# Clinical trial results:
# A randomised, double-blind, placebo-controlled, parallel group dose-finding study of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus.

## Summary

| | |
|---|---|
| EudraCT number | 2009-017004-91 |
| Trial protocol | FR PL IT Outside EU/EEA |
| Global end of trial date | 11 February 2016 |

**Results information**

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

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1218.56 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01342484 |
| 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, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000498-PIP01-08 |
| 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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 14 March 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 February 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 February 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The main objective was to identify the dose of linagliptin in paediatric patients (children and adolescents from 10 to 17 years of age) with type 2 diabetes mellitus (T2DM).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All parents (or the patient's legally accepted representative) and patients were informed that they were free to withdraw their consent at any time during the study without penalty or prejudice. Close monitoring of all subjects was adhered to throughout the trial conduct. An independent Data Safety Monitoring Board (DSMB) was established to ensure that the study met the highest standards of ethics and patient safety. The DSMB monitored the progress of the study. Appropriate criteria were included for the initiation of rescue medication after randomisation. These criteria were based on FPG threshold levels, which decreased as the patient progressed through the treatment period of the trial. The safety of the patient was additionally ensured by discontinuation criteria (e.g. patients had to discontinue if the introduction of rescue medication did not lead to sufficient treatment efficacy). All patients received adequate treatment in case of any clinical concern.

Background therapy:

Most of the patients in the full analysis set (FAS) (26 patients) were drug-naive at screening. All other patients took metformin as background antidiabetic therapy; none of the patients in the FAS were treated with insulin or insulin plus metformin as background antidiabetic therapy.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 22 July 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Guatemala: 4 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Mexico: 25 |
| Country: Number of subjects enrolled | Poland: 9 |
| Country: Number of subjects enrolled | Russian Federation: 22 |
| Country: Number of subjects enrolled | Korea, Republic of: 12 |
| Country: Number of subjects enrolled | United States: 3 |
| Worldwide total number of subjects | 83 |
| EEA total number of subjects | 16 |

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) | 10 |
| Adolescents (12-17 years) | 73 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Randomized, double-blind, placebo-controlled parallel group dose-finding study of Linagliptin over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus. Due to serious GCP breach data for one patient were excluded from all analyses.

### Pre-assignment

Screening details:

All patients suitable after screening underwent a 2-week open-label placebo run-in period before randomisation. Patients who successfully completed this period and who still met the inclusion/exclusion criteria were randomised to the 12-week randomised period in which they received either 1 of the 2 doses of linagliptin or placebo.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matching Linagliptin 1 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 1 mg (1x 1mg tablet) dose once daily for 12 weeks.

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

Dosage and administration details:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 5 mg (1x 5mg tablet) dose once daily for 12 weeks.

| | |
|---|---|
| **Arm title** | Linagliptin 1 mg |

Arm description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks.

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

| | |
|---|---|
| Investigational medicinal product name | Linagliptin 1 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 1 mg (1x 1mg tablet) dose once daily for 12 weeks.

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

Dosage and administration details:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 5 mg (1x 5mg tablet) dose once daily for 12 weeks.

| | |
|---|---|
| **Arm title** | Linagliptin 5 mg |

Arm description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 5 mg (1x 5mg tablet) and placebo matching Linagliptin 1mg (1x 1mg tablet) dose once daily for 12 weeks.

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

Dosage and administration details:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 5 mg (1x 5mg tablet) dose once daily for 12 weeks.

| | |
|---|---|
| Investigational medicinal product name | Placebo matching Linagliptin 1 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 1 mg (1x 1mg tablet) dose once daily for 12 weeks.

| **Number of subjects in period 1[1]** | Placebo | Linagliptin 1 mg | Linagliptin 5 mg |
|---|---|---|---|
| Started | 15 | 10 | 14 |
| Completed | 13 | 10 | 13 |
| Not completed | 2 | 0 | 1 |
| Consent withdrawn by subject | 1 | - | - |
| Other Reasons | 1 | - | - |
| Protocol deviation | - | - | 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 the patients who were randomized after successfully completing the screening period along with 2-weeks open-label placebo run-in period and received at least one dose of the trial medication.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks. | |
| Reporting group title | Linagliptin 1 mg |
| Reporting group description: | |
| The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks. | |
| Reporting group title | Linagliptin 5 mg |
| Reporting group description: | |
| The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 5 mg (1x 5mg tablet) and placebo matching Linagliptin 1mg (1x 1mg tablet) dose once daily for 12 weeks. | |

| Reporting group values | Placebo | Linagliptin 1 mg | Linagliptin 5 mg |
|---|---|---|---|
| Number of subjects | 15 | 10 | 14 |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous | | | |
| Randomised set including all randomised patients, whether treated or not. | | | |
| Units: Years | | | |
| arithmetic mean | 13.7 | 14 | 14.3 |
| standard deviation | ± 2 | ± 1.8 | ± 2.1 |
| Gender, Male/Female | | | |
| Randomised set including all randomised patients, whether treated or not. | | | |
| Units: Participants | | | |
| Female | 8 | 4 | 9 |
| Male | 7 | 6 | 5 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 39 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous | | | |
| Randomised set including all randomised patients, whether treated or not. | | | |
| Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender, Male/Female | | | |
| Randomised set including all randomised patients, whether treated or not. | | | |
| Units: Participants | | | |
| Female | 21 | | |
| Male | 18 | | |

## End points

### End points reporting groups

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

Reporting group description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks.

| Reporting group title | Linagliptin 1 mg |
|---|---|

Reporting group description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks.

| Reporting group title | Linagliptin 5 mg |
|---|---|

Reporting group description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 5 mg (1x 5mg tablet) and placebo matching Linagliptin 1mg (1x 1mg tablet) dose once daily for 12 weeks.

### Primary: Change from baseline in Glycosylated Haemoglobin (HbA1c) (%) after 12 weeks of treatment

| End point title | Change from baseline in Glycosylated Haemoglobin (HbA1c) (%) after 12 weeks of treatment |
|---|---|

End point description:

Change from baseline in Glycosylated haemoglobin (HbA1c) [%] after 12 weeks of treatment with double-blind trial medication. Baseline was defined as the last observation before the first intake of any double-blind randomised trial medication. The number of participants analysed displays the number of participants with available data at the timepoint of interest. Full analysis set (FAS) including all randomised patients who were treated with at least one dose of study drug and had a baseline and at least one on treatment HbA1c assessment. Observed Cases (OC): Only the available data that were observed while patients were on treatment were analysed and values after the use of rescue medication were set to missing.

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

End point timeframe:

Baseline and 12 weeks

| End point values | Placebo | Linagliptin 1 mg | Linagliptin 5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11[1] | 8[2] | 13[3] | |
| Units: Percentage of HbA1c | | | | |
| least squares mean (standard error) | 0.45 (± 0.31) | -0.03 (± 0.38) | -0.19 (± 0.3) | |

Notes:

[1] - FAS-OC

[2] - FAS-OC

[3] - FAS-OC

## Statistical analyses

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

Statistical analysis description:

Superiority of Linagliptin 1 mg vs. placebo: change from baseline in HbA1c using a restricted maximum likelihood (REML) - based mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c and age as linear covariates; treatment, gender, PK/PD subgroup, background therapy, visit and visit by treatment interaction as fixed effects and patient as a random effect.

| | |
|---|---|
| Comparison groups | Placebo v Linagliptin 1 mg |
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.3295 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.47 |
| upper limit | 0.51 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.48 |

Notes:

[4] - The unstructured covariance structure has been used to fit the mixed model. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Mean Difference (Net Values) is actually the adjusted mean difference calculated as Linagliptin 1 mg minus Placebo.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Superiority of Linagliptin 5 mg vs. placebo: change from baseline in HbA1c using a restricted maximum likelihood (REML) - based mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c and age as linear covariates; treatment, gender, PK/PD subgroup, background therapy, visit and visit by treatment interaction as fixed effects and patient as a random effect.

| | |
|---|---|
| Comparison groups | Placebo v Linagliptin 5 mg |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.1447 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.42 |

Notes:

[5] - The unstructured covariance structure has been used to fit the mixed model. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Mean Difference (Net Values) is actually the adjusted mean difference calculated as Linagliptin 5 mg minus Placebo.

## Secondary: Dipeptidyl-peptidase-4 (DPP-4) inhibition (%) at trough at steady state

| | |
|---|---|
| End point title | Dipeptidyl-peptidase-4 (DPP-4) inhibition (%) at trough at |

| | |
|---|---|
| | steady state |

End point description:

DPP-4 inhibition (%) at trough at steady state is the relative change between the measurement of DPP-4 activity taken 0.5 hours before dosing at baseline and the first available on-treatment measurement of DPP-4 activity taken 0.5 hour before dosing at week 4, 8 or 12: DPP-4 inhibition (%) = 100 - (DPP-4 activity at week X / DPP-4 activity at baseline) x 100. Note: The analysis excludes placebo patients and 1 FAS patient from Linagliptin1 mg group.

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

End point timeframe:

Baseline and 4 weeks or 8 weeks or 12 weeks

| **End point values** | Placebo | Linagliptin 1 mg | Linagliptin 5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[6] | 9[7] | 13[8] | |
| Units: Percentage of DPP-4 inhibition | | | | |
| median (inter-quartile range (Q1-Q3)) | ( to ) | 38.4 (26.9 to 48.8) | 78.9 (67.7 to 84) | |

Notes:

[6] - The analysis excludes placebo patients.

[7] - FAS - OR (Original Results)

[8] - FAS - OR (Original Results)

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in fasting plasma glucose (FPG) after 12 weeks of treatment

| | |
|---|---|
| End point title | Change from baseline in fasting plasma glucose (FPG) after 12 weeks of treatment |

End point description:

Change from baseline in FPG (mmol/L) after 12 weeks of treatment with double-blind trial medication. The number of participants analysed displays the number of participants with available data at the timepoint of interest.

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

End point timeframe:

Baseline and 12 weeks

| **End point values** | Placebo | Linagliptin 1 mg | Linagliptin 5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 12[9] | 8[10] | 13[11] | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 1.7 (± 0.85) | 1.39 (± 1.07) | -0.19 (± 0.83) | |

Notes:

[9] - FAS-OC

[10] - FAS-OC

## Statistical analyses

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

Statistical analysis description:

Superiority of Linagliptin 1 mg vs. placebo: change from baseline in FPG using a restricted maximum likelihood (REML) - based mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c, baseline FPG and age as linear covariates; treatment, gender, PK/PD subgroup, background therapy, visit and visit by treatment interaction as fixed effects and patient as a random effect.

| | |
|---|---|
| Comparison groups | Placebo v Linagliptin 1 mg |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.8216 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.08 |
| upper limit | 2.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.36 |

Notes:

[12] - The unstructured covariance structure has been used to fit the mixed model. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Mean Difference (Net Values) is actually the adjusted mean difference calculated as Linagliptin 1 mg minus Placebo.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Superiority of Linagliptin 5 mg vs. placebo: change from baseline in FPG using a restricted maximum likelihood (REML) - based mixed model repeated measures (MMRM) approach. Model includes baseline HbA1c, baseline FPG and age as linear covariates; treatment, gender, PK/PD subgroup, background therapy, visit and visit by treatment interaction as fixed effects and patient as a random effect.

| | |
|---|---|
| Comparison groups | Placebo v Linagliptin 5 mg |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | = 0.1189 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.9 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.31 |
| upper limit | 0.52 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.18 |

Notes:

[13] - The unstructured covariance structure has been used to fit the mixed model. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Mean Difference (Net Values) is actually the adjusted mean difference calculated as Linagliptin 5 mg minus Placebo.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first intake of study drug until 7 days after the last drug administration, up to 13 weeks.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

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

Reporting group description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered placebo matching Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks.

| | |
|---|---|
| Reporting group title | Linagliptin 1 mg |

Reporting group description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 1 mg (1x 1mg tablet) and placebo matching Linagliptin 5mg (1x 5mg tablet) dose once daily for 12 weeks.

| | |
|---|---|
| Reporting group title | Linagliptin 5 mg |

Reporting group description:

The patient who completed the 2 weeks open label placebo run in period was randomized and orally administered Linagliptin 5 mg (1x 5mg tablet) and placebo matching Linagliptin 1mg (1x 1mg tablet) dose once daily for 12 weeks.

| Serious adverse events | Placebo | Linagliptin 1 mg | Linagliptin 5 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (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 |

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

| Non-serious adverse events | Placebo | Linagliptin 1 mg | Linagliptin 5 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 15 (46.67%) | 8 / 10 (80.00%) | 6 / 14 (42.86%) |

| | | | |
|---|---|---|---|
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 4 / 14 (28.57%) |
| occurrences (all) | 4 | 0 | 6 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Eye disorders | | | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lip oedema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|---|---|---|
| disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Conjunctivitis bacterial | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 10 (10.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 3 / 10 (30.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 10 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Vulvovaginitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 2 / 10 (20.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 10 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 December 2010 | It was explained why it was acceptable to start the trial in the paediatric population before the marketing authorisation for linagliptin was granted by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). A process was defined and added to the section on randomisation to ensure pre-specified proportions of treatment groups within strata for patients completing the 12-week randomised treatment period. This process was not implemented and therefore deleted from the Clinical trial protocol (CTP) with Amendment 2. Since Visit 3 was a visit generally performed by telephone, there was no possibility to check treatment compliance by pill count at this visit. It was clarified that there will be no treatment compliance check at Visit 3. It was made clear that no study medication was to be given to patients at Visit 6, since this visit was the end of treatment (EoT) visit. Laboratory parameters were added to the definition of pancreatitis. Instructions for the follow-up of patients with pancreatitis including arrangements for follow-up blood samples to be collected for repeat analysis of lipase were added. The substance to be given to the patient to perform the Boost Challenge was changed to a beverage composed of proteins, lipids and carbohydrates to limit the carbohydrates patient's intake. Furthermore, it contained some administrative changes, additions to achieve consistency between the different sections in the CTP, further clarifications, and an update of the number of patients treated and of the summary of Adverse Events (AEs/SAEs) in the CTP introduction section to be consistent with the latest version of the Investigator Brochure. |
| 18 November 2011 | To follow a request by the FDA, the assumptions for treatment effect as basis for the sample size determination were revised. Sample size was increased to 39 randomised patients in each treatment group leading to a total of 117 randomised patients. A para on the constant surveillance for drug-induced liver injury (DILI) was added to benefit-risk assessment section. A detailed definition of hepatic injury based on alterations in liver laboratory parameters was inserted in the section on the definition of protocol-specified significant AEs. Procedures to follow-up patients with renal events, skin lesions, or pancreatitis were described. Associated laboratory values defining such events were specified. Precise action regarding study drug was provided. A section on the monitoring for allergic reactions and the instructions to patients was added. Section on AEs to be considered as always serious was added to comply with new Boehringer Ingelheim (BI) safety guidelines. Some sections were rephrased to be in accordance with a new BI standards. A body mass index (BMI)>50th percentile for age and sex was added as inclusion criterion 7. For inclusion criteria 4 and 5, it was clarified that lab samples for GAD, ICA and C-peptide were to be taken prior to the randomisation visit but results were to be checked at Visit 2 prior to randomisation. Upper limit for lipase and amylase values was added to the definition of clinically significant hepatic disease in exclusion criterion 8. A history of pancreatitis and hereditary angioedema or of serious hypersensitivity reactions was introduced as exclusion criterion 9. Process to ensure pre-specified proportions of treatment groups within strata for patients completing the 12-week period introduced by Amendment 1 was not implemented and so deleted from the CTP with Amendment 2. It clarified that in the primary analysis the Last Observation Carried Forward (LOCF) approach will be used. An additional sensitivity analysis was introduced. |

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| 18 December 2012 | As agreed with PDCO, patients treated with metformin could be included in addition to drug naive patients with insufficient glycaemic control. All sections of the CTP affected by this change were revised. The sample size was not modified because of the change. 'Background therapy was added as stratification factor. 'Background therapy' and 'background therapy by treatment interaction' were included in the statistical model as fixed classification effects. Metformin was regarded as a NIMP thus the investigator was to assess the causal relationship of the SAE to metformin. Number of patients to be included in the PK rich sampling was increased from 12 to 13 patients per treatment arm due to early termination there were 12 pateint with rich sample. The term 'protocol-defined significant adverse event' was replaced by 'adverse event of special interest'. The number of planned trial centres was increased to around 50 and the following statement was removed: 'At least 2 patients should be randomised at each trial centre. Investigators who fail to screen at least one patient in the first 6 months of the trial may be excluded from further participation'. It was clarified that the results for Islet cell antigen (ICA) and Glutamic acid decarboxylase (GAD) antibodies had to be checked prior to randomisation and when auto-antibodies measurement were performed. For inclusion criterion 1 the relevant visit was changed from the screening visit to the randomisation visit. Contraindications to metformin according to the local label and a medical history of cancer and/or treatment for cancer within the last 5 years were added. Information based on the annual update of the IB was incorporated into the CTP. It was clarified that patients with intermediate PK sampling at Visit 6 had be dosed at Visit 6. Rescue medication was allowed after the randomisation of the patient to allow initiation of rescue medication between Visit 6 and 7. The wording regarding follow-up period was updated. |
| 28 May 2013 | Pancreatitis was added as a reason to stop the study medication. This change was implemented immediately to eliminate hazard. |
| 13 February 2014 | As agreed with the PDCO and the FDA, inclusion criterion 3 was modified and patients on stable basal insulin were allowed into the trial. Basal insulin was added as background therapy permitted during the trial. 'Insulin' and 'metformin in combination with insulin' were added as levels of the stratification factor background therapy. It was defined that for patients treated with insulin, an increase in insulin total daily dose by more than 10% from the prescribed baseline total daily dose for 7 consecutive days or more is considered as initiation of rescue therapy. Patients on short-acting insulin or patients who had received short-acting insulin for more than 3 days within the 3 months prior to randomisation were excluded from the trial (exclusion criterion 3). All sections in the CTP affected by these changes including the study title and the benefit-risk assessment section were revised. The HbA1c range in inclusion criterion 3 was broadened. A rationale was added why the sample size for the final analysis was not changed although the HbA1c inclusion range was broadened. A DPP-4 interim analysis to be performed by the independent DSMB was introduced. In the final analysis DPP-4 inhibition at trough at steady state was introduced as a key secondary endpoint. Relative efficacy response was added as a further efficacy endpoint. PK endpoints were classified as further endpoints. The primary ANCOVA analysis as planned in the original CTP was replaced by an MMRM approach. The assignment of patients to treatment groups was corrected for the FAS. The approach to handle missing data was changed from LOCF to OC. The definitions for AESIs were further specified and detailed. An adjudication committee for pancreatic events was set up. Procedures for glucometer measurements and glucose monitoring were clarified for the investigational sites. Exclusion criteria 1 and 8 were reworded. It was specified that the trial medication had to be taken after the last PK blood sampling. |

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| 26 January 2015 | The following changes were performed to be in line with BI standards and applicable SOPs, the latest version of the IB, and the project requirements: Thyroid neoplasm and thyroid cancer, pancreatic cancer, and cardiac failure were added to the list of AESIs. Further criteria for hepatic events were added to consider them as AESIs. The wording regarding the SAE declaration for events occurring during the screening period was changed. It was clarified what was expected for the assessment of the causal relationship of an SAE and what was expected in terms of follow-up of SAEs. To comply with the both, the PIP agreed with the Paediatric Committee of the European Medicines Agency (PDCO) and the post-marketing requirements and commitments agreed with the FDA, the timing of the DPP-4 interim analysis was modified. It was defined that the interim analysis was to be performed as soon as the PPSDPP4 included at least 8 patients from the linagliptin 1 mg group and 8 patients from the linagliptin 5 mg group. Power calculations based on 8 evaluable patients per linagliptin arm were added to the section on the determination of the sample size for the interim analysis. The focused interim PK/PD analyses were introduced to be performed in case the DPP-4 interim analysis did not lead to premature termination of the trial. In the original CTP it was stated that the popPK analyses are described in a separate report. However, it was decided to include the results of the popPK analyses into the Clinical trial report (CTR). It was clarified that therefore it was not necessary to develop a separate popPK analysis plan. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported