NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Investigational

Study Number

CLAF237A2386

Title

A single-center, double-blind, randomized, placebo-controlled, cross-over study to assess the effect of vildagliptin on glucagon counterregulatory response during hypoglycemia in patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

28 Sep 2006 to 18 Sep 2007

Study Design/Methodology

This is a single-center, randomized, double-blind, placebo controlled, cross-over study. 28 patients with T2DM and HbA_{1c} <= 7.5% were randomized. Each patient attended one screening visit (Week -4) where the inclusion/exclusion criteria was assessed. Eligible patients were randomized at visit 2 (Day 1) and complete two treatment periods, receiving a different blinded study medication during each period (vildagliptin 100 mg qd and placebo, in random order).

When necessary to confirm an initially positive LFT, patients were recalled to the clinic to obtain appropriate samples and instructions. A baseline visit was performed during each of the two treatment periods, at which the patient was assessed and the study medication was dispensed for 4 weeks of outpatient treatment. After 4 weeks of treatment, a hyperinsulinemic glucose clamp test was performed with 3 clamp steps: 1) at hyperglycemia (7.5 mmol/L), 2) at euglycemia (5 mmol/L), and 3) at hypoglycemia (2.5 mmol/L). The study medication was discontinued and a 4 week washout period occured before the next treatment period was started.

Centers

1 center in 1 country: Sweden (1)

Publication

Ahrén B, Schweizer A, Dejager S, Dunning, BE, Nilsson PM, Presson M, and Foley JE.
Vildagliptin enhances islet responsiveness to both hyper-and hypoglycemia in patients with type 2 diabetes.

J Clin Endocrinol Metab. 2009 Apr; 94(4): 1236-43

PMID: 19174497

Objectives

Primary objective(s)

- To demonstrate the effect of 4 week treatment with vildagliptin compared to placebo on the glucagon counterregulatory response to hypoglycemia in patients with T2DM, assessed as mean glucagon level (AUC / sampling period) of the last 30 min of the 2.5 mM hypoglycemic clamp step.

Secondary objective(s)

- To evaluate the effect of 4 week treatment with vildagliptin compared to placebo on the glucagon counterregulatory response to hypoglycemia in patients with T2DM, assessed as glucagon C_{max} of the 2.5 mM hypoglycemic clamp step.
- To evaluate the effect of 4 week treatment with vildagliptin compared to placebo on the 'insulin secretion rate (ISR) relative to glucose' at the hypoglycemic clamp step in patients with T2DM.
- To evaluate the effect of 4 week treatment with vildagliptin compared to placebo on HbA_{1c} and fasting plasma glucose (FPG) in patients with T2DM.

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

- The primary efficacy variable, mean plasma glucagon level of the last 30 minutes of the 2.5 mM hypoglycemic clamp test, is defined as the area under the 225-255 minutes prandial plasma glucagon curve ($AUC_{225\text{-}255min}$) divided by the sampling period after 4 weeks of treatment. During the last 30 minutes of the 2.5 mM hypoglycemic clamp test, plasma glucagon will be measured at the following 3 timepoints (minutes in relation to the meal time): 225, 240 and 255 minutes. The $AUC_{225\text{-}255min}$ will be calculated using the trapezoidal rule.

Secondary variables

- glucagon C_{max} (defined as the highest observed glucagon concentration) of the 2.5 mM hypoglycemic clamp step
- ISR relative to glucose in the last 30 minutes of the hypoglycemic clamp step (defined as the ratio of $AUC_{225\text{-}255min}$ for ISR (calculated by deconvolution using C-peptide levels) to $AUC_{225\text{-}255min}$ for glucose)
- change from first day in period in HbA_{1c}
- change from first day in period in FPG

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 is no difference between vildagliptin 100mg qd and the placebo in mean plasma glucagon level during hypoglycemia. This was analyzed after the fourth week of treatment in each of the two treatment periods. The mean plasma glucagon level was evaluated using a repeated measures mixed model that includes period, sequence, and treatment as fixed effects, and patient-within-sequence as a random effect.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

T2DM patients aged $\geq$ 18 years with $HbA_{1c} \leq 7.5\%$ with a body mass index of 22-35 kg/m^2 inclusive.

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=15 n (%)	Placebo/vildagliptin 100 mg qd N=15 n (%)
Randomized[1]	15	15

Safety[2]	15 (100)	15 (100)
Intent to treat[3]	15 (100)	12 (80)
Completers[4]	14 (93.3)	11 (73.3)
Per protocol[5]	14 (93.3)	11 (73.3)

[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	13 (92.9)	9 (81.8)
Female	1 (7.1)	2 (18.2)
Age (years)		
n	14	11
Mean ± SD	66.6 ± 6.4	60.5 ± 8.3
Median (range)	68.5 (56-74)	62.0 (60-73)
Age group, n (%)		
< 65 years	5 (35.7)	6 (54.5)
>= 65 years	9 (64.3)	5 (45.5)
Height (cm)		
n	14	11
Mean ± SD	178.3 ± 8.1	176.9 (7.7)
Median (range)	177.0 (162-196)	177.0 (165-186)
Weight (kg)		
n	14	11
Mean ± SD	89.7 ± 12.5	86.6 ± 15.0
Median (range)	90.0 (75-113)	82.5 (63-116)
BMI (kg/m2)		
n	14	11
Mean ± SD	28.1 ± 2.7	27.6 ± 3.5
Median (range)	28.4 (24-34)	27.4 (22-34)
BMI categories, n (%)		
< 27 kg/m2	6 (42.9)	5 (45.5)

27 to < 30 kg/m2	5 (35.7)	4 (36.4)
>= 30 kg/m2	3 (21.4)	2 (18.2)
HbA1c (%)		
n	14	11
Mean ± SD	6.41 ± 0.60	6.18 ± 0.61
Median (range)	6.54 (5.3-7.1)	6.20 (5.3-7.3)
FPG (mmol/L)		
n	14	11
Mean ± SD	7.74 ± 1.17	7.21 ± 0.72
Median (range)	8.10 (5.6-9.3)	7.30 (6.1-8.4)
Duration of type 2 diabetes (years)		
n	14	11
Mean ± SD	6.7 ± 7.9	4.2 ± 4.0
Median (range)	3.9 (0-27)	2.0 (1-13)

Demography information is collected on the day of the screening measurement (Week -4, Visit 1).

Weight and BMI for demographic information is calculated at baseline (visit 2).

Duration of type 2 diabetes is collected on the day of the screening measurement (Week -4, Visit 1).

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

Primary Objective Result(s)

Mixed-effect model results for the mean plasma glucagon (pmol/L) of the last 30 minutes of the hypoglycemic clamp step by treatment: Completers population

				Vildagliptin 100mg qd / Placebo		
Treatment	n	Unadjusted Mean (SE)	Geometric LS Mean (SE)	Geometric LS Mean ratio (SE) [1]	95% CI [2]	p-value
Vildagliptin	25	34.98 (1.586)	34.36 (1.044)	0.97 (1.037)	(0.90,1.04)	0.404
Placebo	25	36.19 (1.582)	35.43 (1.044)			

n is the number of patients with observations at both clamp tests and meeting the completers population criteria.

Mean plasma glucagon of last 30 minutes of the hypoglycemic clamp step is defined as the area under the 225-255 minutes prandial plasma glucagon curve (AUC 225-255min).

Tabulated geometric LS mean and geometric LS mean ratio (with associated geometric standard errors (SE)), confidence intervals (95% CI), and p values were obtained from a repeated measures mixed model of covariance with log transformed efficacy parameters as the dependent variable and containing terms for treatment, period, and sequence as fixed effects, and subject within sequence as a random effect. For ease of interpretation, the tabulated values obtained from the model are presented after being transformed back to the arithmetic scale.

[1] When transforming the LS mean difference back to the arithmetic scale, the resulting value is the geometric LS mean ratio (vildagliptin 100mg qd/placebo).

[2] The 95% CI, when transformed back to the arithmetic scale, may not be symmetrical around the ratio of the geometric LS mean.

* indicates statistical significance at 5% level.

Secondary Objective Result(s)

Mixed-effect model results for glucagon Cmax and ISR relative to glucose during hypoglycemic clamps: (Completers population)

				Vildagliptin 100 mg qd - Placebo		
Treatment	n	Unadjusted mean (SE)	Least squares mean (LSM) ± SE	LS mean difference (SE)	95% CI	p-value
Glucagon Cmax (pmol/L)						
Vildagliptin	25	43.1 (2.4)	43.6 ± 2.3	1.09 (2.31)	(-3.68, 5.86)	0.642
Placebo	25	42.4 (2.3)	42.5 ± 2.3			
Insulin secretion relative to glucose (pmol/min/m^2/mM)						
Vildagliptin	25	13.3 (1.7)	13.1 ± 1.5	2.62 (1.52)	(-0.52, 5.77)	0.098
Placebo	25	10.4 (1.2)	10.5 ± 1.5			

n is the number of patients that received at least one dose of study drug and have valid assessments of the primary efficacy variable at both clamp tests.
Glucagon Cmax of the hypoglycemic clamp step is defined as the highest observed glucagon concentration of the hypoglycemic clamp step (210-255 min).
Insulin secretion rate (ISR) relative to glucose during the last 30 minutes of the hypoglycemic clamp step is defined as the ratio of the AUC (225-255min) for ISR to AUC (225-255min) for 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 changes in FPG and HbA1c: Completers population

				Vildagliptin 100 mg qd - Placebo		
Treatment	n	Baseline mean ± SE	Adjusted mean change (AMΔ) ± SE	Mean difference ± SE	95% CI	p-value
FPG (mmol/L)						
Vildagliptin	25	7.6 ± 0.2	-0.5 ± 0.1	-0.7 ± 0.2	(-1.09, -0.35)	<0.001
Placebo	25	7.3 ± 0.2	0.3 ± 0.1			
HbA_{1c} (%)						
Vildagliptin	25	6.3 ± 0.1	-0.2 ± 0.1	-0.3 ± 0.1	(-0.45, -0.12)	0.002
Placebo	25	6.1 ± 0.1	0.1 ± 0.1			

n is the number of patients with observations at both periods and meeting completers population criteria. Change is calculated for patients with valid assessments at both time points (first day in period and endpoint). Endpoint is defined as the final available assessment of the period up to the last regular scheduled visit within the period.
Adjusted mean change and the associated standard errors (SE), confidence intervals (CI), and p values were obtained from a repeated measures mixed-effect model of covariance containing terms for treatment, period, and sequence as fixed effects, subject within sequence as a random effect, and first day in period value as a covariate.
* indicates statistical significance at 5% level.

Safety Results

Adverse Events by System Organ Class

Primary system organ class	Vilda 100mg qd N=28 n (%)	Placebo N=29 n (%)
Any primary system organ class	14 (50.0%)	13 (44.8%)
Infections and infestations	4 (14.3%)	6 (20.7%)
Respiratory, thoracic and mediastinal disorders	3 (10.7%)	1 (3.4%)
Cardiac disorders	2 (7.1%)	2 (6.9%)
Investigations	2 (7.1%)	1 (3.4%)
Musculoskeletal and connective tissue disorders	2 (7.1%)	1 (3.4%)
Skin and subcutaneous tissue disorders	2 (7.1%)	3 (10.3%)
Ear and labyrinth disorders	1 (3.6%)	1 (3.4%)
Gastrointestinal disorders	1 (3.6%)	1 (3.4%)
Metabolism and nutrition disorders	1 (3.6%)	1 (3.4%)
Nervous system disorders	1 (3.6%)	1 (3.4%)
Psychiatric disorders	1 (3.6%)	1 (3.4%)
Renal and urinary disorders	1 (3.6%)	0
Vascular disorders	1 (3.6%)	1 (3.4%)
General disorders and administration site conditions	0	2 (6.9%)

Primary system organ classes are presented in order of decreasing frequency within vildagliptin treatment.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Events occurring in period 1 are assigned to the treatment received in period 1 (visit 2 to visit 3), events occurring in the washout period (visit 3 to visit 4) are assigned to the treatment received in period 1, and events occurring on or after day 1 of period 2 are assigned to the treatment received in period 2 (visit 4 to visit 5).

Serious Adverse Events and Deaths

Preferred term	Vilda 100mg qd N=28 n (%)	Placebo N=29 n (%)
Any SAE	0	3 (10.3%)
Appendicitis	0	1 (3.4%)
Arthritis infective	0	1 (3.4%)
Myocardial infarction	0	1 (3.4%)

A patient with multiple occurrences of an SAE under one treatment is counted only once in the SAE category for that treatment.

No Deaths

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

28 July 2008

Date Inclusion on Novartis Clinical Trial Results Database

28 October 2008

Date of Latest Update

20 October 2009