Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 Diabetes

Approved Indication

Type 2 Diabetes

Study Number

CLAF237A23104

Title

A multicenter, double-blind, randomized parallel-group study to demonstrate the effect of 24 weeks treatment with vildagliptin 100 mg qd as add-on to metformin 500 mg bid compared to metformin up to 1000 mg bid in patients with type 2 diabetes inadequately controlled on metformin 500 mg bid monotherapy

Phase of Development

Phase III

Study Start/End Dates

18-Oct-2006 - 04-Jun-2008

Study Design/Methodology

This was a multicenter, randomized, double-blind study, Patients with T2DM and prior monotherapy treatment with metformin 850-1000 mg daily dose for at least 2 months prior to screening who were inadequately controlled (HbA1c 6.5-9.0% inclusive) was given open label metformin 500 mg bid at visit 1 for a period of 4 weeks. If qualified for randomization, patients were randomized into two treatment arms. In one arm, double-blind metformin 500 mg bid was added (total daily dose (2000 mg) and in the second arm double-blind vildagliptin 100 mg qd was added (total daily dose metformin 1000 mg and vildagliptin 100 mg) for a period of 24 weeks.

Each patient attended a screening visit (Week -4) where the inclusion/exclusion criteria were assessed. Eligible patients were then randomized at baseline (Day 1) and completed eight further visits over a period of 24 weeks.

Centers

A total of 145 centers in 14 countries screened at least 1 patient (number of centers in brackets) Argentina (8), Brazil (5), Czech Republic (5), Ecuador (4), Germany (18), Hungary (3), Italy (16), Korea (5), Peru (6), Slovokia (5), Thailand (3), United Kingdom (26), United States (38) and Venezuela (5).

Publication

Manuscript for this study is under development

Objectives

Primary objective(s)

The primary objective was to demonstrate the efficacy of vildagliptin 100 mg qd used in combination with metformin 500 mg bid in patients with type 2 diabetes inadequately controlled on metformin 500 mg bid monotherapy by testing the hypothesis that the hemoglobin A_{1c} (HbA_{1c}) reduction with the combination is not inferior to that with upward titration of metformin up to 1000 mg bid monotherapy after 24 weeks of treatment.

Secondary objectives

1. To evaluate the safety of vildagliptin 100 mg qd used in combination with metformin 500 mg bid by showing that patients treated with the combination of vildagliptin 100 mg qd and metformin 500 mg bid have a similar adverse event profile compared to those treated with metformin up to 1000 mg bid after 24 weeks of treatment.
2. To evaluate GI tolerability of vildagliptin 100 mg qd used in combination with metformin 500 mg bid by showing that patients treated with the combination of vildagliptin 100 mg qd and metformin 500 mg bid have a superior GI tolerability compared to those treated with metformin up to 1000 mg bid over 24 weeks of treatment.
3. To explore the fasting plasma glucose (FPG) change with vildagliptin 100 mg qd add-on to metformin 500 mg bid versus metformin up to 1000 mg bid after 24 weeks of treatment.
4. To evaluate the responder rates with vildagliptin 100 mg qd add-on to metformin 500 mg bid verses metformin up to 1000 mg bid after 24 weeks of treatment.

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

Vildagliptin 50 mg tablet, taken orally, twice daily

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

Metformin 500mg tablets, taken orally

Criteria for Evaluation

Primary variables

The primary efficacy variable in this study was the change from baseline in HbA_{1c} at the end of the study. HbA_{1c} is the standard measure for glycemic control in diabetic patients.

Secondary variables

- The change from baseline in FPG at the end of the study
- The change from baseline in body weight at the end of the study
- Safety and tolerability assessments consisted of monitoring and recording all AEs, including GI AEs, serious adverse events (SAEs) with their severity and relationship to study drug; regular monitoring of hematology, blood chemistry, and urine (performed at a central laboratory); and regular assessments of vital signs, ECG and physical condition.

Pharmacology

Not Applicable

Other

Not Applicable

Statistical Methods

The primary efficacy variable was change from baseline in HbA1c at Week 24 or at the final visit. The primary hypothesis tested was the non-inferiority of vildagliptin 100 mg qd used in combination with metformin 500mg bid versus metformin up to 1000mg bid, for the effect of reducing HbA1c, based on a 0.4% non-inferiority margin. Change from baseline in primary and secondary endpoints was analyzed using analysis of covariance (ANCOVA) with treatment and pooled center as classification variables and baseline value as a covariate. The null hypothesis was to be rejected and non-inferiority established if the upper limit of the 95% CI for the treatment difference did not exceed 0.4%. Once non-inferiority was demonstrated, superiority was to be tested using the same confidence interval from which non-inferiority was concluded. The primary population was the ITT population, robustness of the results was assessed in the Per Protocol population. The percentage of patients meeting each of the pre-defined responder criteria (categorical changes in HbA1c) was summarized in both the ITT and Per Protocol population.

For the critical secondary endpoint mean change from baseline in FPG, superiority of vildagliptin 100mg qd used in combination with metformin 500mg bid versus metformin up to 1000mg bid was tested for the ITT population using the same ANCOVA model as specified for the primary efficacy variable.

Demographic and background data as well as safety data were summarized by treatment group. The incidence of patients with at least one GI event was compared between treatment groups using a chi squared test.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria: Male or female (non-fertile or using a medically approved birth control method); age 18-78 years; patients with type 2 diabetes who have taken 850-1000 mg daily dose of metformin monotherapy for at least 2 months prior to screening, body mass index of 22-45 kg/m2; HbA1c in the range of 6.5% to 9% inclusive; FPG < 270 mg/dL (15 mmol/L) at screening.

Exclusion criteria: Main exclusion criteria were: a history of type 1 diabetes; diabetes as a result of pancreatic injury or secondary forms of diabetes; acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within the past 6 months; evidence of significant diabetic complications, e.g. symptomatic autonomic neuropathy, gastroparesis, as well as symptoms of worsening hyperglycemia (i.e. polyuria, polydipsia, weight loss). Acute infections. 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 (CHF) requiring pharmacological treatment. Any of the following ECG abnormalities: Torsades de pointes, sustained and clinically relevant ventricular tachycardia or ventricular fibrillation; 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. Chronic insulin treatment (> 4 weeks of treatment in the absence of intercurrent illness) within the past 6 months. 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). Clinically significant renal dysfunction as indicated by serum creatinine levels >= 1.5 mg/dL (132 µmol/L) males, >= 1.4 mg/dL (123 µmol/L) females, or a history of abnormal creatinine clearance. Clinically significant TSH values outside of normal range. Fasting triglycerides > 700 mg/dL (7.9 mmol/L).

Number of Subjects

Disposition Reason	Vilda 100 mg qd + Met 500 mg bid N=456 n (%)	Met up to 1000 mg bid N=458 n (%)	Total N=914 n (%)
Completed	406 (89.0)	392 (85.6)	798 (87.3)
Discontinued	50 (11.0)	66 (14.4)	116 (12.7)
Abnormal laboratory value(s)	3 (0.7)	3 (0.7)	6 (0.7)
Administrative problems	4 (0.9)	1 (0.2)	5 (0.5)
Adverse event(s)	10 (2.2)	12 (2.6)	22 (2.4)
Lost to follow-up	4 (0.9)	10 (2.2)	14 (1.5)
Patient's condition no longer requires study drug	1 (0.2)	2 (0.4)	3 (0.3)
Patient withdrew consent	17 (3.7)	25 (5.5)	42 (4.6)
Protocol violation	4 (0.9)	6 (1.3)	10 (1.1)
Unsatisfactory therapeutic effect	7 (1.5)	7 (1.5)	14 (1.5)

Demographic and Background Characteristics

Demographic variable	Vilda 100 mg qd + Met 500 mg bid N=456	Met up to 1000 mg bid N=458	Total N=914
Age (years)			
Mean ± SD	56.9 ± 9.76	57.0 ± 10.02	57.0 ± 9.89
Median	58.0	57.0	57.5
Min, Max	29.0, 78.0	24.0, 78.0	24.0, 78.0
Age group (years)			
< 65	350 (76.8%)	344 (75.1%)	694 (75.9%)
≥ 65	106 (23.2%)	114 (24.9%)	220 (24.1%)
Sex			
Male	230 (50.4%)	206 (45.0%)	436 (47.7%)
Female	226 (49.6%)	252 (55.0%)	478 (52.3%)
Race			
Caucasian	242 (53.1%)	237 (51.7%)	479 (52.4%)
Asian (non Indian subcontinent)	44 (9.6%)	44 (9.6%)	88 (9.6%)
Hispanic or latino	147 (32.2%)	145 (31.7%)	292 (31.9%)
Black	9 (2.0%)	12 (2.6%)	21 (2.3%)
Asian (indian subcontinent)	3 (0.7%)	5 (1.1%)	8 (0.9%)
Native american	1 (0.2%)	2 (0.4%)	3 (0.3%)
Other	10 (2.2%)	13 (2.8%)	23 (2.5%)
Height (cm)			
Mean ± SD	164.7 ± 10.75	164.0 ± 10.34	164.4 ± 10.54
Median	165.0	164.0	164.0
Min, Max	139.0, 193.0	141.0, 193.0	139.0, 193.0
Body weight (kg)			
Mean ± SD	84.6 ± 17.01	84.4 ± 18.94	84.5 ± 17.99
Median	83.6	81.4	82.8
Min, Max	44.0, 134.5	47.1, 150.0	44.0, 150.0
BMI (kg/m2)**			

Mean ± SD	31.1 ± 5.11	31.2 ± 5.47	31.1 ± 5.29
Median	30.5	30.4	30.5
Min, Max	22.0, 45.3	22.0, 45.0	22.0, 45.3
BMI group (kg/m2)**			
< 30 (kg/m^2)	209 (45.8%)	217 (47.4%)	426 (46.6%)
≥ 30(kg/m^2)	247 (54.2%)	241 (52.6%)	488 (53.4%)
≥ 35 (kg/m^2)	100 (21.9%)	109 (23.8%)	209 (22.9%)
HbA_{1c} (%)	n = 456	n = 457	n = 913
Mean ± SD	7.4 ± 0.78	7.3 ± 0.79	7.3 ± 0.79
Median	7.2	7.2	7.2
Min, Max	5.7, 9.9	5.6, 10.3	5.6, 10.3
HbA_{1c} (%)			
<=7	189 (41.4%)	190 (41.5%)	379 (41.5%)
>7	267 (58.6%)	267 (58.3%)	534 (58.4%)
<=8	375 (82.2%)	376 (82.1%)	751 (82.2%)
>8	81 (17.8%)	81 (17.7%)	162 (17.7%)
FPG (mmol/L)	n = 456	n = 458	n = 914
Mean ± SD	8.7 ± 2.28	8.5 ± 2.25	8.6 ± 2.27
Median	8.2	7.9	8.0
Min, Max	4.6, 25.3	3.0, 18.6	3.0, 25.3
Duration of Type 2 Diabetes (years)	n = 456	n = 458	n = 914
Mean ± SD	4.6 ± 4.91	4.7 ± 4.94	4.7 ± 4.92
Median	3.1	3.0	3.0
Min, Max	0.2, 30.9	0.2, 29.7	0.2, 30.9
GFR (MDRD) (mL/min) per 1.73 m^2			
Normal (>80)	310 (68.0%)	323 (70.5%)	633 (69.3%)
Mild (>=50 - <=80)	143 (31.4%)	132 (28.8%)	275 (30.1%)
Moderate (>=30 - <50)	3 (0.7%)	2 (0.4%)	5 (0.5%)
Severe (<30)	0 (0.0%)	1 (0.2%)	1 (0.1%)
GFR (CG) (mL/min) per 1.73 m^2			
Normal (>80)	378 (82.9%)	372 (81.2%)	750 (82.1%)
Mild (>=50 - <=80)	73 (16.0%)	79 (17.2%)	152 (16.6%)
Moderate (>=30 - <50)	5 (1.1%)	6 (1.3%)	11 (1.2%)
Severe (<30)	0 (0.0%)	1 (0.2%)	1 (0.1%)

Duration of type 2 diabetes is collected on the day of the screening measurement (Week -4, Visit 1). For baseline HbA1c measurements, only patients with at least one pre-randomization measurement are included. Baseline HbA1c and baseline FPG are the sample obtained on Day 1, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing. GFR (MDRD)= GFR estimated using the MDRD formula. GFR (CG)= GFR estimated using the CG formula. GFR is calculated using the serum creatinine and body weight value at the Day 1 measurement, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing.

Primary Efficacy Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to endpoint (ITT population, Per Protocol population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met up to 1000 mg bid (SE)	95% CI	p-value
Intent to treat population						
Vilda 100 mg qd + Met 500 mg bid	446	7.37 (0.04)	-0.51 (0.03)	-0.14 (0.05)	(-0.24,-0.05)*	0.002 **
Met up to 1000 mg bid	449	7.32 (0.04)	-0.37 (0.03)			
Per protocol population						
Vilda 100 mg qd + Met 500 mg bid	410	7.36 (0.04)	-0.54 (0.04)	-0.15 (0.05)	(-0.25,-0.05)*	0.003 **
Met up to 1000 mg bid	391	7.33 (0.04)	-0.39 (0.04)			

Baseline is measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is the final available post-randomization assessment up to the last regular scheduled visit. In the case of a missing scheduled visit sample, the closest unscheduled visit within 7 days of scheduled visit is used.

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 (if applicable) were from an ANCOVA model containing terms for treatment, baseline and pooled centers.

* Indicates non-inferiority to comparator at the one-sided 2.5% alpha level.
Non-inferiority margin is 0.4%. ** Indicates statistical significance for superiority at the 5% alpha level. Primary analysis based on ITT population.

Number of responders at endpoint (ITT population)

	Vilda 100 mg qd + Met 500 mg bid n (%)	Met up to 1000 mg bid n (%)	p-value*
ITT population	N=446	N=450	
N'[1]	446 (100.0)	449 (100.0)	
Responder Criterion			
At least one criterion met	297 (66.6)	232 (51.7)	<0.001
HbA_{1c} < 7% [2]	140/283 (49.5)	124/285 (43.5)	0.154
HbA_{1c} < 7% in patients with baseline HbA_{1c} <= 8% [3]	108/180 (60.0)	94/186 (50.5)	0.069
HbA_{1c} <= 6.5% [2]	159/393 (40.5)	115/385 (29.9)	0.002
Reduction of HbA_{1c} ≥ 1% [1]	107 (24.0)	83 (18.5)	0.044
Reduction of HbA_{1c} ≥ 1% in patients with baseline HbA_{1c} > 9% $	5/16 (31.3)	8/18 (44.4)	0.429
Reduction of HbA_{1c} ≥ 0.7% [1]	175 (39.2)	130 (29.0)	0.001
Reduction of HbA_{1c} ≥ 0.5% [1]	240 (53.8)	185 (41.2)	<0.001
Per protocol population	N=410	N=392	
N'[1]	410 (100.0)	391 (100.0)	
Responder Criterion			
At least one criterion met	283 (69.0)	211 (54.0)	<0.001
HbA_{1c} < 7% [2]	137/261 (52.5)	113/249 (45.4)	0.108
HbA_{1c} < 7% in patients with baseline HbA_{1c} <= 8% [3]	106/168 (63.1)	86/163 (52.8)	0.057

HbA_{1c} <= 6.5% [2]	154/365 (42.2)	108/339 (31.9)	0.005
Reduction of HbA_{1c} ≥ 1% [1]	102 (24.9)	80 (20.5)	0.136
Reduction of HbA_{1c} ≥ 1% in patients with baseline HbA1c > 9% $	4/14 (28.6)	8/15 (53.3)	0.176
Reduction of HbA_{1c} ≥ 0.7% [1]	167 (40.7)	123 (31.5)	0.006
Reduction of HbA_{1c} ≥ 0.5% [1]	228 (55.6)	172 (44.0)	0.001

Baseline is measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is the final available post-randomization assessment up to the last regular scheduled visit. In the case of a missing scheduled visit sample, the closest unscheduled visit within 7 days of scheduled visit is used.

* Chi-square test for Vilda 100 mg qd + Met 500 mg bid vs. Met up to 1000 mg bid.

[1] Number of patients with both baseline and endpoint HbA1c measurements, which is used as denominator unless specified otherwise.
[2] Denominator includes only patients with baseline HbA1c >= 7% (> 6.5%) and endpoint HbA1c measurement.
[3] Denominator includes only patients with 7% < baseline HbA1c <= 8% and endpoint HbA1c measurement.
$ Denominator includes only patients with baseline HbA1c >9% and endpoint HbA1c measurement.

Mean changes from baseline in HbA1c (%) at endpoint: subgroup analyses (ITT population)

		Vilda 100 mg qd + Met 500 mg bid N = 446			Met up to 1000 mg bid N = 450		
Subgroup	**Category**	**n**	**BL mean**	**Change (SE)**	**n**	**BL mean**	
HbA_{1c} at baseline (%)	<= 8	366	7.08	-0.46 (0.03)	372	7.05	-0.31 (0.03)
	> 8	80	8.68	-0.65 (0.13)	77	8.62	-0.51 (0.12)
	<= 7	186	6.67	-0.34 (0.04)	186	6.63	-0.19 (0.03)
	> 7	260	7.87	-0.61 (0.05)	263	7.81	-0.46 (0.05)
BMI at baseline (kg/m^2)	< 30 kg/m^2	206	7.37	-0.51 (0.05)	213	7.34	-0.41 (0.05)
	>= 30kg/m^2	240	7.37	-0.49 (0.05)	236	7.30	-0.29 (0.05)
	>= 35kg/m^2	97	7.44	-0.45 (0.07)	109	7.26	-0.29 (0.07)
Age(years)	< 65 years	343	7.42	-0.50 (0.04)	337	7.32	-0.35 (0.04)
	>= 65 years	103	7.19	-0.50 (0.06)	112	7.33	-0.33 (0.06)
Gender	Male	224	7.32	-0.43 (0.05)	200	7.32	-0.33 (0.05)
	Female	222	7.42	-0.57 (0.05)	249	7.32	-0.36 (0.04)
Race	Caucasian	240	7.28	-0.42 (0.04)	234	7.25	-0.28 (0.04)
	Black	6	7.13	0.32 (0.26)	11	7.36	-0.11 (0.18)
	Asian (non Indian subcontinent)	42	7.43	-0.72 (0.07)	44	7.43	-0.49 (0.11)
	Asian (Indian subcontinent)	2	7.40	-0.70 (0.30)	5	7.08	0.14 (0.33)
	Hispanic or Latino	145	7.52	-0.60 (0.07)	140	7.43	-0.45 (0.07)
	Native American	1	6.30	-0.80	2	7.90	-0.80 (0.40)
	Other	10	7.34	-0.36 (0.12)	13	7.02	-0.22 (0.26)

Baseline is measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is the final available post-randomization assessment up to the last regular scheduled visit. In the case of a missing scheduled visit sample, the closest unscheduled visit within 7 days of scheduled visit is used.

n is the number of patients with observations at both baseline and endpoint.

Secondary Efficacy Result(s)

ANCOVA results for change in FPG (mmol/L) from baseline to endpoint (ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met up to 1000 mg bid (SE)	95% CI	p-value
Intent to treat population						
Vilda 100 mg qd + Met 500 mg bid	446	8.66 (0.11)	-0.77 (0.07)	-0.18 (0.10)	(-0.38, 0.02)	0.070
Met up to 1000 mg bid	450	8.42 (0.10)	-0.59 (0.07)			
Per protocol population						
Vilda 100 mg qd + Met 500 mg bid	410	8.71 (0.11)	-0.83 (0.08)	-0.20 (0.10)	(-0.41, 0.00)	0.050
Met up to 1000 mg bid	392	8.44 (0.11)	-0.63 (0.08)			

Baseline is measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement is missing. Endpoint is the final available post-randomization assessment up to the last regular scheduled visit. In the case of a missing scheduled visit sample, the closest unscheduled visit within 7 days of scheduled visit is used.

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 (if applicable) were from an ANCOVA model containing terms for treatment, baseline and pooled centers.

* Indicates statistical significance at the 5% alpha level. Primary analysis based on ITT population.

ANCOVA results for change in body weight (kg) from baseline to endpoint (ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met up to 1000 mg bid (SE)	95% CI	p-value
Vilda 100 mg qd + Met 500 mg bid	446	84.29 (0.81)	-0.62 (0.14)	0.74 (0.19)	(0.36, 1.11)	<0.001*
Met up to 1000 mg bid	449	84.11 (0.90)	-1.35 (0.14)			

Safety Results

Adverse Events by System Organ Class

Primary system organ class	Vilda 100 mg qd + Met 500 mg bid N=456 n (%)	Met up to 1000 mg bid N=458 n (%)
Any primary system organ class	220 (48.2)	237 (51.7)
Blood and lymphatic system disorders	2 (0.4)	2 (0.4)
Cardiac disorders	11 (2.4)	9 (2.0)
Congenital, familial and genetic disorders	0 (0.0)	1 (0.2)
Ear and labyrinth disorders	5 (1.1)	8 (1.7)
Endocrine disorders	1 (0.2)	0 (0.0)
Eye disorders	18 (3.9)	11 (2.4)
Gastrointestinal disorders	70 (15.4)	96 (21.0)
General disorders and administr. site conditions	28 (6.1)	25 (5.5)
Hepatobiliary disorders	1 (0.2)	1 (0.2)
Immune system disorders	2 (0.4)	3 (0.7)
Infections and infestations	87 (19.1)	94 (20.5)
Injury, poisoning and procedural complications	19 (4.2)	20 (4.4)
Investigations	5 (1.1)	5 (1.1)
Metabolism and nutrition disorders	9 (2.0)	10 (2.2)
Musculoskeletal and connective tissue disorders	49 (10.7)	55 (12.0)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	3 (0.7)	2 (0.4)
Nervous system disorders	49 (10.7)	54 (11.8)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0 (0.0)
Psychiatric disorders	21 (4.6)	21 (4.6)
Renal and urinary disorders	9 (2.0)	9 (2.0)
Reproductive system and breast disorders	3 (0.7)	3 (0.7)
Respiratory, thoracic and mediastinal disorders	14 (3.1)	18 (3.9)
Skin and subcutaneous tissue disorders	18 (3.9)	22 (4.8)
Social circumstances	1 (0.2)	0 (0.0)
Vascular disorders	13 (2.9)	16 (3.5)

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 + Met 500 mg bid N=456 n (%)	Met up to 1000 mg bid N=458 n (%)
Any Preferred term	220 (48.2)	237 (51.7)
Diarrhea	21 (4.6)	39 (8.5)
Headache	18 (3.9)	28 (6.1)
Nasopharyngitis	15 (3.3)	13 (2.8)
Back pain	14 (3.1)	18 (3.9)
Dizziness	14 (3.1)	16 (3.5)
Flatulence	13 (2.9)	8 (1.7)
Upper respiratory tract infection	13 (2.9)	10 (2.2)
Arthralgia	11 (2.4)	6 (1.3)
Hypertension	11 (2.4)	12 (2.6)
Nausea	11 (2.4)	22 (4.8)

Serious Adverse Events and Deaths

Preferred Term	Vilda 100 mg qd + Met 500 mg bid N=456 n (%)	Met up to 1000 mg bid N=458 n (%)
Deaths	0	0
SAEs	11 (2.4)	13 (2.8)
Discontinuation of study drug due to AEs	12 (2.6)	14 (3.1)
AEs causing dose adjustment or study drug interruption	20 (4.4)	17 (3.7)
Clinically significant CCV AEs	6 (1.3)	5 (1.1)
Clinically significant IM AEs	3 (0.7)	1 (0.2)
Other clinically significant AEs	25 (5.5)	31 (6.8)

These categories are not mutually exclusive.

Other Relevant Findings

Hypoglycemic events (Safety population)

	Vilda 100 mg qd + Met 500 mg bid N=456 n (%)	Met up to 1000 mg bid N=458 n (%)
Number of patients with at least one hypoglycemic event	1 (0.2)	1 (0.2)
Number of patients with 1 hypoglycemic event	1 (0.2)	1 (0.2)
Number of patients who discontinued due to hypoglycemic events	0 (0.0)	0 (0.0)
Number of patients with grade 2 hypoglycemic events	0 (0.0)	0 (0.0)
Total number of hypoglycemic events	1 (0.2)	1 (0.2)
Plasma glucose value (mmol/L) >2.8-<3.1	1 (0.2)	1 (0.2)
Grade		
Grade 1	1 (0.2)	1 (0.2)
Severity		
Mild	1 (0.2)	1 (0.2)
Action taken		
Non-drug therapy given	1 (0.2)	1 (0.2)
Relationship to drug		
Suspected	1 (0.2)	1 (0.2)
Clinical symptom		
Asthenia	1 (0.2)	1 (0.2)
Tremor	1 (0.2)	0 (0.0)

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).
A patient may have had more than one type of event.

Date of Clinical Trial Report

19-Dec-2008

Date Inclusion on Novartis Clinical Trial Results Database

01-June-2009

Date of Latest Update

20-May-2009