Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Investigational

Study Number

CLAF237A2387

Title

A single-center, double-blind, randomized, placebo-controlled, cross-over study to assess the effect of vildagliptin on the incretin effect in patients with type 2 diabetes treated with metformin.

Phase of Development

Phase III

Study Start/End Dates

30 Oct 2006 to 14 Nov 2007

Study Design/Methodology

This was a single-center, double-blind, placebo-controlled, cross-over study using vildagliptin 100 mg and vildagliptin 100 mg matching placebo. All patients underwent two treatment periods (one period of vildagliptin treatment and one period of matching placebo treatment) during which an oral glucose challenge (75 g glucose) was performed on Day 13 (Day 55 during period 2) and an “isoglycemic” i.v. glucose infusion was performed on Day 14 (Day 56 during period 2). Patients underwent a 4-week washout before crossing over to the next period with the alternative

treatment.

Centers

1 center in 1 country: Germany (1)

Publication

Ongoing

Objectives

Primary objective(s)

- To demonstrate the effect of vildagliptin on the incretin mediated enhancement of insulin secretion (75 g oral glucose vs. matched i.v. glucose) in patients with T2DM treated with metformin by testing the hypothesis that the improvement of the incretin effect assessed as C-peptide IAUC(0-4hr) with vildagliptin 100 mg qd is superior to that with placebo after 2 weeks of treatment.

Secondary objective(s)

- To demonstrate the effect of vildagliptin on the incretin mediated enhancement of insulin secretion (75 g oral glucose vs. matched i.v. glucose) in patients with T2DM treated with metformin by testing the hypothesis that the improvement of the incretin effect assessed as 'insulin secretion rate (ISR) relative to glucose (0-2hr)' with vildagliptin 100 mg qd is superior to that with placebo after 2 weeks of treatment.
- To evaluate the prandial responses to vildagliptin in patients with T2DM treated with metformin by testing the hypothesis that vildagliptin 100 mg qd has favorable effects relative to placebo on postprandial parameters (derived from C-peptide, insulin, glucagon, GLP-1, and GIP) following an oral glucose challenge or "isoglycemic" intravenous glucose infusion after 2 weeks of treatment.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral tablets of vildagliptin 100 mg once daily

Reference Product(s), Dose(s), and Mode(s) of Administration

Oral tablets of placebo 100 mg once daily

Criteria for Evaluation

Primary variables

- Incretin effect, calculated as: [C-peptide IAUC(0-4hr) (oral) – C-peptide IAUC(0-4hr) (i.v.)] / [C-peptide IAUC(0-4hr) (oral)] x 100%.

Secondary variables

- $ISR_{(0\text{-}2hr)}$ incretin effect, calculated as: [ISR relative to $glucose_{(0\text{-}2hr)}$ (oral) – ISR relative to $glucose_{(0\text{-}2hr)}$ (i.v.) / ISR relative to $glucose_{(0\text{-}2hr)}$ (oral)] x 100].
- $AUC_{0\text{-}2hr}$ for C-peptide, insulin, glucagon, GLP-1 (total and intact), and GIP (intact)
- ISR relative to $glucose_{(0\text{-}2hr)}$, calculated as: $AUC_{0\text{-}2hr}$ of ISR / $AUC_{0\text{-}2hr}$ of glucose.

Safety and tolerability

Safety assessments consisted of collecting all AEs, serious AEs (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at a central laboratory and regular assessments of vital signs, ECG, physical condition, and body weight.

Tolerability- Not applicable

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The primary null hypothesis tested was that there was no difference between vildagliptin 100 mg qd and placebo in mean plasma incretin effect after the 4-hour oral glucose challenge. This was analyzed after the second week of treatment in each of the two treatment periods using a repeated measures mixed model that included period, sequence, and treatment as fixed effects, and patient-within-sequence as a random effect. The least squares mean plasma incretin effect for each treatment, the difference of the least square mean of the two treatments (vildagliptin to placebo), and the two-sided 95% confidence interval (CI) for this difference along with the p-value for the

difference were reported based on the fitted model. The superiority of vildagliptin over placebo was established if the above difference between least square means of the two treatments (vildagliptin and placebo) was greater than 0 and if the p-value was less than 0.05.

The primary hypothesis was based on the completers population with additional sensitivity analyses performed on the per protocol and intent-to-treat (ITT) populations.

All secondary and exploratory efficacy variables were analyzed using a 2-sided test for superiority of vildagliptin versus placebo with overall alpha of 0.05. No adjustments were made for multiple comparisons. The completers population alone was used for the analyses of these variables.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

T2DM patients aged 30-78 years with HbA_{1c} in the range of 7.0-9.0% and fasting plasma glucose (FPG) < 11.1 mmol/L (200 mg/dL) who had received metformin for ≥ 3 months at a stable dose of ≥ 1500 mg daily for at least 4 weeks before Visit 1.

Exclusion criteria:

Evidence of significant diabetic complications; history of Torsades de pointes; clinically relevant ventricular tachycardia or ventricular fibrillation; percutaneous coronary intervention within the past 3 months; history in the past 6 months of myocardial infarction, coronary artery bypass surgery, unstable angina, or stroke; congestive heart failure requiring pharmacologic treatment; liver disease; and significant renal dysfunction.

Number of Subjects

Population	Vildagliptin 100 mg qd / placebo N=11 n (%)	Placebo / vildagliptin 100 mg qd N=11 n (%)
Randomized[1]	11	11
Safety[2]	11 (100)	11 (100)
Intent to treat[3]	10 (90.9)	11 (100)
Completers[4]	9 (81.8)	11 (100)
Per protocol[5]	9 (81.8)	11 (100)

[1]Randomized population consisted of all randomized patients.

[2]Safety population consisted of all patients randomized that received at least one dose of study drug.

[3]Intent-to-treat population consisted of all patients randomized that received at least one dose of study drug and had at least one valid assessment of the primary efficacy variable.

[4]Completers population consisted of all patients randomized that received at least one dose of study drug and had a valid assessment of the primary efficacy variable for both treatment periods.

[5]Per protocol population consisted of all completers that had at least 10 days of treatment prior to the oral glucose tolerance test and at least 11 days of treatment prior to the intravenous glucose infusion in each treatment period, a valid assessment of the primary efficacy variable for both treatment periods, and had no other major protocol violations. Percentages are based on number of randomized subjects.

Demographic and Background Characteristics

Baseline characteristic	Vildagliptin 100 mg qd / placebo N=11	Placebo / vildagliptin 100 mg qd N=11
Sex, n (%)		
Male	10 (90.9)	9 (81.8)
Female	1 (9.1)	2 (18.2)
Age (years)		
n	11	11
Mean ± SD	57.0 ± 9.1	60.5 ± 8.3
Median (range)	56.0 (35-68)	61.0 (41-69)
Age group, n (%)		
< 65 years	8 (72.7)	6 (54.5)
≥ 65 years	3 (27.3)	5 (45.5)
Height (cm)		
n	11	11
Mean ± SD	174.5 ± 7.5	173.7 (9.2)
Median (range)	173.0 (163-192)	171.0 (164-194)
Weight (kg)		
n	11	11
Mean ± SD	87.3 ± 13.8	87.2 ± 9.3
Median (range)	87.0 (69-107)	86.0 (76-110)
BMI (kg/m2)		
n	11	11
Mean ± SD	28.5 ± 2.9	28.9 ± 2.1
Median (range)	28.7 (23-33)	29.2 (25-32)
BMI categories, n (%)		
< 27 kg/m2	2 (18.2)	2 (18.2)
27 to < 30 kg/m2	6 (54.5)	6 (54.5)
≥ 30 kg/m2	3 (27.3)	3 (27.3)
HbA1c (%)		
n	11	11
Mean ± SD	7.23 ± 0.46	7.29 ± 0.66
Median (range)	7.30 (6.6-7.9)	7.10 (6.8-9.2)
FPG (mmol/L)		
n	11	11
Mean ± SD	9.70 ± 2.09	9.25 ± 2.53
Median (range)	9.70 (6.2-12.5)	9.00 (4.6-14.4)
Duration of type 2 diabetes (years)		
n	11	11
Mean ± SD	5.4 ± 3.2	6.2 ± 3.2
Median (range)	4.4 (0-11)	5.9 (0-10)
Metformin dose (mg/day)		

n	11	11
Mean ± SD	1984 ± 337	1932 ± 290
Median (range)	2000 (1500-2550)	2000 (1500-2550)
Duration of prior metformin use (months)		
n	11	11
Mean ± SD	55.5 ± 32.1	71.9 ± 41.0
Median (range)	51.0 (5-115)	71.0 (5-124)

Abbreviations: BMI = body mass index, FPG = fasting plasma glucose, SD = standard deviation.

Demography information and duration of type 2 diabetes were collected on the day of the screening measurement (Day -28, Visit 1).

Baseline HbA1c and FPG were the sample obtained on the day of randomization or the sample obtained on an earlier visit (scheduled or unscheduled) that was closest to Visit 2, if the Day 1 (Visit 2) measurement was missing.

Primary Objective Result(s)

Mixed-effect model results for the incretin effect (%) calculated using C-peptide IAUC 0-4hr from 75 g Oral Glucose Challenge vs. matched IV Glucose Infusion: Intent-to-treat

				Difference in LS means Vildagliptin 100mg qd - Placebo		
Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	LS Mean difference (SE)	95% CI	p-value
Vildagliptin 100 mg qd	21	38.73 (4.779)	38.26 (4.383)	1.16 (6.024)	(-11.49,13.82)	0.8489
Placebo	20	37.12 (4.388)	37.10 (4.508)			

n is the number of patients with observations at both the oral glucose challenge and the isoglycemic glucose infusion for both periods and meeting the completers population criteria.

Incremental AUC (IAUC) is calculated as the total area under the curve minus the area under the baseline (time 0 mins) value. The formula for the incretin effect is: [C-peptide IAUC (0-4hr) (oral) - C-peptide IAUC (0-4hr) (i.v.)] /[C-peptide IAUC(0-4hr) (oral)] x 100%.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level.

Mixed-effect model results for the incretin effect (%) calculated using C-peptide IAUC 0-4hr from 75 g Oral Glucose Challenge vs. matched IV Glucose Infusion: per protocol

				Difference in LS means Vildagliptin 100mg qd - Placebo		
Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	LS Mean difference (SE)	95% CI	p-value
Vildagliptin 100 mg qd	20	40.40 (4.705)	39.55 (4.478)	2.35 (6.063)	(-10.39,15.09)	0.7030
Placebo	20	37.12 (4.388)	37.21 (4.478)			

n is the number of patients with observations at both the oral glucose challenge and the isoglycemic glucose infusion for both periods and meeting the completers population criteria.

Incremental AUC (IAUC) is calculated as the total area under the curve minus the area under the baseline (time 0 mins) value. The formula for the incretin effect is: [C-peptide IAUC (0-4hr) (oral) - C-peptide IAUC (0-4hr) (i.v.)] /[C-peptide IAUC(0-4hr) (oral)] x 100%.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level.

Mixed-effect model results for the incretin effect (%) calculated using C-peptide IAUC 0-4hr from 75 g Oral Glucose Challenge vs. matched IV Glucose Infusion: completers

				Difference in LS means Vildagliptin 100mg qd - Placebo		
Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	LS Mean difference (SE)	95% CI	p-value
Vildagliptin 100 mg qd	20	40.40 (4.705)	39.55 (4.478)	2.35 (6.063)	(-10.39, 15.09)	0.7030
Placebo	20	37.12 (4.388)	37.21 (4.478)			

n is the number of patients with observations at both the oral glucose challenge and the isoglycemic glucose infusion for both periods and meeting the completers population criteria.

Incremental AUC (IAUC) is calculated as the total area under the curve minus the area under the baseline (time 0 mins) value. The formula for the incretin effect is: [C-peptide IAUC (0-4hr) (oral) - C-peptide IAUC(0-4hr) (i.v.)] /[C-peptide IAUC(0-4hr) (oral)] x 100%.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level.

Secondary Objective Result(s)

Mixed-effect model results for the incretin effect (%) calculated using ISR relative to glucose 0-2hr from 75 g Oral Glucose Challenge vs. matched IV Glucose Infusion: Completers population

				Difference in LS means Vildagliptin 100mg qd - Placebo		
Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	LS Mean difference (SE)	95% CI	p-value
Vildagliptin 100 mg qd	20	29.42 (3.647)	28.81 (3.302)	0.53 (3.587)	(-7.01,8.06)	0.8848
Placebo	20	28.40 (3.029)	28.28 (3.302)			

n is the number of patients with observations at both the oral glucose challenge and the isoglycemic glucose infusion for both periods and meeting the completers population criteria.

Incretin effect is assessed using the Insulin Secretion Rate (ISR) relative to glucose.

ISR is derived from C-peptide deconvolution. ISR relative to glucose = AUC (0-2hr) of ISR / AUC (0-2hr) of glucose.

The formula for incretin effect is: [ISR relative to glucose (0-2hr) (oral) - ISR relative to glucose (0-2hr) (IV) / ISR relative to glucose (0-2hr) (oral)] x 100%.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level.

Mixed-effect model results for ISR (pmol/min/m²) relative to Glucose (mmol*min/L) 0-2hr: Completers population

Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	Difference in LS means Vildagliptin 100mg qd - Placebo: LS Mean difference (SE)	95% CI	p-value
Oral Intake						
Vildagliptin 100 mg qd	20	28.05 (2.344)	28.26 (1.974)	7.41 (1.639)	(3.97,10.86)	0.0003*
Placebo	20	20.71 (1.463)	20.85 (1.974)			
IV Infusion						
Vildagliptin 100 mg qd	20	19.39 (1.695)	19.71 (1.312)	5.03 (1.089)	(2.74,7.32)	0.0002*
Placebo	20	14.52 (1.006)	14.68 (1.312)			

n is the number of patients with observations at both the oral glucose challenge and the isoglycemic glucose infusion for both periods and meeting the completers population criteria.

ISR is derived from C-peptide deconvolution. ISR relative to glucose = AUC (0-2hr) of ISR / AUC(0-2hr) of glucose.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level.

Mixed-effect model results for C-peptide (nmol*min/L) 0-2hr: Completers population

Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	Difference in LS means Vildagliptin 100mg qd - Placebo: LS Mean difference (SE)	95% CI	p-value
Oral Intake						
Vildagliptin 100 mg qd	20	299.07 (18.838)	301.80 (16.912)	43.57 (9.248)	(24.13,63.00)	0.0002*
Placebo	20	255.78 (15.879)	258.24 (16.912)			
IV Infusion						
Vildagliptin 100 mg qd	20	222.86 (18.825)	226.70 (14.885)	35.55 (9.465)	(15.67,55.44)	0.0014*
Placebo	20	188.75 (12.954)	191.14 (14.885)			

n is the number of patients with observations at the oral glucose challenge and the IV glucose infusion for both periods and meeting completers population criteria.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level

Mixed-effect model results for Insulin (pmol*min/L) 0-2hr: Completers population

Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	Difference in LS means Vildagliptin 100mg qd - Placebo: LS Mean difference (SE)	95% CI	p-value
Oral Intake						
Vildagliptin 100 mg qd	20	42544 (4879.7)	43360 (3929.1)	9795 (2455.3)	(4637,14954)	0.0009*
Placebo	20	32855 (3352.5)	33565 (3929.1)			
IV Infusion						
Vildagliptin 100 mg qd	20	25632 (3749.8)	26468 (2804.4)	5918 (1987.8)	(1742,10094)	0.0081
Placebo	20	20030 (2396.1)	20550 (2804.4)			

n is the number of patients with observations at the oral glucose challenge and the IV glucose infusion for both periods and meeting completers population criteria.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level

Mixed-effect model results for Glucagon (pmol*min/L) 0-2hr: Completers population

				Difference in LS means Vildagliptin 100mg qd - Placebo		
Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	LS Mean difference (SE)	95% CI	p-value
Oral Intake						
Vildagliptin 100 mg qd	20	1889.13 (134.857)	1897.64 (127.196)	-217.26 (117.545)	(-464.21,29.69)	0.0811
Placebo	20	2101.25 (116.233)	2114.90 (127.196)			
IV Infusion						
Vildagliptin 100 mg qd	20	1746.88 (114.907)	1754.61 (127.915)	-46.69 (127.365)	(-314.28,220.89)	0.7182
Placebo	20	1794.13 (134.418)	1801.30 (127.915)			

n is the number of patients with observations at the oral glucose challenge and the IV glucose infusion for both periods and meeting completers population criteria.

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level

Mixed-effect model results for Intact GLP-1 (pmol*min/L) 0-2hr: Completers population

				Difference in LS means Vildagliptin 100mg qd - Placebo		
Treatment	n	Unadjusted Mean (SE)	LS Mean (SE)	LS Mean difference (SE)	95% CI	p-value
Oral Intake						
Vildagliptin 100 mg qd	18	445.14 (101.913)	423.70 (78.245)	292.96 (89.498)	(103.24,482.69)	0.0048*
Placebo	20	135.50 (40.608)	130.73 (73.263)			
IV Infusion						
Vildagliptin 100 mg qd	20	141.50 (29.521)	142.60 (25.134)	93.79 (28.851)	(33.17,154.40)	0.0044*
Placebo	20	48.25 (17.929)	48.81 (25.134)			

n is the number of patients with observations at the oral glucose challenge and the IV glucose infusion for both periods and meeting completers population criteria.

Note: Intact = Active

LS mean and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed model of covariance containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

* indicates statistical significance at 5% level

Safety Results

Adverse Events by System Organ Class and Preferred Term n (%)

Primary system organ class Preferred term	Vildagliptin 100mg qd N=22 n (%)	Placebo N=21 n (%)
Any primary system organ class		
-Total	4 (18.2%)	1 (4.8%)
Gastrointestinal disorders		
-Total	2 (9.1%)	0
Abdominal pain	1 (4.5%)	0
Dysphagia	1 (4.5%)	0
Nausea	1 (4.5%)	0
Infections and infestations		
-Total	2 (9.1%)	1 (4.8%)
Helicobacter infection	1 (4.5%)	0
Urinary tract infection	1 (4.5%)	1 (4.8%)
Metabolism and nutrition disorders		
-Total	1 (4.5%)	0
Hyperlipidaemia	1 (4.5%)	0

Serious Adverse Events and Deaths

Primary system organ class Preferred term	Vildagliptin 100mg qd N=22 n (%)	Placebo N=21 n (%)

No Records Meet the Criteria for this Table

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

05 March 2009

Date Inclusion on Novartis Clinical Trial Results Database

30 September 2008

Date of Latest Update

28 September 2010