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 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 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.

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.

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