



Clinical trial results:

The efficacy and safety of liraglutide adjunct to insulin treatment in type 1 diabetes. A 26 week randomised, insulin capped, placebo-controlled, double-blind, parallel group, multinational, multi-centre trial

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2012-005778-74 |
| Trial protocol | AT FI BG SE IT ES BE NL DK FR |
| Global end of trial date | 27 April 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 12 May 2016 |
| First version publication date | 12 May 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN9211-4083 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02098395 |
| WHO universal trial number (UTN) | U1111-1138-0619 |

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 | 27 April 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 April 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of liraglutide compared to placebo, both adjunct to insulin treatment, on glycaemic control, after 26 weeks of treatment in subjects with established type 1 diabetes in inadequate glycaemic control.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (October 2013) and ICH Good Clinical Practice (May 1996) and 21 CFR 312.120.

Background therapy:

Subjects continued their pre-trial insulin treatment (either basal bolus insulin treatment or continuous subcutaneous insulin infusion [CSII] treatment) throughout the trial. The type and brand of basal or bolus insulin was not to be changed (unless for safety of the subject) throughout the trial, as differences in insulin action and profiles could have the potential to interfere with the endpoints of the trial.

Evidence for comparator:

Not applicable

| | |
|---|-------------|
| Actual start date of recruitment | 08 May 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 27 |
| Country: Number of subjects enrolled | Spain: 63 |
| Country: Number of subjects enrolled | Sweden: 33 |
| Country: Number of subjects enrolled | Austria: 40 |
| Country: Number of subjects enrolled | Belgium: 64 |
| Country: Number of subjects enrolled | Bulgaria: 54 |
| Country: Number of subjects enrolled | Denmark: 32 |
| Country: Number of subjects enrolled | Finland: 41 |
| Country: Number of subjects enrolled | France: 41 |
| Country: Number of subjects enrolled | Italy: 69 |
| Country: Number of subjects enrolled | Canada: 57 |
| Country: Number of subjects enrolled | United States: 267 |
| Country: Number of subjects enrolled | South Africa: 47 |
| Worldwide total number of subjects | 835 |
| EEA total number of subjects | 464 |

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) | 783 |
| From 65 to 84 years | 51 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Subjects were randomised at 113 sites in 13 countries: Austria 2 sites, Belgium 9 sites, Bulgaria 5 sites, Canada 9 sites, Denmark 4 sites, Finland 6 sites, France 9 sites, Italy 7 sites, Netherlands 5 sites, South Africa 2 sites, Spain 5 sites, Sweden 5 sites, United States 45 sites.

Pre-assignment

Screening details:

Not applicable.

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 | Subject, Investigator |

Blinding implementation details:

Subjects were randomised to either liraglutide (0.6 mg, 1.2 mg or 1.8 mg) or placebo in a double-blinded manner; to preserve blinding, the dose volume (0.1 ml, 0.2 ml, 0.3 ml) in the liraglutide placebo groups were matched to the relevant active group (0.6 mg, 1.2 mg and 1.8 mg).

Arms

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

Arm description:

Subjects randomised to 0.6 mg liraglutide treatment as an add-on to their pre-trial insulin treatment and remained on this dose throughout the trial (26 weeks).

| | |
|--|--|
| 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, administered subcutaneously (s.c., under the skin) once daily.

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

Arm description:

Subjects randomised to 1.2 mg liraglutide treatment as an add-on to their pre-trial insulin treatment received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 24 weeks.

| | |
|--|--|
| 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:

Subjects received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 24 weeks. Administered subcutaneously (s.c., under the skin) once daily.

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

Arm description:

Subjects randomised to 1.8 mg liraglutide treatment as an add-on to their pre-trial insulin treatment

received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 2 weeks. After 4 weeks of treatment subjects received 1.8 mg liraglutide for 22 weeks.

| | |
|--|--|
| 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:

Subjects received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 2 weeks. After 4 weeks of treatment subjects received 1.8 mg liraglutide for 22 weeks. Administered subcutaneously (s.c., under the skin) once daily.

| | |
|------------------|---------------------|
| Arm title | Liraglutide placebo |
|------------------|---------------------|

Arm description:

Subjects randomised to 3 different placebo arms as an add-on to their pre-trial insulin treatment. Administered subcutaneously (s.c., under the skin) once daily. All the 3 arms were pooled together for data analysis.

- a. Placebo 0.1 mL arm: Subjects received 0.1 mL placebo throughout the trial.
- b. Placebo 0.2 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 24 weeks.
- c. Placebo 0.3 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 2 weeks and 0.3 mL for next 22 weeks of the trial period.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Liraglutide 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:

- a. Placebo 0.1 mL arm: Subjects received 0.1 mL placebo throughout the trial.
- b. Placebo 0.2 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 24 weeks.
- c. Placebo 0.3 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 2 weeks and 0.3 mL for next 22 weeks of the trial period.

| Number of subjects in period 1 | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|---------------------------------------|--------------------|--------------------|--------------------|
| Started | 212 | 209 | 207 |
| Exposed | 211 | 209 | 206 |
| Completed | 186 | 177 | 165 |
| Not completed | 26 | 32 | 42 |
| Adverse event, non-fatal | 12 | 19 | 34 |
| Unclassified | - | - | 3 |
| Lost to follow-up | 2 | 1 | - |
| Protocol deviation | 2 | 2 | - |
| Withdrawal by subject | 10 | 10 | 5 |

| Number of subjects in period 1 | Liraglutide placebo |
|---------------------------------------|---------------------|
| Started | 207 |
| Exposed | 206 |

| | |
|--------------------------|-----|
| Completed | 180 |
| Not completed | 27 |
| Adverse event, non-fatal | 2 |
| Unclassified | 2 |
| Lost to follow-up | 3 |
| Protocol deviation | 7 |
| Withdrawal by subject | 13 |

Baseline characteristics

Reporting groups

| | |
|---|---------------------|
| Reporting group title | Liraglutide 0.6 mg |
| Reporting group description: Subjects randomised to 0.6 mg liraglutide treatment as an add-on to their pre-trial insulin treatment and remained on this dose throughout the trial (26 weeks). | |
| Reporting group title | Liraglutide 1.2 mg |
| Reporting group description: Subjects randomised to 1.2 mg liraglutide treatment as an add-on to their pre-trial insulin treatment received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 24 weeks. | |
| Reporting group title | Liraglutide 1.8 mg |
| Reporting group description: Subjects randomised to 1.8 mg liraglutide treatment as an add-on to their pre-trial insulin treatment received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 2 weeks. After 4 weeks of treatment subjects received 1.8 mg liraglutide for 22 weeks. | |
| Reporting group title | Liraglutide placebo |
| Reporting group description: Subjects randomised to 3 different placebo arms as an add-on to their pre-trial insulin treatment. Administered subcutaneously (s.c., under the skin) once daily. All the 3 arms were pooled together for data analysis. a. Placebo 0.1 mL arm: Subjects received 0.1 mL placebo throughout the trial. b. Placebo 0.2 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 24 weeks. c. Placebo 0.3 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 2 weeks and 0.3 mL for next 22 weeks of the trial period. | |

| Reporting group values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|--|--------------------|--------------------|--------------------|
| Number of subjects | 212 | 209 | 207 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Baseline age values were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: years | | | |
| arithmetic mean | 43.9 | 42.8 | 43.2 |
| standard deviation | ± 12.88 | ± 13.31 | ± 12.9 |
| Gender categorical | | | |
| Baseline gender data were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: Subjects | | | |
| Female | 118 | 106 | 113 |
| Male | 93 | 103 | 92 |
| Not recorded | 1 | 0 | 2 |

| | | | |
|---|----------|----------|---------|
| Glycosylated haemoglobin (HbA1c) | | | |
| Baseline HbA1c values were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: Percent (%) glycosylated haemoglobin | | | |
| arithmetic mean | 8.09 | 8.07 | 8.04 |
| standard deviation | ± 0.743 | ± 0.731 | ± 0.736 |
| Body weight | | | |
| Baseline body weight values were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | 83.1 | 84.69 | 83.64 |
| standard deviation | ± 16.137 | ± 18.155 | ± 17.62 |

| Reporting group values | Liraglutide placebo | Total | |
|------------------------|---------------------|-------|--|
| Number of subjects | 207 | 835 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|---------|-----|--|
| Age continuous | | | |
| Baseline age values were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: years | | | |
| arithmetic mean | 42.7 | | |
| standard deviation | ± 12.97 | - | |
| Gender categorical | | | |
| Baseline gender data were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: Subjects | | | |
| Female | 112 | 449 | |
| Male | 94 | 382 | |
| Not recorded | 1 | 4 | |

| | | | |
|---|---------|---|--|
| Glycosylated haemoglobin (HbA1c) | | | |
| Baseline HbA1c values were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: Percent (%) glycosylated haemoglobin | | | |
| arithmetic mean | 8.12 | | |
| standard deviation | ± 0.723 | - | |

| | | | |
|---|----------|---|--|
| Body weight | | | |
| Baseline body weight values were collected for full analysis set (FAS = 831 subjects). In FAS, number of subjects in liraglutide 0.6 mg arm was 211; number of subjects in liraglutide 1.2 mg arm was 209; number of subjects in liraglutide 1.8 mg arm was 205; number of subjects in liraglutide placebo arm was 206. Out of 835 randomised subjects, 4 were excluded from FAS: 1 subject each in the liraglutide 1.8 mg, 0.6 mg and placebo arm were not exposed to trial treatment and 1 subject in the liraglutide 1.8 mg arm had no post-baseline measurements. | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | 84.2 | | |
| standard deviation | ± 16.539 | - | |

End points

End points reporting groups

| | |
|---|---------------------|
| Reporting group title | Liraglutide 0.6 mg |
| Reporting group description: Subjects randomised to 0.6 mg liraglutide treatment as an add-on to their pre-trial insulin treatment and remained on this dose throughout the trial (26 weeks). | |
| Reporting group title | Liraglutide 1.2 mg |
| Reporting group description: Subjects randomised to 1.2 mg liraglutide treatment as an add-on to their pre-trial insulin treatment received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 24 weeks. | |
| Reporting group title | Liraglutide 1.8 mg |
| Reporting group description: Subjects randomised to 1.8 mg liraglutide treatment as an add-on to their pre-trial insulin treatment received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 2 weeks. After 4 weeks of treatment subjects received 1.8 mg liraglutide for 22 weeks. | |
| Reporting group title | Liraglutide placebo |
| Reporting group description: Subjects randomised to 3 different placebo arms as an add-on to their pre-trial insulin treatment. Administered subcutaneously (s.c., under the skin) once daily. All the 3 arms were pooled together for data analysis. a. Placebo 0.1 mL arm: Subjects received 0.1 mL placebo throughout the trial. b. Placebo 0.2 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 24 weeks. c. Placebo 0.3 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 2 weeks and 0.3 mL for next 22 weeks of the trial period. | |

Primary: Change from baseline in glycosylated haemoglobin (HbA1c)

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|--|--|
| End point title | Change from baseline in glycosylated haemoglobin (HbA1c) |
| End point description: Change from baseline in glycosylated haemoglobin (HbA1c), after 26 weeks of treatment. Missing data imputed from a mixed model for repeated measurements with treatment, stratification and country as fixed factors and baseline value as a fixed covariate, all nested within visit. Full analysis set (FAS) included all randomised subjects who had received at least one dose and had any post-randomisation data (FAS = 831 subjects). Number subject analysed were subjects from FAS with available HbA1c data for week 26. Out of the 831 subjects in FAS, 22 subjects in lira 0.6 mg arm, 33 subjects in lira 1.2 mg arm, 35 subjects in lira 1.8 mg arm and 16 in placebo arm did not contribute to this analysis. | |
| End point type | Primary |
| End point timeframe: After 26 weeks of treatment | |

| End point values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Liraglutide placebo |
|---|--------------------|--------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 189 | 176 | 170 | 190 |
| Units: Percent (%) glycosylated haemoglobin | | | | |
| arithmetic mean (standard deviation) | -0.23 (± 0.744) | -0.23 (± 0.731) | -0.32 (± 0.73) | 0.01 (± 0.674) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Liraglutide 1.8 mg v Liraglutide placebo |
| Number of subjects included in analysis | 360 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | -0.2 |

Notes:

[1] - Superiority of liraglutide 1.8 mg versus placebo was planned to be concluded if and only if the upper limit of the two-sided 95% confidence interval for the estimated difference in HbA1c was less than zero.

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 |
| Comparison groups | Liraglutide 1.2 mg v Liraglutide placebo |
| Number of subjects included in analysis | 366 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.0021 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | -0.08 |

Notes:

[2] - Superiority of liraglutide 1.2 mg was planned to be evaluated only if superiority for liraglutide 1.8 mg was concluded.

| | |
|-----------------------------------|--|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | Liraglutide 0.6 mg v Liraglutide placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 379 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.0011 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.39 |
| upper limit | -0.1 |

Notes:

[3] - Superiority of liraglutide 0.6 mg versus placebo was planned to be evaluated only if superiority of liraglutide 1.2 mg was concluded.

Secondary: Change from baseline in body weight

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

End point description:

Change from baseline in body weight after 26 weeks of treatment. Missing data imputed from a mixed model for repeated measurements with treatment, stratification and country as fixed factors and baseline value as a fixed covariate, all nested within visit. Full analysis set (FAS) included all randomised subjects who had received at least one dose and had any post-randomisation data (FAS = 831 subjects). Number subject analysed were subjects from FAS with available body weight data for week 26. Out of the 831 subjects in FAS, 27 subjects in lira 0.6 mg arm, 38 subjects in lira 1.2 mg arm, 35 subjects in lira 1.8 mg arm and 26 in placebo arm did not contribute to the analysis.

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

End point timeframe:

After 26 weeks of treatment

| End point values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Liraglutide placebo |
|--------------------------------------|--------------------|--------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 184 | 171 | 170 | 180 |
| Units: kilogram(s) | | | | |
| arithmetic mean (standard deviation) | -2.37 (± 3.015) | -4.03 (± 3.677) | -5.1 (± 3.787) | -0.26 (± 2.782) |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent symptomatic hypoglycaemic episodes

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

End point description:

Number of treatment-emergent symptomatic hypoglycaemic episodes during 26 weeks of treatment. Symptomatic hypoglycaemic episodes were defined as episodes that were severe according to the American Diabetes Association (ADA) classification or a self measured plasma glucose (SMPG) value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia. Safety analysis set (SAS)

included all subjects exposed to at least one dose of randomised liraglutide or placebo (SAS = 832 subjects). Severe hypoglycaemia as per ADA classification is defined as an episode that required assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. Plasma glucose (PG) concentration may not have been available during an event, but neurological recovery following the return of PG to normal was considered sufficient evidence that the event was induced by a low PG concentration.

| | |
|------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| During 26 weeks of treatment | |

| End point values | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Liraglutide placebo |
|-----------------------------|--------------------|--------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 211 ^[4] | 209 ^[5] | 206 ^[6] | 206 ^[7] |
| Units: Number of episodes | 1437 | 1943 | 1490 | 1567 |

Notes:

[4] - 1437 episodes of symptomatic hypoglycaemia were reported by 166 subjects.

[5] - 1943 episodes of symptomatic hypoglycaemia were reported by 175 subjects.

[6] - 1490 episodes of symptomatic hypoglycaemia were reported by 160 subjects.

[7] - 1567 episodes of symptomatic hypoglycaemia were reported by 162 subjects.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first day of exposure (week 0) to randomised treatment to 7 days after the last day of randomised treatment (week 26).

Adverse event reporting additional description:

Safety analysis set (SAS) included all subjects exposed to at least one dose of randomised liraglutide or placebo.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

Reporting groups

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

Reporting group description:

Subjects randomised to 0.6 mg liraglutide treatment as an add-on to their pre-trial insulin treatment and remained on this dose throughout the trial (26 weeks).

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

Reporting group description:

Subjects randomised to 1.2 mg liraglutide treatment as an add-on to their pre-trial insulin treatment received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 24 weeks.

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

Reporting group description:

Subjects randomised to 1.8 mg liraglutide treatment as an add-on to their pre-trial insulin treatment received 0.6 mg liraglutide for 2 weeks followed by 1.2 mg liraglutide for 2 weeks. After 4 weeks of treatment subjects received 1.8 mg liraglutide for 22 weeks.

| | |
|-----------------------|---------------------|
| Reporting group title | Liraglutide placebo |
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Reporting group description:

Subjects randomised to 3 different placebo arms as an add-on to their pre-trial insulin treatment. Administered subcutaneously (s.c., under the skin) once daily. All the 3 arms were pooled together for data analysis.

a. Placebo 0.1 mL arm: Subjects received 0.1 mL placebo throughout the trial.

b. Placebo 0.2 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 24 weeks.

c. Placebo 0.3 mL arm: Subjects received 0.1 mL placebo for 2 weeks followed by 0.2 mL for 2 weeks and 0.3 mL for next 22 weeks of the trial period.

| 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 | 20 / 211 (9.48%) | 21 / 209 (10.05%) | 14 / 206 (6.80%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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|--|-----------------|-----------------|-----------------|
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Surgical and medical procedures | | | |
| Wrist surgery | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

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|---|-----------------|-----------------|-----------------|
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Forearm fracture | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Intervertebral disc injury | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |

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|---|-----------------|-----------------|-----------------|
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 1 / 209 (0.48%) | 0 / 206 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic fracture | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Myocardial ischaemia | | | |

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|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 | | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 coma | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 unconsciousness | | | |
| subjects affected / exposed | 3 / 211 (1.42%) | 6 / 209 (2.87%) | 2 / 206 (0.97%) |
| occurrences causally related to treatment / all | 1 / 5 | 5 / 7 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculopathy | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vlth nerve paralysis | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |

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|---|-----------------|-----------------|-----------------|
| Anaemia | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 2 / 209 (0.96%) | 0 / 206 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 |
| Volvulus | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 2 / 209 (0.96%) | 0 / 206 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |

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|---|-----------------|-----------------|-----------------|
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 nephropathy | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 / 211 (0.00%) | 0 / 209 (0.00%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 | | | |

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|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 0 / 209 (0.00%) | 0 / 206 (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 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 0 / 206 (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 | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 211 (0.47%) | 1 / 209 (0.48%) | 0 / 206 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 0 / 209 (0.00%) | 2 / 206 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 211 (0.00%) | 1 / 209 (0.48%) | 0 / 206 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 5 / 211 (2.37%) | 2 / 209 (0.96%) | 1 / 206 (0.49%) |
| occurrences causally related to treatment / all | 4 / 6 | 2 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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|---|---------------------|--|--|
| Serious adverse events | Liraglutide placebo | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 206 (6.80%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

| | | | |
|---|-----------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Wrist surgery | | | |
| subjects affected / exposed | 0 / 206 (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 discomfort | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|--|--|
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Forearm fracture | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc injury | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Traumatic fracture | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemic unconsciousness | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| With nerve paralysis | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Volvulus | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| 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 | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic nephropathy | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| 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 | 137 / 211 (64.93%) | 164 / 209 (78.47%) | 162 / 206 (78.64%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 16 / 211 (7.58%) | 26 / 209 (12.44%) | 30 / 206 (14.56%) |
| occurrences (all) | 27 | 33 | 43 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 13 / 211 (6.16%) | 17 / 209 (8.13%) | 22 / 206 (10.68%) |
| occurrences (all) | 13 | 18 | 25 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 211 (1.42%) | 14 / 209 (6.70%) | 7 / 206 (3.40%) |
| occurrences (all) | 4 | 18 | 7 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 211 (3.79%) | 8 / 209 (3.83%) | 14 / 206 (6.80%) |
| occurrences (all) | 8 | 13 | 17 |
| Constipation | | | |
| subjects affected / exposed | 6 / 211 (2.84%) | 23 / 209 (11.00%) | 14 / 206 (6.80%) |
| occurrences (all) | 6 | 29 | 15 |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 211 (6.64%) | 25 / 209 (11.96%) | 30 / 206 (14.56%) |
| occurrences (all) | 17 | 30 | 43 |
| Dyspepsia | | | |
| subjects affected / exposed | 8 / 211 (3.79%) | 19 / 209 (9.09%) | 24 / 206 (11.65%) |
| occurrences (all) | 9 | 23 | 35 |
| Nausea | | | |
| subjects affected / exposed | 68 / 211 (32.23%) | 97 / 209 (46.41%) | 102 / 206 (49.51%) |
| occurrences (all) | 81 | 122 | 170 |

| | | | |
|--|---|---|---|
| Vomiting subjects affected / exposed occurrences (all) | 19 / 211 (9.00%) 25 | 29 / 209 (13.88%) 40 | 35 / 206 (16.99%) 65 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 10 / 211 (4.74%) 12 | 4 / 209 (1.91%) 4 | 14 / 206 (6.80%) 19 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 3 / 211 (1.42%) 4 | 5 / 209 (2.39%) 6 | 8 / 206 (3.88%) 10 |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 211 (2.84%) 7 15 / 211 (7.11%) 15 44 / 211 (20.85%) 59 7 / 211 (3.32%) 7 14 / 211 (6.64%) 20 | 11 / 209 (5.26%) 11 18 / 209 (8.61%) 23 40 / 209 (19.14%) 52 11 / 209 (5.26%) 12 11 / 209 (5.26%) 13 | 8 / 206 (3.88%) 9 18 / 206 (8.74%) 19 47 / 206 (22.82%) 67 3 / 206 (1.46%) 3 11 / 206 (5.34%) 14 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) | 21 / 211 (9.95%) 21 10 / 211 (4.74%) 14 | 40 / 209 (19.14%) 42 13 / 209 (6.22%) 17 | 50 / 206 (24.27%) 55 12 / 206 (5.83%) 16 |

| | | | |
|--|---------------------|--|--|
| Non-serious adverse events | Liraglutide placebo | | |
| Total subjects affected by non-serious | | | |

| | | | |
|--|--------------------|--|--|
| adverse events | | | |
| subjects affected / exposed | 125 / 206 (60.68%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 30 / 206 (14.56%) | | |
| occurrences (all) | 40 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 5 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 6 / 206 (2.91%) | | |
| occurrences (all) | 7 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 206 (2.43%) | | |
| occurrences (all) | 5 | | |
| Constipation | | | |
| subjects affected / exposed | 9 / 206 (4.37%) | | |
| occurrences (all) | 12 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 17 / 206 (8.25%) | | |
| occurrences (all) | 22 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 34 / 206 (16.50%) | | |
| occurrences (all) | 40 | | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 206 (3.40%) | | |
| occurrences (all) | 8 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 6 / 206 (2.91%) | | |
| occurrences (all) | 10 | | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 14 / 206 (6.80%) | | |
| occurrences (all) | 15 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 6 / 206 (2.91%) | | |
| occurrences (all) | 6 | | |
| Influenza | | | |
| subjects affected / exposed | 17 / 206 (8.25%) | | |
| occurrences (all) | 20 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 46 / 206 (22.33%) | | |
| occurrences (all) | 56 | | |
| Sinusitis | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 4 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 25 / 206 (12.14%) | | |
| occurrences (all) | 31 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 206 (4.37%) | | |
| occurrences (all) | 10 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported