# Clinical trial results:
# A 24 week randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of once daily linagliptin, 5 milligrams orally, as add on to basal insulin in elderly Type 2 Diabetes Mellitus patients with insufficient glycaemic control

## Summary

| | |
|---|---|
| EudraCT number | 2014-000904-88 |
| Trial protocol | GR ES DK GB FI DE BE IE |
| Global end of trial date | 25 April 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 10 May 2018 |
| First version publication date | 10 May 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1218.149 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02240680 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.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 | 30 May 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 April 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 April 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the efficacy, safety, and tolerability of linagliptin 5 mg once daily compared with placebo as add-on therapy for 24 weeks to stable basal insulin treatment in elderly (≥60 years) patients with type 2 diabetes mellitus and insufficient glycaemic control.

Protection of trial subjects:

Safety was to be ensured by monitoring the patients for AEs clinically, by laboratory testing, and by home blood glucose monitoring (HBGM). Patients who were not adequately controlled could have their permitted background medication adjusted or new antidiabetic medications introduced to ensure their safety. In case the patient developed any condition/disease or AE which did not allow – according to investigator's judgement – the patient's safe continuation of the trial, the patient was to be prematurely discontinued from the trial. Symptoms that could be attributed to hypoglycaemia were to be closely monitored during the trial. General risks associated with participating in this trial were related to trial-specific procedures such as blood sampling. The amount of blood taken during the whole course of the trial was considered to be of no or negligible risk to the patients. The trial design with a 1-week placebo run-in phase is a well-established design for trials in type 2 diabetes. Daily monitoring of blood glucose was performed by patients with the HBGM device and patients were to be discontinued if there was any indication that the patient was not stable enough. Thus the risk of the 1-week placebo treatment was minimal.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Colombia: 12 |
| Country: Number of subjects enrolled | Denmark: 31 |
| Country: Number of subjects enrolled | Finland: 10 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Greece: 16 |
| Country: Number of subjects enrolled | Ireland: 1 |
| Country: Number of subjects enrolled | Japan: 108 |
| Country: Number of subjects enrolled | Mexico: 33 |
| Country: Number of subjects enrolled | New Zealand: 12 |
| Country: Number of subjects enrolled | Poland: 31 |

| | |
|---|---|
| Country: Number of subjects enrolled | Romania: 21 |
| Country: Number of subjects enrolled | South Africa: 26 |
| Country: Number of subjects enrolled | Spain: 56 |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Country: Number of subjects enrolled | United States: 133 |
| Worldwide total number of subjects | 525 |
| EEA total number of subjects | 194 |

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) | 32 |
| From 65 to 84 years | 475 |
| 85 years and over | 18 |

## Subject disposition

### Recruitment

Recruitment details:

This was randomised, double blinded, placebo controlled, parallel study. Total 525 patients with type 2 diabetes mellitus (T2DM) and insufficient glycaemic control were screened. 302 patients were randomised into two groups. The trial was extended to 52 weeks for Japanese patients. 102 patients were identified and observed for the extended period.

### Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (Up to 24 weeks) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst |

Blinding implementation details:

The randomised period of this trial was double blind, i.e. after randomisation neither the patient nor the investigator nor anyone involved in analysing trial data or with an interest in this double blind trial were aware of a treatment assignment.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo (Up to 24 weeks) |

Arm description:

Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral adminstration of placebo tablets (Matching Linagliptin) once daily up to 24 weeks.

| | |
|---|---|
| **Arm title** | Linagliptin 5 milligram (Up to 24 weeks) |

Arm description:

Patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 24 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Linagliptin 5 milligram |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral adminstation of Linagliptin 5 milligram film coated tablets once daily up to 24 weeks

| **Number of subjects in period 1[1]** | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) |
|---|---|---|
| Started | 151 | 151 |
| Completed | 136 | 143 |
| Not completed | 15 | 8 |
| Adverse event, serious fatal | - | 1 |
| Consent withdrawn by subject | 3 | 1 |
| Adverse event, non-fatal | 6 | 5 |
| Other than specified | 1 | - |
| Lost to follow-up | 1 | - |
| Protocol deviation | 4 | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomized after successfully completing the screening period and received at least one dose of the trial medication.

## Period 2

| | |
|---|---|
| Period 2 title | Japanese Patients (Up to 52 weeks) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst |

Blinding implementation details:

The randomised period of this trial was double-blind, i.e. after randomisation neither the patient nor the investigator nor anyone involved in analysing trial data or with an interest in this double-blind trial were aware of a treatment assignment.

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo (Up to 52 weeks) |

Arm description:

Only Japanese patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 52 weeks

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral adminstration of placebo tablets (Matching Linagliptin) once daily up to 52 weeks.

| | |
|---|---|
| **Arm title** | Linagliptin 5 milligram (Up to 52 weeks) |

Arm description:

Only Japanese patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 52 weeks

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Linagliptin 5 milligram |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral adminstation of Linagliptin 5 milligram film coated tablets once daily up to 52 weeks.

| **Number of subjects in period 2[2]** | Placebo (Up to 52 weeks) | Linagliptin 5 milligram (Up to 52 weeks) |
|---|---|---|
| Started | 50 | 52 |
| Completed | 42 | 45 |
| Not completed | 8 | 7 |
| Consent withdrawn by subject | 1 | - |
| Adverse event, non-fatal | 6 | 7 |
| Protocol deviation | 1 | - |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: This issue is because of the trial design. We do not have two period in the study but had to present the data in two periods because of the extension of time period for Japanese patients

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo (Up to 24 weeks) |
| Reporting group description: | |
| Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks | |
| Reporting group title | Linagliptin 5 milligram (Up to 24 weeks) |
| Reporting group description: | |
| Patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 24 weeks. | |

| Reporting group values | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) | Total |
|---|---|---|---|
| Number of subjects | 151 | 151 | 302 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous | | | |
| Data of age collected for all included patients in the study. | | | |
| Units: Years | | | |
| arithmetic mean | 72.5 | 72.3 | |
| standard deviation | ± 5.6 | ± 5.1 | - |
| Sex: Female, Male | | | |
| Data of Gender collected of all patients included in the study. | | | |
| Units: Subjects | | | |
| Female | 60 | 59 | 119 |
| Male | 91 | 92 | 183 |
| Race (NIH/OMB) | | | |
| Data for Race of patients collected under protocol for all included patients in the study. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 7 | 4 | 11 |
| Asian | 52 | 52 | 104 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 10 | 8 | 18 |
| White | 81 | 84 | 165 |
| More than one race | 1 | 2 | 3 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Data for Ethnicity of patients collected under protocol for all included patients in the study. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 19 | 15 | 34 |
| Not Hispanic or Latino | 132 | 136 | 268 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Hemoglobin A1c (HbA1c) at baseline | | | |
| HbA1c values measured at baseline in percent. HbA1c is a form of hemoglobin, a blood pigment that carries oxygen, which is bound to glucose. The term HbA1c also refers to glycated hemoglobin. High levels of HbA1c (Normal range is less than 6%) indicate poorer control of diabetes than level in normal range. | | | |
| Units: Percentage (%) of HbA1c | | | |

| | | | |
|---|---|---|---|
| arithmetic mean | 8.1 | 8.2 | |
| standard deviation | ± 0.7 | ± 0.8 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo (Up to 24 weeks) |
| Reporting group description: | |
| Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks | |
| Reporting group title | Linagliptin 5 milligram (Up to 24 weeks) |
| Reporting group description: | |
| Patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 24 weeks. | |
| Reporting group title | Placebo (Up to 52 weeks) |
| Reporting group description: | |
| Only Japanese patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 52 weeks | |
| Reporting group title | Linagliptin 5 milligram (Up to 52 weeks) |
| Reporting group description: | |
| Only Japanese patients were orally administered with Linagliptin 5 milligram film-coated tablets once daily up to 52 weeks | |

### Primary: Change from baseline in Hemoglobin A1c (HbA1c) after 24 weeks of treatment.

| | |
|---|---|
| End point title | Change from baseline in Hemoglobin A1c (HbA1c) after 24 weeks of treatment. |
| End point description: | |
| This outcome has measured difference between HbA1c values from baseline to 24 weeks post treatment. The term 'baseline' refers to the last observation prior to the administration of any randomised study medication. HbA1c is a form of hemoglobin, a blood pigment that carries oxygen, which is bound to glucose. The term HbA1c also refers to glycated hemoglobin. High levels of HbA1c (Normal range is less than 6%) indicate poorer control of diabetes than level in normal range. Population set used for analysis: Full analysis set observed cases (FAS (OC)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. These analyses used available data as observed while patients were on treatment. All values collected after a patient started rescue medication were excluded from the analysis. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and Week 24 | |

| End point values | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 113[1] | 134[2] | | |
| Units: Percentage (%) of HbA1c | | | | |
| least squares mean (standard error) | -0.38 (± 0.07) | -1.01 (± 0.06) | | |

Notes:

[1] - Full analysis set observed cases (FAS (OC))

[2] - Full analysis set observed cases (FAS (OC))

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Mixed model repeated measures (MMRM) included treatment, week and interaction as fixed effects, baseline HbA1c, daily basal insulin dose as covariates

| | |
|---|---|
| Comparison groups | Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks) |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.81 |
| upper limit | -0.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.09 |

Notes:

[3] - MMRM including fixed effects treatment, week and treatment by week interaction linear covariates baseline HbA1c, baseline daily basal insulin and baseline HbA1c by week interaction and random effect for patient. Within−patient errors are modelled by unstructured covariance matrix. Adjusted mean is based on all patients in the model (not only patients with a baseline and week 24 measurement).

## Secondary: Percentage of patients experiencing at least one hypoglycaemia accompanied by a prespecified glucose value.

| End point title | Percentage of patients experiencing at least one hypoglycaemia accompanied by a prespecified glucose value. |
|---|---|

End point description:

Hypoglycaemia accompanied by a prespecified glucose value is defined as any investigator reported hypoglycaemia (event or AE) with a reported blood glucose level of less than 54 milligram/deciLitre (3.0 millimole/Litre) or any investigator reported symptomatic hypoglycaemic AE with a reported blood glucose level of less or equal 70 milligram/deciLitre (3.9millimole/Litre) or any severe hypoglycaemic AE. Severe hypoglycaemia is an event that requires the assistance of another person to actively administer carbohydrates or glucagon because the patient is unable to take the substance on his or her own. The confidence intervals mentioned in measure of dispersion are exact 95% confidence interval by Clopper and Pearson. The proportion of patients with at least one hypoglycaemia accompanied by a glucose value less than 54mg/dL alone has also represented separately according to American Diabetes Association definition of clinically significant hypoglycaemia.

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

End point timeframe:

24 Weeks

| End point values | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 147[4] | 149[5] | | |
| Units: Percentage of patients (%) | | | | |
| number (confidence interval 95%) | | | | |
| Prespecified glucose value | 23.8 (17.2 to 31.5) | 30.9 (23.6 to 39.0) | | |

| | | | | |
|---|---|---|---|---|
| Glucose value <54 mg/dL | 15.0 (9.6 to 21.8) | 16.8 (11.2 to 23.8) | | |

Notes:

[4] - Full analysis set observed cases (FAS (OC))

[5] - Full analysis set observed cases (FAS (OC))

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 2-Prespecified glucose value |
|---|---|

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. The logistic regression analysis showed that patients treated with linagliptin and placebo were equally likely to observe occurrence of hypoglycaemia.The dispersion value standard error of the mean is actually standard error for odds ratio.

| | |
|---|---|
| Comparison groups | Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks) |
| Number of subjects included in analysis | 296 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1594 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.464 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.861 |
| upper limit | 2.491 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.397 |

| **Statistical analysis title** | Statistical Analysis 3- Glucose value < 54mg/dL |
|---|---|

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. The logistic regression analysis showed that patients treated with linagliptin and placebo were equally likely to observe occurrence of hypoglycaemia.The dispersion value standard error of the mean is actually standard error for odds ratio.

| | |
|---|---|
| Comparison groups | Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks) |
| Number of subjects included in analysis | 296 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| P-value | = 0.672 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.149 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.604 |
| upper limit | 2.188 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.377 |

Notes:

[6] - The proportion of patients with at least one hypoglycaemia accompanied by a glucose value less than 54mg/dL alone has also represented separately according to American Diabetes Association definition of clinically significant hypoglycaemia.

### Secondary: Proportions of patients with HbA1c<8.0%

| | |
|---|---|
| End point title | Proportions of patients with HbA1c<8.0% |

End point description:

This is the proportion of patients with HbA1c on treatment <8.0% after 24 weeks of treatment. The confidence intervals mentioned in method of dispersion are exact 95% CI by Clopper and Pearson. Population set used for analysis: Full analysis set (Non-completers considered failure)(FAS (NCF)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. This analyses regarded missing values for binary efficacy endpoints as failure.

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

End point timeframe:

24 Weeks

| End point values | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 87[7] | 87[8] | | |
| Units: Percentage of patients (%) | | | | |
| number (confidence interval 95%) | 40.2 (29.9 to 51.3) | 70.1 (59.4 to 79.5) | | |

Notes:

[7] - Full analysis set (Non-completers considered failure)(FAS (NCF))

[8] - Full analysis set (Non-completers considered failure)(FAS (NCF))

### Statistical analyses

| Statistical analysis title | Statistical Analysis 4 |
|---|---|

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. This analysis showed that patients teated with linagliptin were more likely to achieve these responses than in the placebo group.The dispersion value standard error of the mean is actually standard error for odds ratio.

| | |
|---|---|
| Comparison groups | Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks) |
| Number of subjects included in analysis | 174 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 5.018 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.468 |
| upper limit | 10.206 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.818 |

## Secondary: Proportion of patients with HbA1c on treatment <7.0%

| | |
|---|---|
| End point title | Proportion of patients with HbA1c on treatment <7.0% |

End point description:

This is the proportion of patients with HbA1c on treatment <7.0% after 24 weeks of treatment. The confidence intervals mentioned in method of dispersion are exact 95% CI by Clopper and Pearson. Population set used for analysis: Full analysis set (Non-completers considered failure)(FAS (NCF)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. This analyses regarded missing values for binary efficacy endpoints as failure.

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

End point timeframe:

24 Weeks

| **End point values** | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 144[9] | 143[10] | | |
| Units: Percentage of patients (%) | | | | |
| number (confidence interval 95%) | 14.6 (9.3 to 21.4) | 37.8 (29.8 to 46.2) | | |

Notes:

[9] - Full analysis set (Non-completers considered failure)(FAS (NCF))

[10] - Full analysis set (Non-completers considered failure)(FAS (NCF))

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 5 |
|---|---|

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. This analysis showed that patients teated with linagliptin were more likely to achieve these responses than in the placebo group.The dispersion value standard error of the mean is actually standard error for odds ratio.

| | |
|---|---|
| Comparison groups | Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks) |
| Number of subjects included in analysis | 287 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.689 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.485 |
| upper limit | 8.848 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.519 |

## Secondary: Proportion of patients with HbA1c lowering by at least 0.5%.

| | |
|---|---|
| End point title | Proportion of patients with HbA1c lowering by at least 0.5%. |

End point description:

The proportions of patients who attained lowering of HbA1c by ≥0.5% from baseline after 24 weeks of treatment were analysed. The confidence intervals mentioned in method of dispersion are exact 95% CI by Clopper and Pearson. Population set used for analysis: Full analysis set (Non-completers considered failure)(FAS (NCF)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. This analyses regarded missing values for binary efficacy endpoints as failure.

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

End point timeframe:

24 Weeks

| **End point values** | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55[11] | 103[12] | | |
| Units: Percentage of patients (%) | | | | |
| number (confidence interval 95%) | 37.4 (29.6 to 45.8) | 69.1 (61.0 to 76.4) | | |

Notes:

[11] - Full analysis set (Non-completers considered failure)(FAS (NCF))

[12] - Full analysis set (Non-completers considered failure)(FAS (NCF))

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 6 |
|---|---|

Statistical analysis description:

A logistic regression model with treatment as fixed effect and baseline HbA1c and baseline daily basal insulin dose as linear covariates was applied. This analysis showed that patients teated with linagliptin were more likely to achieve these responses than in the placebo group.The dispersion value standard error of the mean is actually standard error for odds ratio.

| | |
|---|---|
| Comparison groups | Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks) |
| Number of subjects included in analysis | 158 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.731 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.302 |
| upper limit | 6.048 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.92 |

## Secondary: Change from baseline in Fasting Plasma Glucose (FPG)

| | |
|---|---|
| End point title | Change from baseline in Fasting Plasma Glucose (FPG) |

End point description:

This outcome has measured difference between FPG values from baseline to 24 weeks post treatment. The term 'baseline' refers to the last observation prior to the administration of any randomised study medication. Population set used for analysis: Full analysis set observed cases (FAS (OC)): Includes all patients randomised in the Treated Set who had a baseline and at least one on-treatment HbA1c value. These analyses used available data as observed while patients were on treatment. All values collected after a patient started rescue medication were excluded from the analysis.

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

End point timeframe:

Baseline and Week 24

| End point values | Placebo (Up to 24 weeks) | Linagliptin 5 milligram (Up to 24 weeks) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110[13] | 134[14] | | |
| Units: milligram/decilitre | | | | |
| least squares mean (standard error) | 0.2 (± 3.6) | -11.3 (± 3.3) | | |

Notes:

[13] - Full analysis set observed cases (FAS (OC))

[14] - Full analysis set observed cases (FAS (OC))

### Statistical analyses

| Statistical analysis title | Statistical Analysis 7 |
|---|---|

Statistical analysis description:

Adjusted mean of all differences between HbA1c at baseline and after 24 weeks. It is based on all patients in the model (not only patients with a baseline and week 24 measurement).

| | |
|---|---|
| Comparison groups | Placebo (Up to 24 weeks) v Linagliptin 5 milligram (Up to 24 weeks) |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.0178 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -11.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21 |
| upper limit | -2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.8 |

Notes:

[15] - MMRM including fixed effects treatment, week and treatment by week interaction, linear covariates baseline HbA1c, baseline daily basal insulin, baseline FPG and baseline FPG by week interaction and random effect for patient. Within−patient errors are modelled by unstructured covariance matrix. Adjusted mean is based on all patients in the model (not only patients with a baseline and week 24 measurement).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first drug administration up to 24 weeks, until 7 days after last drug administration for overall population. And from first drug administration up to 52 weeks, until 7 days after last drug administration for Japanese population.

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence, including an exacerbation of a preexisting condition, in a patient in a clinical investigation who received a pharmaceutical product. A treated set (TS) was used for AE analysis. TS includes patients who were dispensed study medication and taken at least one dose of investigational treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Linagliptin 5 mg (Up to 24 weeks) |

Reporting group description:

Patients were orally administered with Linagliptin 5 mg film-coated tablets once daily up to 24 weeks.

| | |
|---|---|
| Reporting group title | Placebo (Up to 24 weeks) |

Reporting group description:

Patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 24 weeks

| | |
|---|---|
| Reporting group title | Placebo (Up to 52 weeks) |

Reporting group description:

Japanese patients were orally administered with Placebo tablets (matching Linagliptin) once daily up to 52 weeks

| | |
|---|---|
| Reporting group title | Linagliptin 5mg (Up to 52 weeks) |

Reporting group description:

Japanese patients were orally administered with Linagliptin 5 mg film-coated tablets once daily up to 52 weeks.

| Serious adverse events | Linagliptin 5 mg (Up to 24 weeks) | Placebo (Up to 24 weeks) | Placebo (Up to 52 weeks) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 151 (12.58%) | 21 / 151 (13.91%) | 7 / 50 (14.00%) |
| number of deaths (all causes) | 2 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Colorectal cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Enchondromatosis | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 pain | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Cough | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 2 / 151 (1.32%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Femoral neck fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 1 / 50 (2.00%) |
| 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 dislocation | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 0 / 50 (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 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Arrhythmia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 | 2 / 151 (1.32%) | 0 / 151 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 1 / 151 (0.66%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 2 / 151 (1.32%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Nervous system disorders | | | |
| Brain stem infarction | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 151 (0.66%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral arteriosclerosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 0 / 151 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glaucoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 0 / 151 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Haematuria | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 1 / 151 (0.66%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 151 (0.66%) | 0 / 50 (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 / 151 (0.00%) | 1 / 151 (0.66%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 0 / 50 (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 |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 151 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Linagliptin 5mg (Up to 52 weeks) | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 52 (25.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colorectal cancer | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enchondromatosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 52 (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 / 52 (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 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Investigations | | | | |
| Lipase increased | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |
| Fall | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Joint dislocation | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple fractures | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rib fracture | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|---|---|---|---|
| Spinal compression fracture | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina pectoris | | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina unstable | | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arrhythmia | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bradycardia | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure congestive | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery disease | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery stenosis | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Brain stem infarction | | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebral arteriosclerosis | | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebral infarction | | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxic-ischaemic encephalopathy | | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lumbar radiculopathy | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bronchitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 52 (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 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Linagliptin 5 mg (Up to 24 weeks) | Placebo (Up to 24 weeks) | Placebo (Up to 52 weeks) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 72 / 151 (47.68%) | 58 / 151 (38.41%) | 19 / 50 (38.00%) |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 1 / 151 (0.66%) | 0 / 50 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |

| | | | |
|---|---|---|---|
| Large intestine polyp | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 0 / 151 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 3 / 151 (1.99%) | 1 / 151 (0.66%) | 0 / 50 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 5 / 151 (3.31%) | 6 / 151 (3.97%) | 3 / 50 (6.00%) |
| occurrences (all) | 5 | 6 | 3 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 7 / 151 (4.64%) | 4 / 151 (2.65%) | 0 / 50 (0.00%) |
| occurrences (all) | 9 | 4 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 10 / 151 (6.62%) | 9 / 151 (5.96%) | 1 / 50 (2.00%) |
| occurrences (all) | 11 | 11 | 1 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 11 / 151 (7.28%) | 8 / 151 (5.30%) | 3 / 50 (6.00%) |
| occurrences (all) | 12 | 9 | 4 |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 51 / 151 (33.77%) | 38 / 151 (25.17%) | 14 / 50 (28.00%) |
| occurrences (all) | 142 | 162 | 107 |

| **Non-serious adverse events** | Linagliptin 5mg (Up to 52 weeks) | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 52 (71.15%) | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | | |
| occurrences (all) | 3 | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | | |
| occurrences (all) | 3 | | |
| Reproductive system and breast | | | |

| | | | |
|---|---|---|---|
| disorders<br>Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all) | <br><br>3 / 52 (5.77%)<br>3 | | |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 52 (3.85%)<br>2 | | |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | <br><br>5 / 52 (9.62%)<br>6<br><br>1 / 52 (1.92%)<br>1<br><br>11 / 52 (21.15%)<br>16 | | |
| Metabolism and nutrition disorders<br>Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all) | <br><br>20 / 52 (38.46%)<br>58 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 October 2015 | The amendment was implemented after approval by the IEC/IRB/competent authority. The main changes introduced by the amendment were: *There was a change in Coordinating Investigator *The inclusion criteria were modified to allow patients from 60 years old (lower age limit) and with a lower HbA1c limit of 7.0% to be eligible for the trial *There was a change in the secondary endpoint regarding the proportion of patients with HbA1c <7.5% at the end of the trial – this was changed to HbA1c <7.0% *The key secondary endpoint was designated as a secondary endpoint *The sample size was reduced to 300 patients, with 100 randomised patients required in Japan *Exclusion criteria no. 1 was clarified for dementia scores excluding patients from undergoing further additional assessment, thereby excluding these patients from participation clarify the Saint Louis University Mental Status Examination scores for mild neurocognitive disorder *Exclusion criteria no. 4 was modified to add STEMI and/or unstable angina pectoris *Exclusion criteria no.10 was modified to add meglitinides and bromocriptine *The permitted antidiabetic therapy that was to be considered rescue therapy was clarified *The definition of hypoglycaemia as ≤70 mg/dL was clarified *The process for AESIs was updated and clarified *It was clarified that the results of pharmacogenetic sampling would be reported separately from the main clinical trial report |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For patients in Japan, a local protocol amendment was introduced, and according to it the study was extended to 52 weeks for Japanese population only.

Notes: