Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 Diabetes

Approved Indication

Type 2 Diabetes

Study Number

CLAF237A2381

Title

A single-center, double-blind, randomized, parallel-group study to compare the effect of 52 weeks treatment with Vildagliptin to placebo on beta-cell function in drug-naïve patients with type 2 diabetes and mild hyperglycemia

Phase of Development

Phase III

Study Start/End Dates

24-Nov-2005 - 11-Dec-2008

Study Design/Methodology

This was a single-center, randomized, double-blind, placebo controlled study. In the original protocol drug-naïve patients with type 2 diabetes and mild hyperglycemia (HbA_{1c} <= 7.5%) were randomized equally to Vildagliptin 50 mg qd and placebo. Following implementation of amendment 2, all eligible patients were randomized equally to Vildagliptin 100 mg qd and placebo. Patients already randomized as part of the original protocol before implementation of amendment 2 continued their treatment regimens unchanged. All patients underwent individualized lifestyle counseling by a behavioral change program with the use of problem solving therapy (e.g. to reduce weight by lowering intake of fat and total calories, to follow a heart healthy diet and to increase physical activity).

Each patient attended one screening visit (Week -4) where the inclusion/exclusion criteria were

assessed. Eligible patients were then randomized at visit 3 (Baseline; Day 1) and completed 11 further visits and one phone call over a period of 52 weeks of treatment with Vildagliptin or placebo followed by 4 visits over an additional 12 week active treatment-free period, during which all patients received placebo.

Three standard meal challenges and three eu-hypergylcemic clamps (combined euglycemic-hyperglycemic clamps) were performed in the study: at Baseline (Week -2 for meal challenge and Day 1 for eu-hyperglycemic clamp), after 1 year of treatment (Week 50 for meal challenge and Week 52 for eu-hyperglycemic clamp) and following an additional 10-12 week active treatment-free period (Week 62 for meal challenge and Week 64 for eu-hyperglycemic clamp).

Number of patients (planned and analyzed): In the original protocol, 42 patients per treatment group were to be randomized to Vildagliptin 50 mg qd and matching placebo. This recruitment was prematurely stopped, but patients already randomized as part of the original protocol before implementation of amendment 2 continue their treatment regimens unchanged. For the amended protocol, 60 additional patients were to be randomized to Vildagliptin 100 mg qd and matching placebo.

Centers

A total of one center in one country screened at least 1 patient (number of centers in brackets): Netherlands (1).

Publication

Manuscripts for this study is under development

Objectives

Primary objective(s)

The primary objective was to demonstrate the effect of Vildagliptin on β-cell function in patients with type 2 diabetes and mild hyperglycemia (HbA_{1c} <= 7.5%) by testing the hypothesis that the improvement of hyperglycemia- and arginine-stimulated first phase insulin secretion (assessed as incremental AUC C-peptide of the first 10 minutes of the arginine-stimulated hyperglycemic clamp) with Vildagliptin 100 mg qd is superior to that with placebo at Week 52.

Secondary objectives

1. To evaluate the effect of Vildagliptin on β-cell function in patients with type 2 diabetes and mild hyperglycemia by testing the hypothesis that the improvement of the disposition index (assessed as incremental AUC C-peptide of the first 10 minutes of the arginine-stimulated hyperglycemic clamp, multiplied by the glucose requirement during the last 30 minutes of the euglycemic clamp (M-value)) with Vildagliptin 100 mg qd is superior to that with placebo at Week 52.
2. To evaluate the effect of Vildagliptin on β-cell function by testing the hypothesis that the improvement of hyperglycemia- and arginine-stimulated second phase insulin secretion (assessed as incremental AUC C-peptide of the last 20 minutes of the arginine-stimulated hyperglycemic clamp) with Vildagliptin 100 mg qd is superior to that with placebo at Week 52.
3. To evaluate the effect of Vildagliptin on β-cell function by testing the hypothesis that the improvement of additional β-cell function parameters derived from the hyperglycemic clamp with Vildagliptin 100 mg qd are superior to those with placebo at Week 52.
4. To evaluate the effect of Vildagliptin on α-cell function by testing the hypothesis that the improvement of the suppression of glucagon levels during the euglycemic clamp with Vildagliptin 100 mg qd is superior to that with placebo at Week 52.
5. To evaluate the effect of Vildagliptin on β-cell function by testing the hypothesis that the improvement of β-cell function parameters derived from a standard meal challenge with Vildagliptin 100 mg qd are superior to those with placebo at Week 50.

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

Vildagliptin 50 mg tablet, taken orally, twice daily

Vildagliptin 100 mg tablet, taken orally, once daily

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

NA

Criteria for Evaluation

Primary variables

The primary efficacy variable was arginine-stimulated first phase insulin secretion during a hyperglycemic clamp, specifically, the incremental AUC C-peptide during a 10 minute period beginning at 290 minutes, corrected for the basal value obtained immediately prior to the start of the hyperglycemic clamp (average of 200 and 205 minute measurements). The primary analysis was based on change from baseline (Day 1, visit 3) to Week 52.

Secondary variables

The secondary efficacy variables included: various β-cell function parameters derived from the eu-hyperglycemic clamp; suppression of glucagon levels during euglycemic clamp; β-cell function parameters derived from standard meal challenge (e.g. relationship between insulin secretion and glucose using the Mari model); postprandial parameters, including area under the 0-2 hour prandial curve (AUC0-2hr) for plasma glucose, insulin, C-peptide, proinsulin, lipids (triglycerides, HDL cholesterol, free fatty acids), ghrelin, hs-CRP, glucagon, Active GLP-1 and 2-hr absolute glucose level, following a standard meal challenge; HbA_{1c}, FPG, fasting lipids (triglycerides, FFA, apo-A, apo-B, total cholesterol, calculated LDL, HDL, calculated VLDL, non-HDL cholesterol), body weight; slope of FPG (measured in 4-week intervals) during a 12 week active treatment-free period (Week 52 to Week 64); insulin sensitivity parameter derived from the eu-hyperglycemic clamp (M-value: average glucose requirement during the last 30 minutes of the euglycemic clamp).

Pharmacology

Not Applicable

Other

Not Applicable

Statistical Methods

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria: Male or female (non-fertile or using a medically approved birth control method); drug-naïve patients with type 2 diabetes and mild hyperglycemia (HbA_{1c} <= 7.5%) aged >= 30 years, and body mass index of 22-45 kg/m^2 at screening.

Exclusion criteria: Main exclusion criteria were: a history of type 1 diabetes, diabetes that is a result of pancreatic injury, or secondary forms of diabetes, e.g. Cushing's syndrome and acromegaly; acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma), evidence of significant diabetic complications, e.g. symptomatic autonomic neuropathy, gastroparesis, acute infections within 4 weeks prior to visit 1, a history of Torsades de Pointes, sustained and clinically relevant ventricular tachycardia or ventricular fibrillation; percutaneous

coronary intervention within the past 3 months; any of the following within the past 6 months: myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention; unstable angina or stroke; congestive heart failure NYHA class III or IV; any of the following ECG abnormalities: second degree AV block (Mobitz 1 and 2), third degree AV block, prolonged QTc (> 500 msec); malignancy including leukemia and lymphoma (not including basal cell skin cancer) within the last 5 years; liver disease such as cirrhosis or chronic active hepatitis; ALT, AST > 2 times the upper limit of the normal range (ULN); total bilirubin > 2 times the ULN and/or direct bilirubin > ULN; a positive Hepatitis B test (surface antigen HBsAg); positive Hepatitis C test (HCV antibodies); serum creatinine levels > 2.5 mg/dL (220 µmol/L), TSH outside normal range, fasting triglycerides > 700 mg/dL (> 7.9 mmol/L).

Number of Subjects

Disposition Reason	Vilda 100 mg qd N=29 n (%)	Placebo (100 mg qd) N=30 n (%)	Vilda 50 mg qd N=16 n (%)	Placebo (50 mg qd) N=14 n (%)
Completed	27 (93.1)	27 (90.0)	12 (75.0)	13 (92.9)
Discontinued	2 (6.9)	3 (10.0)	4 (25.0)	1 (7.1)
Adverse Event(s)	0	1 (3.3)	2 (12.5)	1 (7.1)
Abnormal laboratory value(s)	0	1 (3.3)	0	0
Abnormal test procedure result(s)	0	0	0	0
Unsatisfactory therapeutic effect	1 (3.4)	0	1 (6.3)	0
Subject's condition no longer requires study drug	0	0	0	0
Protocol violation	1 (3.4)	0	1 (6.3)	0
Subject withdrew consent	0	1 (3.3)	0	0
Lost to follow-up	0	0	0	0
Administrative problems	0	0	0	0
Death	0	0	0	0

Demographic and Background Characteristics

Demographic Variable	Vilda 100 mg qd N=29	Placebo (100 mg qd) N=30	Vilda 50 mg qd N=16	Placebo (50 mg qd) N=14
Age (years)				
n	29	30	16	14
Mean	57.4	57.0	61.3	62.8
SD	9.42	6.69	7.66	7.86
Min	36.0	44.0	44.0	50.0
Median	60.0	58.5	60.5	62.5
Max	77.0	70.0	72.0	75.0
Age group				
<65 years	23 (79.3)	28 (93.3)	10 (62.5)	9 (64.3)
>= 65 years	6 (20.7)	2 (6.7)	6 (37.5)	5 (35.7)
Sex				
Male	17 (58.6)	18 (60.0)	11 (68.8)	11 (78.6)
Female	12 (41.4)	12 (40.0)	5 (31.3)	3 (21.4)
Race				
Caucasian	28 (96.6)	27 (90.0)	16 (100)	14 (100)
Black	0	0	0	0
Asian (non indian subcontinent)	0	1 (3.3)	0	0
Asian (indian subcontinent)	0	0	0	0
Hispanic or latino	0	0	0	0
Japanese	0	0	0	0

Demographic Variable	Vilda 100 mg qd N=29	Placebo (100 mg qd) N=30	Vilda 50 mg qd N=16	Placebo (50 mg qd) N=14
Native american	0	0	0	0
Pacific islander	0	0	0	0
Other	1 (3.4)	2 (6.7)	0	0
Waist circumference (cm)				
n	29	30	16	14
Mean	100.7	99.5	101.7	102.4
SD	10.88	12.81	7.94	9.84
Min	77.0	79.0	90.0	87.0
Median	102.0	99.0	102.5	105.5
Max	124.0	128.0	114.0	117.0
Height (cm)				
n	29	30	16	14
Mean	173.6	172.3	175.4	176.6
SD	10.46	11.06	8.48	10.74
Min	155.0	151.0	165.0	158.0
Median	171.0	174.0	174.5	179.0
Max	197.0	192.0	189.0	193.0
Body weight (kg)				
n	29	30	16	14
Mean	90.2	87.6	87.4	88.8
SD	15.87	19.06	11.04	11.57
Min	64.2	50.5	69.5	65.5
Median	90.0	87.9	85.4	87.2
Max	120.2	132.0	106.8	108.9
BMI (kg/m**2)				
n	29	30	16	14
Mean	29.9	29.2	28.4	28.5
SD	4.87	4.43	2.35	2.95
Min	23.0	22.1	24.6	24.1
Median	29.6	29.2	28.5	28.7
Max	39.9	40.5	33.2	34.3
BMI group				
<30 kg/m**2	16 (55.2)	16 (53.3)	12 (75.0)	10 (71.4)
>=30 kg/m**2	13 (44.8)	14 (46.7)	4 (25.0)	4 (28.6)

Primary Efficacy Result(s)

ANCOVA results for change baseline in arginine-stimulated first phase insulin secretion to Week 52 endpoint by treatment ITT population

		Baseline		Adjusted change from baseline		Difference in adjusted mean change (Vilda - Placebo)			
Treatment	n	mean	(SE)	mean	(SE)	mean	(SE)	(95% CI)	P-Value
Vilda 100 mg qd	26	39.04	(3.58)	5.00	(1.81)	5.77	(2.58)	(0.58, 10.96)	0.030 *
Placebo (100 mg qd)	25	39.05	(4.56)	-0.77	(1.84)				

Arginine-stimulated first phase insulin secretion is assessed via the incremental AUC of C-peptide during a 10 minute period beginning at 290 minutes. Unit is nmol/L * min. Baseline for the incremental AUC of C-peptide is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected). Week 52 endpoint is the final available post-randomization assessment up to the end of the double-blind period (up to and including day of visit 11). n is the number of patients with observations at both baseline and endpoint. Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment and baseline.

* indicates statistical significance at 5% level.

Secondary Efficacy Result(s)

ANCOVA results for change from baseline in disposition index to Week 52 endpoint by treatment (ITT population)

		Baseline		Adjusted change from baseline		Difference in adjusted mean change (Vilda - Placebo)			
Treatment	n	mean	(SE)	mean	(SE)	mean	(SE)	(95% CI)	P-Value
Vilda 100 mg qd	25	146.17	(14.84)	49.56	(15.03)	31.97	(21.40)	(-11.08, 75.02)	0.142
Placebo (100 mg qd)	25	123.28	(13.00)	17.60	(15.03)				

Disposition index is defined as the incremental AUC C-peptide of the first 10 minutes of the arginine-stimulated hyperglycemic clamp (i.e. clamp time 290 - 300 minutes), multiplied by the M-value (glucose requirement during the last 30 minutes of the euglycemic clamp (i.e. clamp time 120 - 150 minutes). Unit is nmol*mg/(L*kg). Baseline for the disposition index is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected). Week 52 endpoint is the final available post-randomization assessment up to the end of the double-blind period (up to and including day of visit 11). n is the number of patients with observations at both baseline and endpoint. Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment and baseline.

* indicates statistical significance at 5% level.

ANCOVA results for change from baseline in hyperglycemia- and arginine-stimulated second phase insulin secretion to Week 52 endpoint by treatment (ITT population)

Treatment	n	Baseline mean	(SE)	Adjusted change from baseline mean	(SE)	Difference in adjusted mean change (Vilda - Placebo) mean	(SE)	(95% CI)	P-Value
Vilda 100 mg qd	27	53.36	(5.69)	14.93	(4.37)	11.38	(6.39)	(-1.46, 24.23)	0.081
Placebo (100 mg qd)	24	48.42	(5.00)	3.54	(4.64)				

Hyperglycemia- and arginine-stimulated second phase insulin secretion is assessed via the incremental AUC C-peptide of the last 20 minutes of the arginine-stimulated hyperglycemic clamp (i.e. clamp time 300 - 320 minutes). Unit is nmol/L * min. Baseline for the incremental AUC C-peptide is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected). Week 52 endpoint is the final available post-randomization assessment up to the end of the double-blind period (up to and including day of visit 11). n is the number of patients with observations at both baseline and endpoint. Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment and baseline.

* indicates statistical significance at 5% level.

ANCOVA results for change from baseline in hyperglycemia-stimulated ß-cell function to Week 52 endpoint by treatment (ITT population)

Treatment	n	Baseline mean	(SE)	Adjusted change from baseline mean	(SE)	Difference in adjusted mean change (Vilda - Placebo) mean	(SE)	(95% CI)	P-Value
First phase insulin secretion: Clamp time 210-220 minutes									
Vilda 100 mg qd	26	2.94	(0.61)	0.75	(0.26)	0.77	(0.38)	(0.01, 1.53)	0.047 *
Placebo (100 mg qd)	25	2.95	(0.58)	-0.02	(0.27)				
Stimulated insulin secretion: Clamp 270-290 minutes									
Vilda 100 mg qd	27	35.06	(3.60)	8.82	(2.21)	9.89	(3.19)	(3.49, 16.29)	0.003 *
Placebo (100 mg qd)	25	34.05	(4.10)	-1.07	(2.29)				
ß-cell integrity : Clamp time 210-270 minutes									
Vilda 100 mg qd	27	417.88	(57.40)	89.40	(38.91)	114.12	(56.19)	(1.20, 227.04)	0.048 *
Placebo (100 mg qd)	25	479.26	(104.13)	-24.72	(40.44)				

Hyperglycemia-stimulated first phase insulin secretion is assessed via the incremental AUC C-peptide of the first 10 minutes of the hyperglycemic clamp (i.e. clamp time 210 - 220 minutes). Unit is nmol/L * min. Baseline for the incremental AUC C- peptide is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected). Week 52 endpoint is the final available post-randomization assessment up to the end of the double-blind period (up to and including day of visit 11). n is the number of patients with observations at both baseline and endpoint. Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment and baseline.

Hyperglycemia-stimulated insulin secretion is assessed via the incremental AUC C-peptide 60-80 minutes of the hyperglycemic clamp (i.e. clamp time 270 - 290 minutes). Unit is nmol/L * min. Baseline for the incremental AUC C-peptide is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected).

ß-cell integrity is assessed via the incremental AUC proinsulin of the first 60 minutes of the hyperglycemic clamp (i.e. clamp time 210 - 270 minutes). Unit is pmol/L * min. Baseline for the incremental AUC proinsulin is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected).

* indicates statistical significance at 5% level.

ANCOVA results for change from baseline in α-cell function to Week 52 endpoint by treatment (ITT population)

		Baseline		Adjusted change from baseline		Difference in adjusted mean change (Vilda - Placebo)			
Treatment	n	mean	(SE)	mean	(SE)	mean	(SE)	(95% CI)	P-Value
Fasting glucagon levels:									
Vilda 100 mg qd	27	12.62	(0.63)	-0.81	(0.58)	1.02	(0.85)	(-0.69, 2.73)	0.238
Placebo (100 mg qd)	25	14.77	(1.35)	-1.83	(0.61)				
AUC glucagon of the last 30 minutes of the eu-glycemic clamp									
Vilda 100 mg qd	27	226.61	(13.93)	-17.13	(12.61)	-5.91	(18.50)	(-43.10, 31.29)	0.751
Placebo (100 mg qd)	24	257.38	(24.86)	-11.23	(13.38)				
Incremental AUC glucagon of the last 30 minutes of the eu-glycemic clamp									
Vilda 100 mg qd	27	-151.89	(13.58)	11.35	(13.11)	-33.44	(19.36)	(-72.37, 5.49)	0.091
Placebo (100 mg qd)	24	-196.50	(25.81)	44.79	(13.93)				

Fasting glucagon levels are defined as the arithmetic mean of the glucagon values at clamp time 0 and 15 minutes. Baseline for fasting glucagon levels is defined as the value calculated with the Visit 3 measurements if (or closest prior measurement if Visit 3 measurements are not collected). Unit is pmol/L * min. Week 52 endpoint is the final available post-randomization assessment up to the end of the double-blind period (up to and including day of visit 11). n is the number of patients with observations at both baseline and endpoint. Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment and baseline.

AUC glucagon of the last 30 minutes of the eu-glycemic clamp (i.e. clamp time 120-150 minutes). Baseline for AUC glucagon is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected).

Incremental AUC glucagon of the last 30 minutes of the eu-glycemic clamp (i.e. clamp time 120-150 minutes). Baseline for incremental AUC glucagon is defined as the value calculated with the Visit 3 measurements (or closest prior measurement if Visit 3 measurements are not collected).

* indicates statistical significance at 5% level.

ANCOVA results for change from baseline in insulin secretion rate relative to glucose (0-2h) during the meal challenge to Week 50 endpoint by treatment (ITT population)

		Baseline		Adjusted change from baseline		Difference in adjusted mean change (Vilda - Placebo)			
Treatment	n	mean	(SE)	mean	(SE)	mean	(SE)	(95% CI)	P-Value
Vilda 100 mg qd	28	47.21	(4.67)	0.83	(1.46)	1.37	(2.10)	(-2.84, 5.58)	0.517
Placebo (100 mg qd)	26	46.17	(3.39)	-0.54	(1.51)				

Insulin secretion rate relative to glucose is defined as the ratio AUC(0-2h) ISR / AUC(0-2h) glucose during the meal challenge. Unit is pmol/min/m2/mmol/L. Baseline for the insulin secretion rate relative to glucose is defined as the value calculated with the Visit 2 measurements (or measurement closest to Visit 2 and prior to Visit 3 if Visit 2 measurements are not collected). Week 50 endpoint is the final available post-randomization assessment up to the end of the double-blind period (up to and including day of visit 11). n is the number of patients with observations at both baseline and endpoint. Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment and baseline.

* indicates statistical significance at 5% level.

Safety Results

Adverse Events by System Organ Class

Primary system organ class Preferred term	Vilda 100 mg qd N=29 n (%)	Placebo (100 mg qd) N=30 n (%)	Vilda 50 mg qd N=16 n (%)	Placebo (50 mg qd) N=14 n (%)
-Any primary system organ class	26 (89.7)	27 (90.0)	14 (87.5)	13 (92.9)
Blood and lymphatic system disorders	0	0	0	1 (7.1)
Cardiac disorders	1 (3.4)	0	2 (12.5)	2 (14.3)
Eye disorders	1 (3.4)	1 (3.3)	1 (6.3)	0
Gastrointestinal disorders	6 (20.7)	4 (13.3)	2 (12.5)	1 (7.1)
General disorders and administration site conditions	3 (10.3)	1 (3.3)	1 (6.3)	2 (14.3)
Hepatobiliary disorders	1 (3.4)	0	0	0
Immune system disorders	0	1 (3.3)	0	0
Infections and infestations	19 (65.5)	19 (63.3)	6 (37.5)	7 (50.0)
Injury, poisoning and procedural complications	1 (3.4)	0	2 (12.5)	1 (7.1)
Investigations	1 (3.4)	1 (3.3)	0	0
Metabolism and nutrition disorders	4 (13.8)	2 (6.7)	3 (18.8)	2 (14.3)
Musculoskeletal and connective tissue disorders	10 (34.5)	9 (30.0)	3 (18.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.4)	0	2 (12.5)	1 (7.1)
Nervous system disorders	5 (17.2)	5 (16.7)	3 (18.8)	3 (21.4)
Psychiatric disorders	0	1 (3.3)	2 (12.5)	2 (14.3)
Renal and urinary disorders	2 (6.9)	0	1 (6.3)	1 (7.1)
Respiratory, thoracic and mediastinal disorders	1 (3.4)	0	1 (6.3)	1 (7.1)
Skin and subcutaneous tissue disorders	3 (10.3)	3 (10.0)	2 (12.5)	1 (7.1)
Social circumstances	1 (3.4)	0	0	0
Vascular disorders	0	3 (10.0)	0	4 (28.6)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Preferred term	Vilda 100 mg qd N=29 n (%)	Placebo (100 mg qd) N=30 n (%)	Vilda 50 mg qd N=16 n (%)	Placebo (50 mg qd) N=14 n (%)
-**Any Preferred term**	26 (89.7)	27 (90.0)	14 (87.5)	13 (92.9)
Nasopharyngitis	13 (44.8)	9 (30.0)	2 (12.5)	4 (28.6)
Bronchitis	3 (10.3)	3 (10.0)	2 (12.5)	1 (7.1)
Cystitis	2 (6.9)	3 (10.0)	2 (12.5)	0
Dizziness	2 (6.9)	3 (10.0)	2 (12.5)	1 (7.1)
Hypercholesterolaemia	2 (6.9)	0	2 (12.5)	2 (14.3)
Influenza	2 (6.9)	6 (20.0)	1 (6.3)	0
Gastroenteritis	2 (6.9)	4 (13.3)	1 (6.3)	2 (14.3)
Myalgia	2 (6.9)	0	1 (6.3)	0
Musculoskeletal pain	2 (6.9)	2 (6.7)	0	0
Tremor	2 (6.9)	1 (3.3)	0	0

Preferred terms are sorted by descending order of incidence in the Vildagliptin 100 mg qd.

Serious Adverse Events and Deaths

Preferred Term	Vilda 100 mg qd N=29 n (%)	Placebo (100 mg qd) N=30 n (%)	Vilda 50 mg qd N=16 n (%)	Placebo (50 mg qd) N=14 n (%)
Deaths	0	0	0	0
SAEs	2 (6.9)	1 (3.3)	5 (31.3)	4 (28.6)
Discontinuation of study drug due to AEs	0	1 (3.3)	2 (12.5)	0
AEs causing dose adjustment or study drug interruption	0	1 (3.3)	2 (12.5)	0
Clinically significant CCV AEs	0	0	2 (12.5)	3 (21.4)
Clinically significant IM AEs	0	0	0	1 (7.1)
Other clinically significant AEs	5 (17.2)	3 (10.0)	1 (6.3)	1 (7.1)

These categories are not mutually exclusive.

Other Relevant Findings

Hypoglycemic events (Safety population)

	Vilda 100 mg qd N=29 n (%)	Placebo (100 mg qd) N=30 n (%)	Vilda 50 mg qd N=16 n (%)	Placebo (50 mg qd) N=14 n (%)
Number of patiens with at least one hypoglycemic event	0	0	1	0
Number of patients with 1 hypoglycemic event	0	0	1	0
Number of patients who discontinued due to hypoglycemic events	0	0	0	0
Number of patients with grade 2 hypoglycemic events	0	0	0	0
Total number of hypoglycemic events	0	0	1 (100)	0
Plasma glucose value (mmol/L) <=2.2	0	0	1 (100)	0
Grade				
Grade 1	0	0	1 (100)	0
Severity				
Mild	0	0	1 (100)	0
Action taken				
None taken	0	0	0	0
Relationship to drug				
Not suspected	0	0	1(100)	0
Clinical symptom				
SHORT OF BREATH AFTER VISIT TOILET	0	0	1(100)	0
Precipitating event				
Missed/delayed meal	0	0	1(100)	0

Hypoglycemic events are defined as a) symptoms suggestive of hypoglycemia, where the patient is able to initiate self-treatment and plasma glucose measurement is < 3.1 mmol/L (grade 1), b) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and plasma glucose measurement is <3.1 mmol/L (grade 2), and c) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and no plasma glucose measurement is available (suspected grade 2).

More than one action could be taken per event and a symptomatic event may have more than one symptom.

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