline. Missing values were handled by using a MMRM. Full analysis set. Number of subjects analysed=subjects with any post-baseline total insulin daily dose data.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

After 52 weeks of treatment

| End point values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 337 | 328 | 331 | 341 |
| Units: ratio | | | | |
| geometric mean (geometric coefficient of variation) | 1.04 (± 23.75) | 0.98 (± 26.66) | 0.95 (± 24.21) | 1.04 (± 26.69) |

## Statistical analyses

| Statistical analysis title | Liraglutide 1.8 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was done using MMRMs where all post-baseline measurements for specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as dependent variable, and visit, treatment, country and stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate. The measurements were log-transformed before analysis

| | |
|---|---|
| Comparison groups | Liraglutide 1.8 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 672 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment ratio |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 0.96 |

| **Statistical analysis title** | Liraglutide 0.6 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was done using MMRMs where all post-baseline measurements for specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as dependent variable, and visit, treatment, country and stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate. The measurements were log-transformed before analysis

| | |
|---|---|
| Comparison groups | Liraglutide 0.6 mg v Placebo |
| Number of subjects included in analysis | 678 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9615 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment ratio |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.04 |

| **Statistical analysis title** | Liraglutide 1.2 mg vs Placebo |
|---|---|

Statistical analysis description:

Analysis was done using MMRMs where all post-baseline measurements for specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as dependent variable, and visit, treatment, country and stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate. The measurements were log-transformed before analysis

| | |
|---|---|
| Comparison groups | Liraglutide 1.2 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 669 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0148 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment ratio |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 0.99 |

## Secondary: Number of treatment-emergent symptomatic hypoglycaemic episodes

| | |
|---|---|
| End point title | Number of treatment-emergent symptomatic hypoglycaemic episodes |

End point description:

This is a confirmatory secondary endpoint. Symptomatic hypoglycaemic episodes were defined as episodes that were:
1) Severe according to the American Diabetes Association (ADA) classification
OR
2) Self-monitoring of plasma glucose value of < 3.1 mmol/L, with symptoms consistent with hypoglycaemia.
ADA classification of severe hypoglycemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions.
A treatment emergent episode is defined as an episode with onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.
The safety analysis set included all randomised subjects exposed to at least one dose of liraglutide or placebo.

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

End point timeframe:

During 52 weeks of treatment

| **End point values** | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 350 | 348 | 347 | 348 |
| Units: episodes | 4954 | 4602 | 4614 | 3654 |

### Statistical analyses

| **Statistical analysis title** | Liraglutide 1.8 mg vs Placebo |
|---|---|

Statistical analysis description:

The endpoint was analysed using a negative binomial regression model with a log-link function and the log of the time period in which an occurrence of a hypoglycaemic episode was considered treatment emergent as offset. The model included fixed factors (treatment, country, stratification group) and a covariate (baseline HbA1c). The actual number of subjects in this analysis was 693 instead of 695.

| | |
|---|---|
| Comparison groups | Liraglutide 1.8 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 695 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0081 |
| Method | Negative binomial regression |
| Parameter estimate | Rate ratio |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.07 |
| upper limit | 1.59 |

| **Statistical analysis title** | Liraglutide 1.2 mg vs Placebo |
|---|---|

Statistical analysis description:

The endpoint was analysed using a negative binomial regression model with a log-link function and the log of the time period in which an occurrence of a hypoglycaemic episode was considered treatment emergent as offset. The model included fixed factors (treatment, country, stratification group) and a covariate (baseline HbA1c). The actual number of subjects in this analysis was 693 instead of 696.

| | |
|---|---|
| Comparison groups | Liraglutide 1.2 mg v Placebo |
| Number of subjects included in analysis | 696 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0219 |
| Method | Negative binomial regression |
| Parameter estimate | Rate ratio |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 1.55 |

| **Statistical analysis title** | Liraglutide 0.6 mg vs Placebo |
|---|---|

Statistical analysis description:

The endpoint was analysed using a negative binomial regression model with a log-link function and the log of the time period in which an occurrence of a hypoglycaemic episode was considered treatment emergent as offset. The model included fixed factors (treatment, country, stratification group) and a covariate (baseline HbA1c). The actual number of subjects in this analysis was 697 instead of 698.

| | |
|---|---|
| Comparison groups | Liraglutide 0.6 mg v Placebo |
| Number of subjects included in analysis | 698 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1079 |
| Method | Negative binomial regression |
| Parameter estimate | Rate ratio |
| Point estimate | 1.17 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.43 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 52 weeks

Adverse event reporting additional description:

A treatment emergent adverse event is defined as an event with onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Liraglutide 0.6 mg |

Reporting group description:

Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment.

| | |
|---|---|
| Reporting group title | Liraglutide 1.2 mg |

Reporting group description:

Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

| | |
|---|---|
| Reporting group title | Liraglutide 1.8 mg |

Reporting group description:

Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously an add-on to their pre-trial insulin treatment. All the 3 placebo doses pooled together for data analysis.
Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks.
Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52.
Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52.

| **Serious adverse events** | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 35 / 350 (10.00%) | 36 / 348 (10.34%) | 29 / 347 (8.36%) |
| number of deaths (all causes) | 1 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemangioma of bone | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive lobular breast carcinoma | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Popliteal artery entrapment syndrome | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| Obesity surgery | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toe amputation | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cyst | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillar inflammation | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression suicidal | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Biopsy prostate | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Suture related complication | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Melkersson-Rosenthal syndrome | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrospinal fluid leakage | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic unconsciousness | | | |
| subjects affected / exposed | 5 / 350 (1.43%) | 3 / 348 (0.86%) | 6 / 347 (1.73%) |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 3 | 3 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular oedema | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinopathy | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal prolapse | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder prolapse | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint effusion | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision site infection | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis streptococcal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 3 / 347 (0.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 350 (0.00%) | 1 / 348 (0.29%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 3 / 350 (0.86%) | 1 / 348 (0.29%) | 3 / 347 (0.86%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 350 (0.86%) | 3 / 348 (0.86%) | 3 / 347 (0.86%) |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 4 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 1 / 347 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperosmolar hyperglycaemic state | | | |
| subjects affected / exposed | 0 / 350 (0.00%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 3 / 350 (0.86%) | 7 / 348 (2.01%) | 5 / 347 (1.44%) |
| occurrences causally related to treatment / all | 3 / 4 | 6 / 8 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 350 (0.29%) | 0 / 348 (0.00%) | 0 / 347 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Placebo | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 38 / 348 (10.92%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemangioma of bone | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive lobular breast carcinoma | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Popliteal artery entrapment syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Obesity surgery | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toe amputation | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cyst | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tonsillar inflammation | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| Alcoholism | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Completed suicide | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Depression | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Depression suicidal | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Panic attack | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Suicide attempt | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Biopsy prostate | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| Post procedural haemorrhage | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Suture related complication | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tibia fracture | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congenital, familial and genetic disorders | | | | |
| Melkersson-Rosenthal syndrome | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Angina pectoris | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

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|---|---|---|---|---|
| Coronary artery disease | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocarditis | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Cerebrospinal fluid leakage | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoglycaemic seizure | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoglycaemic unconsciousness | | | | |
| subjects affected / exposed | 6 / 348 (1.72%) | | | |
| occurrences causally related to treatment / all | 5 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Migraine | | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transient ischaemic attack | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ear and labyrinth disorders | | | | |

| | | | |
|---|---|---|---|
| Vertigo | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Macular oedema | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinopathy | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal prolapse | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Urticaria | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder prolapse | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| Joint effusion | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal pain | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteoarthritis | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal column stenosis | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Abscess | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abscess limb | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arthritis bacterial | | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arthritis infective | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Incision site infection | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis externa | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperosmolar hyperglycaemic state | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 13 / 348 (3.74%) | | |
| occurrences causally related to treatment / all | 9 / 16 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 259 / 350 (74.00%) | 263 / 348 (75.57%) | 282 / 347 (81.27%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 56 / 350 (16.00%) | 46 / 348 (13.22%) | 49 / 347 (14.12%) |
| occurrences (all) | 78 | 85 | 119 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 17 / 350 (4.86%) | 22 / 348 (6.32%) | 18 / 347 (5.19%) |
| occurrences (all) | 18 | 24 | 21 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 20 / 350 (5.71%) | 16 / 348 (4.60%) | 29 / 347 (8.36%) |
| occurrences (all) | 32 | 20 | 41 |
| Constipation | | | |
| subjects affected / exposed | 17 / 350 (4.86%) | 28 / 348 (8.05%) | 26 / 347 (7.49%) |
| occurrences (all) | 20 | 30 | 28 |
| Diarrhoea | | | |
| subjects affected / exposed | 41 / 350 (11.71%) | 50 / 348 (14.37%) | 64 / 347 (18.44%) |
| occurrences (all) | 52 | 69 | 92 |
| Dyspepsia | | | |
| subjects affected / exposed | 26 / 350 (7.43%) | 27 / 348 (7.76%) | 38 / 347 (10.95%) |
| occurrences (all) | 37 | 41 | 48 |
| Nausea | | | |
| subjects affected / exposed | 112 / 350 (32.00%) | 141 / 348 (40.52%) | 172 / 347 (49.57%) |
| occurrences (all) | 146 | 196 | 271 |
| Vomiting | | | |
| subjects affected / exposed | 24 / 350 (6.86%) | 44 / 348 (12.64%) | 64 / 347 (18.44%) |
| occurrences (all) | 26 | 58 | 106 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 14 / 350 (4.00%) | 7 / 348 (2.01%) | 10 / 347 (2.88%) |
| occurrences (all) | 14 | 8 | 12 |

| | | | |
|---|---|---|---|
| Oropharyngeal pain | | | |
| subjects affected / exposed | 15 / 350 (4.29%) | 22 / 348 (6.32%) | 28 / 347 (8.07%) |
| occurrences (all) | 17 | 24 | 32 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 15 / 350 (4.29%) | 22 / 348 (6.32%) | 18 / 347 (5.19%) |
| occurrences (all) | 17 | 24 | 19 |
| Infections and infestations | | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 12 / 350 (3.43%) | 6 / 348 (1.72%) | 18 / 347 (5.19%) |
| occurrences (all) | 14 | 6 | 24 |
| Gastroenteritis | | | |
| subjects affected / exposed | 21 / 350 (6.00%) | 15 / 348 (4.31%) | 29 / 347 (8.36%) |
| occurrences (all) | 25 | 17 | 32 |
| Influenza | | | |
| subjects affected / exposed | 29 / 350 (8.29%) | 17 / 348 (4.89%) | 25 / 347 (7.20%) |
| occurrences (all) | 32 | 26 | 28 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 105 / 350 (30.00%) | 81 / 348 (23.28%) | 83 / 347 (23.92%) |
| occurrences (all) | 175 | 124 | 145 |
| Sinusitis | | | |
| subjects affected / exposed | 24 / 350 (6.86%) | 17 / 348 (4.89%) | 16 / 347 (4.61%) |
| occurrences (all) | 35 | 22 | 21 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 33 / 350 (9.43%) | 23 / 348 (6.61%) | 43 / 347 (12.39%) |
| occurrences (all) | 37 | 37 | 59 |
| Urinary tract infection | | | |
| subjects affected / exposed | 18 / 350 (5.14%) | 14 / 348 (4.02%) | 20 / 347 (5.76%) |
| occurrences (all) | 28 | 21 | 26 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 31 / 350 (8.86%) | 43 / 348 (12.36%) | 64 / 347 (18.44%) |
| occurrences (all) | 32 | 45 | 70 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 17 / 350 (4.86%) | 17 / 348 (4.89%) | 22 / 347 (6.34%) |
| occurrences (all) | 29 | 26 | 38 |

| | | | |
|---|---|---|---|
| Hypoglycaemia | | | |
| subjects affected / exposed | 26 / 350 (7.43%) | 13 / 348 (3.74%) | 20 / 347 (5.76%) |
| occurrences (all) | 32 | 18 | 37 |

| **Non-serious adverse events** | Placebo | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 224 / 348 (64.37%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 40 / 348 (11.49%) | | |
| occurrences (all) | 77 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 16 / 348 (4.60%) | | |
| occurrences (all) | 18 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 348 (2.30%) | | |
| occurrences (all) | 9 | | |
| Constipation | | | |
| subjects affected / exposed | 9 / 348 (2.59%) | | |
| occurrences (all) | 11 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 38 / 348 (10.92%) | | |
| occurrences (all) | 50 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 8 / 348 (2.30%) | | |
| occurrences (all) | 8 | | |
| Nausea | | | |
| subjects affected / exposed | 42 / 348 (12.07%) | | |
| occurrences (all) | 52 | | |
| Vomiting | | | |
| subjects affected / exposed | 21 / 348 (6.03%) | | |
| occurrences (all) | 26 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 21 / 348 (6.03%) | | |
| occurrences (all) | 24 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 13 / 348 (3.74%) | | |
| occurrences (all) | 15 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 16 / 348 (4.60%) | | |
| occurrences (all) | 16 | | |
| Infections and infestations | | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 8 / 348 (2.30%) | | |
| occurrences (all) | 10 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 15 / 348 (4.31%) | | |
| occurrences (all) | 21 | | |
| Influenza | | | |
| subjects affected / exposed | 24 / 348 (6.90%) | | |
| occurrences (all) | 30 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 85 / 348 (24.43%) | | |
| occurrences (all) | 130 | | |
| Sinusitis | | | |
| subjects affected / exposed | 21 / 348 (6.03%) | | |
| occurrences (all) | 31 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 40 / 348 (11.49%) | | |
| occurrences (all) | 58 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 11 / 348 (3.16%) | | |
| occurrences (all) | 15 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 6 / 348 (1.72%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|---|---|---|
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all) | 17 / 348 (4.89%)<br>28 | | |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all) | 24 / 348 (6.90%)<br>35 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 April 2013 | 1) Correcting a discrepancy between the wording of the key exclusion criteria in the summary section and the exclusion criteria stated in the protocol so the text is in alignment.<br>2) The model for calculating within-subject variability in self-measured fasting plasma glucose for insulin dose titration was simplified to employ a fewer number of parameters.<br>3) A discrepancy in the wording of the MESI regarding administration of an accidental overdose in the protocol and Appendix were corrected. |
| 26 February 2014 | 1) Further instruction/clarification was added to ensure that the insulin dose was reduced correctly when trial drug was started.<br>2) Endpoints of hypoglycaemia were slightly revised. The endpoint hypoglycaemia with concurrent presence of both hypoglycaemic symptoms and low glucose value was added.<br>3) Severe hypoglycaemic events were to undergo independent review to evaluate if the event was a severe hypoglycaemic event. It was decided to follow the same set-up and present the severe hypoglycaemic events to the EAC as described in the current protocol for other MESI requiring event adjudication.<br>4) Statistical consideration was updated in regards to the definition of the hypoglycaemic events. A figure illustrating the updated ADA definition of hypoglycaemic events was included.<br>5) An Investigator Portal was used to exchange documents between Novo Nordisk and the sites. Text regarding the Investigator Portal was added to provide clarification for sites.<br>6) Changes in the protocol were made for clarification and consistency purposes. The rationale for adjudicating the MESIs Fatal. Acute Coronory Syndrome and Cerebrovascular events was updated to clarify that this was performed in all Novo Nordisk trials with Victoza®. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported