Clinical trial results:
Multicentric cross-over trial to assess the glycemic profiles on 8 weeks of vildagliptin and sitagliptin treatment, each, in type 2 diabetic patients with a pre-existing cardiovascular disease pre-treated with insulin, using a PROBE design.
Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2011-006118-15
Trial protocol	DE
Global end of trial date	08 September 2014

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	CLAF237ADE07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01686932
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	08 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that vildagliptin leads to a more favorable hypoglycemic profile than sitagliptin, after 8 weeks of treatment, each, when used in combination with insulin.

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: -

Evidence for comparator: -

Actual start date of recruitment	21 November 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: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Period 1: 8 weeks treatment with vildagliptin 50mg BID or sitagliptin 100mg QD, 1-4 weeks wash-out, followed by Period 2, 8 weeks treatment with sitagliptin 100mg QD or vildagliptin 50mg BID

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vildagliptin followed by Sitagliptin

Arm description:

Period 1: vildagliptin 50mg BID for 8 weeks; followed by Washout then Period 2: sitagliptin 100mg QD for 8 weeks

Arm type	Experimental
Investigational medicinal product name	vildagliptin
Investigational medicinal product code	LAF237
Other name	Galvus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vildagliptin 50 mg tablets for oral administration-1 tablet in the morning and in the evening

Arm title	Sitagliptin followed by Vildagliptin

Arm description:

Period 1: sitagliptin 100mg QD for 8 weeks; followed by Washout then Period 2: vildagliptin 50mg BID for 8 weeks

Arm type	Active comparator
Investigational medicinal product name	sitagliptin
Investigational medicinal product code	
Other name	januvia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin 100 mg tablets for oral administration -1 tablet in the morning

Number of subjects in period 1	Vildagliptin followed by Sitagliptin	Sitagliptin followed by Vildagliptin
Started	25	26
Completed	24	25
Not completed	1	1
Adverse event, non-fatal	1	1

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Vildagliptin followed by Sitagliptin

Arm description:

Period 1: vildagliptin 50mg BID for 8 weeks; followed by Washout then Period 2: sitagliptin 100mg QD for 8 weeks

Arm type	Experimental
Investigational medicinal product name	vildagliptin
Investigational medicinal product code	LAF237
Other name	Galvus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vildagliptin 50 mg tablets for oral administration-1 tablet in the morning and in the evening

Arm title	Sitagliptin followed by Vildagliptin

Arm description:

Period 1: sitagliptin 100mg QD for 8 weeks; followed by Washout then Period 2: vildagliptin 50mg BID for 8 weeks

Arm type	Active comparator
Investigational medicinal product name	sitagliptin
Investigational medicinal product code	
Other name	januvia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin 100 mg tablets for oral administration -1 tablet in the morning

Number of subjects in period 2	Vildagliptin followed by Sitagliptin	Sitagliptin followed by Vildagliptin
Started	24	25
Completed	24	25

Baseline characteristics

Reporting groups	
Reporting group title	Vildagliptin followed by Sitagliptin
Reporting group description:	
Period 1: vildagliptin 50mg BID for 8 weeks; followed by Washout then Period 2: sitagliptin 100mg QD for 8 weeks	
Reporting group title	Sitagliptin followed by Vildagliptin
Reporting group description:	
Period 1: sitagliptin 100mg QD for 8 weeks; followed by Washout then Period 2: vildagliptin 50mg BID for 8 weeks	

Reporting group values	Vildagliptin followed by Sitagliptin	Sitagliptin followed by Vildagliptin	Total
Number of subjects	25	26	51
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	14	26
From 65-84 years	13	12	25
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	64.8	65.2	
standard deviation	± 6	± 8.6	-
Gender, Male/Female Units: participants			
Male	21	20	41
Female	4	6	10

Subject analysis sets	
Subject analysis set title	Vitagliptin
Subject analysis set type	Full analysis
Subject analysis set description:	
For all Vitagliptin 50mg BID for 8 weeks in Period 1 and 8 weeks in Period 2	
Subject analysis set title	Sitagliptin
Subject analysis set type	Full analysis
Subject analysis set description:	
For all Sitagliptin 100mg QD for 8 weeks in Period 1 and 8 weeks in Period 2	

Reporting group values	Vitagliptin	Sitagliptin	
Number of subjects	49	49	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	14	
From 65-84 years	13	12	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Gender, Male/Female Units: participants			
Male			
Female			

End points

End points reporting groups

Reporting group title	Vildagliptin followed by Sitagliptin
Reporting group description:	
Period 1: vildagliptin 50mg BID for 8 weeks; followed by Washout then Period 2: sitagliptin 100mg QD for 8 weeks	
Reporting group title	Sitagliptin followed by Vildagliptin
Reporting group description:	
Period 1: sitagliptin 100mg QD for 8 weeks; followed by Washout then Period 2: vildagliptin 50mg BID for 8 weeks	
Reporting group title	Vildagliptin followed by Sitagliptin
Reporting group description:	
Period 1: vildagliptin 50mg BID for 8 weeks; followed by Washout then Period 2: sitagliptin 100mg QD for 8 weeks	
Reporting group title	Sitagliptin followed by Vildagliptin
Reporting group description:	
Period 1: sitagliptin 100mg QD for 8 weeks; followed by Washout then Period 2: vildagliptin 50mg BID for 8 weeks	
Subject analysis set title	Vitagliptin
Subject analysis set type	Full analysis
Subject analysis set description:	
For all Vitagliptin 50mg BID for 8 weeks in Period 1 and 8 weeks in Period 2	
Subject analysis set title	Sitagliptin
Subject analysis set type	Full analysis
Subject analysis set description:	
For all Sitagliptin 100mg QD for 8 weeks in Period 1 and 8 weeks in Period 2	

Primary: Hypoglycemic profile of vildagliptin compared to sitagliptin over 4 days after 8 weeks of treatment in Period 1 & 2

End point title	Hypoglycemic profile of vildagliptin compared to sitagliptin over 4 days after 8 weeks of treatment in Period 1 & 2
End point description:	
The hypoglycemic profile is defined as the area under the curve glucose-time profile obtained by continuous glucose monitoring Interstitial glucose values below 3.9 mmol/L (averaged over 5 minutes) were considered relevant for the estimation of the interstitial glucose AUC in the hypoglycemic range These AUC<3.9mmol/L/5min. values were summed up over 4 days (unit: mmol/L/4d) or over 24 hours at measurement Days 2, 3, 4, and 5 (unit: mmol/L/24h). Lower values for AUC reflect less intense hypoglycemia.	
End point type	Primary
End point timeframe:	
after 8 weeks (end of period 1 and 2)	

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: mmol/L/4d				
arithmetic mean (standard deviation)	11.2 (± 25.65)	5.3 (± 11.7)		

Statistical analyses

Statistical analysis title	Hypoglycemic profile

Statistical analysis description:

The hypoglycemic profile is defined as the area under the curve glucose-time profile obtained by continuous glucose monitoring Interstitial glucose values below 3.9 mmol/L (averaged over 5 min were considered relevant for the estimation of the interstitial glucose AUC in the hypoglycemic rangeThese AUC<3.9mmol/L/5min. values were summed up over 4 days (unit: mmol/L/4d) or over 24 hours at measurement Days 2, 3, 4, and 5 (unit: mmol/L/24h). Lower values for AUC reflect less intense hypoglycemia

Comparison groups	Vitagliptin v Sitagliptin
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1179
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	6.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	13.7

Secondary: Number of hypoglycemic events during vildagliptin treatment compared to sitagliptin treatment.

End point title	Number of hypoglycemic events during vildagliptin treatment compared to sitagliptin treatment.

End point description:

Hypoglycemic events are defined as blood glucose values <70 mg/dL measured by a self-monitored blood glucose (SMBG) or continuous glucose monitoring (CGM) measurement regardless of any symptoms suggestive of low blood glucose.

End point type	Secondary

End point timeframe:

after 8 weeks period 1 and Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: number of hypoglycemic events				
continuous glucose monitoring (CGM)	69	37		
self-monitored blood glucose (SMBG)	29	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean duration of hypoglycemic events (min.) measured with continuous glucose monitoring (CGM) over 4 days after 8 weeks of treatment for Period 1 & Period 2

End point title	Mean duration of hypoglycemic events (min.) measured with continuous glucose monitoring (CGM) over 4 days after 8 weeks of treatment for Period 1 & Period 2

End point description:

the mean duration of hypoglycemic events is detected by continuous glucose monitoring (CGM)measurement.

End point type	Secondary

End point timeframe:

after 8 weeks for Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: minutes				
arithmetic mean (standard deviation)	29.1 (± 44.71)	28 (± 51.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean amplitudes of hypoglycemic events (mmol/L) measured with continuous glucose monitoring (CGM) over 4 days after 8 weeks of treatment for Period 1 & Period 2

End point title	Mean amplitudes of hypoglycemic events (mmol/L) measured with continuous glucose monitoring (CGM) over 4 days after 8 weeks of treatment for Period 1 & Period 2

End point description:

To evaluate by CGM measurement the grade of severity of hypoglycemia measured as the mean amplitude over 4 days after 8 weeks of treatment in Period 1 & Period 2

End point type	Secondary

End point timeframe:

after 8 weeks Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: mmol/L				
arithmetic mean (standard deviation)	0.2 (± 0.32)	0.2 (± 0.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of severe hypoglycemic events during vildagliptin treatment compared to sitagliptin treatment after 8 weeks of treatment in Period 1 and Period 2

End point title	Number of severe hypoglycemic events during vildagliptin treatment compared to sitagliptin treatment after 8 weeks of treatment in Period 1 and Period 2

End point description:

Severe hypoglycemic events are defined as any episode requiring the assistance of another party or measured plasma glucose levels of <40 mg /dL. Assessed by self-monitored blood glucose (SMBG)After 8 weeks of treatment in Period 1 and Period 2

End point type	Secondary

End point timeframe:

after 8 weeks Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: severe hypoglycemic events	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Glucose fluctuations during the day under vildagliptin treatment compared to sitagliptin treatment on Day 2 after 8 weeks of treatment Period 1 & Period 2

End point title	Glucose fluctuations during the day under vildagliptin treatment compared to sitagliptin treatment on Day 2 after 8 weeks of treatment Period 1 & Period 2

End point description:

Glucose fluctuations are assessed by the mean amplitude of glycemic excursions (MAGE) and standard deviations (SD) (Service et al., 1970). on day 2 after 8 weeks of treatment Period 1 & Period 2

End point type	Secondary

End point timeframe:

Day 2 after 8 weeks of treatment Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: mmol/L				
arithmetic mean (standard deviation)	4.7 (± 1.69)	4.6 (± 1.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with ECG abnormalities depending on hypoglycemic events after 8 weeks of treatment Period 1 & Period 2

End point title	Number of participants with ECG abnormalities depending on hypoglycemic events after 8 weeks of treatment Period 1 & Period 2

End point description:

ECG abnormalities are defined as either: • Occurrence of >30 ventricular extrasystoles (VES) per hour or • Occurrence of ≥2 consecutive VES (Couplets) or • Occurrence of ≥3 consecutive VES (Triplets) or • QT-time corrected for heart rate (QTc) >440 ms. after 8 weeks of treatment Period 1 & Period 2

End point type	Secondary

End point timeframe:

after 8 weeks of treatment Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: participants				
Patients with hypoglycemia (n=21,17)	14	10		
Patients without hypoglycemia (n=28,32)	19	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of inflammatory biomarkers high sensitivity C-reactive protein (hsCRP) after 8 weeks of treatment in Period 1 & Period 2

End point title	Change from Baseline of inflammatory biomarkers high

	sensitivity C-reactive protein (hsCRP) after 8 weeks of treatment in Period 1 & Period 2

End point description:

The inflammatory biomarkers hsCRP was assessed at baseline and after 8 weeks of treatment Period 1 & Period 2

End point type	Secondary

End point timeframe:

Baseline, after 8 weeks Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: mg/L				
arithmetic mean (standard deviation)	0.79 (± 4.96)	0.6 (± 2.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of inflammatory biomarkers Interleukin 6 (IL-6) after 8 weeks of treatment in Period 1 & Period 2

End point title	Change from Baseline of inflammatory biomarkers Interleukin 6 (IL-6) after 8 weeks of treatment in Period 1 & Period 2

End point description:

The inflammatory biomarkers IL-6 was assessed at baseline and after 8 weeks of treatment Period 1 & Period 2

End point type	Secondary

End point timeframe:

Baseline, after 8 weeks Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: pg/L				
arithmetic mean (standard deviation)	0.4 (± 3.9)	0.08 (± 0.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from baseline of pro-insulin/C-peptide ratios after 8 weeks of treatment Period 1 & Period 2

End point title	Percentage Change from baseline of pro-insulin/C-peptide ratios after 8 weeks of treatment Period 1 & Period 2

End point description:

Percentage Change from baseline of pro-insulin/C-peptide ratios after 8 weeks of treatment Period 1 & Period 2 Higher pro-insulin / C-peptide ratios (expressing disproportional hyperproinsulinemia) may be associated with increasing beta cell dysfunction and more inefficient pro-insulin processing

End point type	Secondary

End point timeframe:

Baseline, after 8 weeks Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: Percentage Change				
arithmetic mean (standard deviation)	-0.34 (± 0.47)	-0.31 (± 0.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Occurrence of pre-defined ECG findings during 4 days of continuous ECG monitoring at baseline and in the 8th week of Periods 1 and 2

End point title	Number of Occurrence of pre-defined ECG findings during 4 days of continuous ECG monitoring at baseline and in the 8th week of Periods 1 and 2

End point description:

Number of Occurrence of pre-defined ECG findings during 4 days of continuous ECG monitoring at baseline and in the 8th week of Periods 1 and 2. ECG data were continuously recorded and analyzed over a period of 4 days simultaneously with continuous glucose monitoring. It assessed number of any Vertical Electric(al) Sounding (VES), number of 2 consecutive VES [couplets], and number of >3 consecutive VES [salves]

End point type	Secondary

End point timeframe:

after 8 weeks Period 1 & Period 2

End point values	Vitagliptin	Sitagliptin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: number of occurrence				
arithmetic mean (standard deviation)				
# any VES Per.1 n=23, 25	879.7 (± 1405.2)	2786.7 (± 6507.7)		
# any VES Per.2 n=25, 23	4389.9 (± 16692)	1060.2 (± 1812.4)		
# couplets VES Per.1 n=23, 25	12.8 (± 32.5)	115 (± 405.9)		
# couplets VES Per.2 n=25, 23	6.7 (± 10.3)	2.4 (± 3)		

# salves VES Per.1 n=23, 25	1 (± 2.4)	15.8 (± 52.6)		
# salves VES Per.2 n=25, 23	0.8 (± 1.7)	0.9 (± 1.9)		

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	17.1

Reporting groups

Reporting group title	Vildagliptin
Reporting group description:	
Vildagliptin	
Reporting group title	Total
Reporting group description:	
Total	
Reporting group title	Sitagliptin
Reporting group description:	
Sitagliptin	

Serious adverse events	Vildagliptin	Total	Sitagliptin
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	1 / 50 (2.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
PERICARDITIS			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
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	Vildagliptin	Total	Sitagliptin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 50 (36.00%)	23 / 51 (45.10%)	12 / 50 (24.00%)
Investigations			
BLOOD GLUCOSE DECREASED			
subjects affected / exposed	4 / 50 (8.00%)	6 / 51 (11.76%)	3 / 50 (6.00%)
occurrences (all)	4	12	8
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	1 / 50 (2.00%)
occurrences (all)	2	3	1
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	1 / 50 (2.00%)
occurrences (all)	3	4	1

Psychiatric disorders RESTLESSNESS subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 3	3 / 51 (5.88%) 6	2 / 50 (4.00%) 3
Metabolism and nutrition disorders HYPOGLYCAEMIA subjects affected / exposed occurrences (all)	13 / 50 (26.00%) 27	18 / 51 (35.29%) 36	7 / 50 (14.00%) 9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2012	Amendment 1 The protocol was amended to include several clarifications related to the definition of the term "coronarogram", adverse event reporting and test meals. Furthermore, one exclusion criterion was removed due to new findings regarding the use of CGM in patients treated with anticoagulants. These changes were considered substantial and thus required IRB/IEC approval prior to implementation.
20 November 2012	Amendment 2 The protocol was amended to align the exclusion criteria regarding liver function with the current SmPC of vildagliptin, where liver function was determined via AST/ALT-values, but not via bilirubin. Additionally, accepted HbA1c values were lowered to 7.0 % to include patients with a moderate disease status as well. Furthermore, the number of center digits was adapted to be in accordance with the CRF. These changes were considered substantial and thus required IRB/IEC approval prior to implementation.
29 October 2013	Amendment 3 The protocol was amended with changes in inclusion criteria, including the insulin background medication and the patient's history of CV events. The rationale of the amendment was based on new study data showing that patients on an intensified conventional therapy may benefit from an additional DPP-4-inhibitor treatment. Thus, inclusion criterion No. 3 was modified to allow the additional inclusion of patients with stable ICT for at least 12 weeks prior to Visit 1. Moreover, the modification of inclusion criterion No. 6 regarding the CV history was modified to allow also the inclusion of fragile patients with at least 2 risk factors. This modification reflected a very important and relevant patient population, which is prominent in real-life clinical practice. Further, the section on study drug discontinuation was modified to clarify the need for study drug discontinuation, and to avoid unclarity in the study protocol. These changes were considered substantial and thus required IRB/IEC approval prior to implementation.
09 January 2014	Amendment 4 The protocol was amended to adapt the protocol according to the valid approval of the independent EC and health authorities, and to correct inconsistencies that were erroneously introduced with previous amendments. As per Amendment 3, ICT patients were additionally allowed to be enrolled and inclusion criterion No. 3 was modified Novartis accordingly but, erroneously, exclusion criterion No. 2.a was still not adjusted, thereby still precluding the enrollment of ICT patients by excluding the use of rapid- or short-acting insulin except in pre-mixed formulations with intermediate or long-acting insulin, and by excluding insulin administration more frequently than twice-daily. Therefore, also exclusion criterion 2.a was modified accordingly. Further, a typing error was corrected and the row "serum pregnancy test" in the schedule of assessments was corrected in order to reflect assessments defined in the section on pregnancy and assessments of fertility. Overall, the changes introduced with Amendment 4 were regarded as non-substantial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: