Clinical trial results:
A randomized open-label study to compare safety and efficacy of vildagliptin versus NPH insulin add-on to glimepiride in patients with type 2 diabetes mellitus that do not reach adequate glycemic control on their current sulfonylurea monotherapy

Summary

EudraCT number	2012-001143-46
Trial protocol	DE
Global end of trial date	10 October 2013

Results information

Result version number	v1 (current)
This version publication date	17 April 2016
First version publication date	17 April 2016

Trial information

Trial identification

Sponsor protocol code	CLAF237ADE08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01649466
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To demonstrate that vildagliptin in addition to glimepiride is superior to Neutrales Protamin Hagedorn (NPH) insulin in addition to glimepiride with respect to the incidence of the combined endpoint, defined as achieving the blood glucose target level of HbA1c <7.0% without any confirmed hypoglycemic event (HE) (defined as blood glucose (BG) measurement <3.9 mmol/L [<71 mg/dL]) and weight gain (defined as increase of at least 3%) in Type II diabetes mellitus (T2DM) patients.
2. To demonstrate that vildagliptin in addition to glimepiride is superior to NPH insulin in addition to glimepiride with respect to the rate of confirmed HEs (defined as BG measurement <3.9 mmol/L [<71 mg/dL]) in T2DM patients.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

Randomized patients were on a stable dose of glimepiride of 4 mg (or if not tolerated, the maximal tolerated dose up to 4 mg) for at least 4 weeks prior to Visit 1. The glimepiride background therapy had to be kept at a stable dose throughout the study.

Evidence for comparator: -

Actual start date of recruitment	27 August 2012
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	Germany: 162
Worldwide total number of subjects	162
EEA total number of subjects	162

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	58
From 65 to 84 years	103
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited to participate at 54 sites in Germany.

Pre-assignment

Screening details:

294 patients were screened over a 1-week period. 162 completed and randomized but 161 got exposed to study drug.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Vildagliptin

Arm description:

Subjects received Vildagliptin with glimepiride for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Vildagliptin
Investigational medicinal product code	
Other name	Galvus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg per os once daily as an add-on to the current glimepiride background therapy. The vildagliptin dose had to be kept stable after randomization (Visit 2) throughout the study.

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered 4 mg once daily or, if not tolerated, the maximal tolerated dose up to 4 mg.

Arm title	Neutrales Protamin Hagedorn (NPH) Insulin

Arm description:

Subjects received NPH insulin with glimepiride for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	NPH Insulin U100
Investigational medicinal product code	
Other name	Protaphane
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

1 subcutaneous dose per day, forced titration as an add-on to the current glimepiride background therapy. Insulin treatment was to be initiated with a single starting dose of 0.3 – 0.4 U/kg based on glimepiride dosing and BMI (0.3 U/kg, if both glimepiride ≤4 mg and BMI <25 kg/m2, and 0.4 U/kg, if glimepiride ≤4 mg and BMI ≥25 kg/m2). Afterwards, insulin doses were to be titrated individually during the first 4 weeks of treatment using a pre-defined titration regimen in order to achieve a target

fasting blood glucose (FBG) concentration of <100 mg/dL (<5.5 mmol/L) without significant hypoglycemia.

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered 4 mg once daily or, if not tolerated, the maximal tolerated dose up to 4 mg.

Number of subjects in period 1	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin
Started	83	79
Completed	58	70
Not completed	25	9
Adverse event, serious fatal	1	1
Adverse event, non-fatal	4	1
Protocol violation	4	-
Unsatisfactory therapeutic effect	14	2
Withdrew consent	1	4
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Vildagliptin
Reporting group description:	
Subjects received Vildagliptin with glimepiride for 24 weeks.	
Reporting group title	Neutrales Protamin Hagedorn (NPH) Insulin
Reporting group description:	
Subjects received NPH insulin with glimepiride for 24 weeks.	

Reporting group values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin	Total
Number of subjects	83	79	162
Age categorical Units: Subjects			
≤65 years	35	30	65
>65 years	48	49	97
Gender categorical Units: Subjects			
Female	36	31	67
Male	47	48	95

End points

End points reporting groups

Reporting group title	Vildagliptin
Reporting group description:	
Subjects received Vildagliptin with glimepiride for 24 weeks.	
Reporting group title	Neutrales Protamin Hagedorn (NPH) Insulin
Reporting group description:	
Subjects received NPH insulin with glimepiride for 24 weeks.	

Primary: Percent of Subjects Reaching Glycosylated Hemoglobin (HbA1c) Below 7.0% Without Confirmed Hypoglycemic Event And Weight Gain

End point title	Percent of Subjects Reaching Glycosylated Hemoglobin (HbA1c) Below 7.0% Without Confirmed Hypoglycemic Event And Weight Gain

End point description:

The percent of subjects achieving the blood glucose target level of HbA1c <7.0% without a hypoglycemic event (HE; defined as blood glucose [BG] measurement <3.9 mmol/L [<71 mg/dL]) and weight gain (defined as increase of at least 3%). HbA1c was monitored at Visits 1 (Screening), 2 (Baseline), 5 (Week 12), and 6 (Week 24). The last available post-baseline HbA1c value was used for the determination of the combined endpoint. Body weight was measured throughout the study at all on-site visits (Visits 1-6). Body weight changes were calculated from the values measured at Visit 2 and Visit 6.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Primary
End point timeframe:	
24 weeks	

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	79		
Units: percent of subjects				
number (not applicable)	35.4	34.2		

Statistical analyses

Statistical analysis title	Analysis of the combined endpoint
Comparison groups	Vildagliptin v Neutrales Protamin Hagedorn (NPH) Insulin

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9646
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.985
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.507
upper limit	1.915

Primary: Rate of Confirmed Hypoglycemic Events Per Year

End point title	Rate of Confirmed Hypoglycemic Events Per Year

End point description:

Co-primary endpoint is to evaluate the rate of confirmed hypoglycemic events (HEs), defined as a blood glucose (BG) measurement < 3.9mM (71mg/dL).
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Primary

End point timeframe:

24 weeks

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	79		
Units: rate of confirmed HEs per year				
arithmetic mean (standard deviation)	1.3 (± 5.9)	5.1 (± 14.7)		

Statistical analyses

Statistical analysis title	Analysis of the rate of confirmed HEs
Comparison groups	Neutrales Protamin Hagedorn (NPH) Insulin v Vildagliptin
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0164
Method	Chi-squared
Parameter estimate	Rate ratio
Point estimate	4.1543

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.299
upper limit	13.29

Secondary: Incidence of Severe Hypoglycemic Events

End point title	Incidence of Severe Hypoglycemic Events

End point description:

A severe hypoglycemic event (HE) was defined as a suspected Grade 2 or a confirmed Grade 2 event. This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	79		
Units: events	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Symptomatic Hypoglycemic Events Per Year

End point title	Rate of Symptomatic Hypoglycemic Events Per Year

End point description:

A symptomatic hypoglycemic event (HE) was defined as an HE not necessarily confirmed by laboratory measurement.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	79		
Units: rate of symptomatic HEs per year				
arithmetic mean (standard deviation)	0.5 (± 2.1)	1.8 (± 6.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects Who Reached Their Blood Glucose Target Without Any Confirmed Hypoglycemic Event

End point title	Percent of Subjects Who Reached Their Blood Glucose Target Without Any Confirmed Hypoglycemic Event

End point description:

The blood glucose (BG) target was defined as HbA1c below 7.0%. A confirmed hypoglycemic event (HE) was defined as BG measurement <3.9 mmol/L [<71 mg/dL]).
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	79		
Units: percent of subjects				
number (not applicable)	37.8	40.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight at End of Treatment

End point title	Change From Baseline in Body Weight at End of Treatment

End point description:

Body weight was measured throughout the study at all on-site visits (Visits 1-6). Body weight changes were calculated from the values measured at baseline and Week 24 (or end of treatment which is last observation until week 24). A negative value indicates a decrease in weight.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at

least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Secondary

End point timeframe:

Baseline, 24 weeks (or end of treatment i.e. Last post-baseline observation until Week 24)

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: kilogram(s)				
arithmetic mean (standard deviation)	-0.09 (± 3.6)	0.1 (± 4.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HbA1c at End of Treatment

End point title	Change From Baseline in HbA1c at End of Treatment

End point description:

HbA1c was monitored at Visits 1 (Screening), 2 (Baseline), 5 (Week 12), and 6 (Week 24). A negative value indicates a decrease in HbA1c percentage.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Secondary

End point timeframe:

Baseline, Week 24 (or end of treatment i.e. Last post-baseline observation until Week 24)

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: percent of HbA1c				
arithmetic mean (standard deviation)	-0.48 (± 0.89)	-0.8 (± 0.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM-9) Scores at End of Treatment

End point title	Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM-9) Scores at End of Treatment

End point description:

The TSQM-9 is a psychometrically sound and valid measure of the major dimensions of patients' satisfaction with medication. The 4 scales of the original TSQM Version 1.4 with 14 items include the effectiveness scale (questions 1 to 3), the side effects scale (questions 4 to 8), the convenience scale (questions 9 to 11), and the global satisfaction scale (questions 12 to 14). In the TSQM-9, the five items related to side effects of medication are not included. The TSQM-9 domain scores range from 0 to 100, with higher scores representing higher satisfaction on that domain. A positive change from baseline indicates that satisfaction has increased.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of randomized study drug, and the Safety Set (SAF), defined as all patients who received at least one dose of study drug whether or not being randomized. The SAF and FAS were identical in this study.

End point type	Secondary

End point timeframe:

24 weeks (or end of treatment i.e. Last post-baseline observation until Week 24)

End point values	Vildagliptin	Neutrales Protamin Hagedorn (NPH) Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	79		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Convenience Score (n=61, 70)	9.6 (± 19.1)	-5.6 (± 22)		
Effectiveness Score (n=61, 70)	7.1 (± 33.2)	7.3 (± 30.3)		
Global Satisfaction Score (n=61, 69)	7.7 (± 21.6)	4.8 (± 18.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Neutrales Protamin Hagedorn (NPH) Insulin

Reporting group description:

Subjects received NPH insulin with glimepiride for 24 weeks.

Reporting group title	Vildagliptin

Reporting group description:

Subjects received Vildagliptin with glimepiride for 24 weeks.

Serious adverse events	Neutrales Protamin Hagedorn (NPH) Insulin	Vildagliptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 79 (7.59%)	11 / 82 (13.41%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
UTERINE LEIOMYOMA			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			

subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
UTERINE CYST			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ALCOHOL POISONING			
subjects affected / exposed	1 / 79 (1.27%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
CONGENITAL CYSTIC KIDNEY DISEASE			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 79 (1.27%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 79 (1.27%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CAROTID ARTERY STENOSIS			

subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONVULSION			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIPLEGIA			
subjects affected / exposed	1 / 79 (1.27%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO POSITIONAL			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTIGO			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE POLYP			

subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	1 / 79 (1.27%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL COLIC			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
GOUTY ARTHRITIS			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
NASOPHARYNGITIS			

subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 79 (1.27%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 79 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Neutrales Protamin Hagedorn (NPH) Insulin	Vildagliptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 79 (51.90%)	29 / 82 (35.37%)	
Nervous system disorders			
TREMOR			
subjects affected / exposed	5 / 79 (6.33%)	2 / 82 (2.44%)	
occurrences (all)	10	7	
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	4 / 79 (5.06%)	1 / 82 (1.22%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	2 / 79 (2.53%)	5 / 82 (6.10%)	
occurrences (all)	2	9	
Infections and infestations			

BRONCHITIS			
subjects affected / exposed	4 / 79 (5.06%)	2 / 82 (2.44%)	
occurrences (all)	4	2	
NASOPHARYNGITIS			
subjects affected / exposed	8 / 79 (10.13%)	9 / 82 (10.98%)	
occurrences (all)	10	12	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	9 / 79 (11.39%)	10 / 82 (12.20%)	
occurrences (all)	24	31	
HYPOGLYCAEMIA			
subjects affected / exposed	23 / 79 (29.11%)	12 / 82 (14.63%)	
occurrences (all)	140	44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2012	The following changes were made to the study protocol: * Direct bilirubin limits were deleted in exclusion criterion No. 4 in order to be consistent with the current SmPC. Nonetheless, total bilirubin limits were maintained for the ongoing trial. * The confirmation of abnormal liver values within 3 working days (re-test) was included for clarification in exclusion criterion No. 4, since re-testing was previously described in Appendix 2 of the study protocol only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported