Sponsor

Novartis

Generic Drug Name

vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Vildagliptin is approved in the EU for the treatment of Type 2 Diabetes Mellitus for use as monotherapy in patients who cannot take metformin and in combination with some of the most frequently prescribed oral anti-diabetes medicines - metformin, sulfonylureas (SUs) or thiazolidinediones (TZDs).

Protocol Number

CLAF237A23135

Title

A 24-week, multi-center, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of vildagliptin 50mg bid as an add-on therapy to insulin, with or without metformin, in patients with type 2 diabetes mellitus

Phase of Development

IIIB

Study Start/End Dates

28 Sep 2010/ 24 Oct 2011

Study Design/Methodology

Multi-center, double-blind, placebo-controlled, parallel group study to assess the efficacy of vildagliptin 50- mg bid add-on therapy to insulin versus placebo in Type 2 diabetic patients following 24 weeks of treatment. Following a 2-week screening period, patients receiving a stable dose of long-acting, intermediate-acting or pre-mixed insulin with or without stable metformin treatment were randomized 1:1 to treatment with vildagliptin 50 mg bid or placebo. Patient enrollment was stratified by metformin use and conducted to achieve a 60/40 ratio of patients receiving concomitant metformin treatment or no metformin treatment, respectively. Additionally, patients were stratified by the type of insulin (long-acting vs. intermediate-acting or pre-mixed insulin). Patients continued on a stable dose of basal long or intermediate-acting or pre-mixed insulin and metformin, if applicable, throughout the study.

Centres

67 centers in 11 countries enrolled at least one patient (number of centers in brackets): Australia (5), Belgium (4), Czech Republic (6), Germany (13), Guatemala (5), Hong-Kong (2), Hungary (5), India (10), Romania (4), Slovakia (9), United Kingdom (4)

Outcome measures

Primary outcome measures(s)

- Reduction of HbA_{1c} after 24 weeks of treatment in patients treated with insulin and metformin

Secondary outcome measures(s)

- Reduction of HbA_{1c} after 24 weeks of treatment in the subpopulation of patients treated with insulin and metformin.
- Reduction HbA_{1c} after 24 weeks of treatment in the subpopulation of patients treated with insulin without metformin
- Compare the safety and tolerability of vildagliptin 50mg bid after 24 weeks treatment .
- Reduction of fasting plasma glucose after 24 weeks of treatment for the overall study population and for the subpopulations of patients receiving or not receiving concomitant metformin therapy.
- Determine the responder rates after 24 weeks treatment for the overall study population and for the subpopulations of patients receiving or not receiving concomitant metformin therapy.
- Assess the incidence of hypoglycemia and severe hypoglycemia during 24 weeks treatment for the overall study population and for the subpopulations of patients receiving or not receiving concomitant metformin therapy

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

Oral tablets of vildagliptin 50mg or matching placebo twice each day

Statistical Methods

The superiority of vildaglitpin 50mg bid over placebo was evaluated by testing the following hypothesis:$H_0 = \delta_{Vilda\ 50mg\ bid} = \delta_{Placebo}$ versus $H_{0a} : \delta_{Vilda\ 50mg\ bid} < \delta_{Placebo}$, where δs are the mean change from baseline to study endpoint in HbA_{1c} in the treatment group indicated.
The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment, pooled center, metformin use stratum and type of insulin stratum as the classification variable and baseline HbA_{1c} as the covariate. To assess the two key secondary efficacy endpoints - the hba1c reduction in subgroups of patients with or without concomitant metformin use, similar hypothesis testing for the primary variable of change from baseline in

HbA_{1c} at study endpoint was also performed in the subgroups of patients on insulin and metformin, and in patients on insulin alone, respectively. Similar ANCOVA models as for primary endpoint were fitted in the change from baseline to study endpoint in HbA1c for subgroups of patients with or without metformin use to evaluate the hypothesis testing for the two key secondary efficacy endpoints.
A closed testing hierarchical methodology was used to adjust for multiplicity of the three tests in the primary and key secondary efficacy variables according to the following order: first the superiority of vildagliptin over placebo in overall population was tested at the one-sided level of 0.025. If overall superiority was successfully established, then a test of superiority of vildagliptin in the subgroup of patients treated with insulin and metformin also at a one-sided level alpha=0.025 was performed. If also this test was successful then a test of superiority was carried out in the subgroup of patients treated with insulin alone with the same significance level as in the preceding two tests.
The analysis of the primary efficacy variable and the key secondary efficacy variables using the FAS was the primary basis of conclusion. The analysis based on the PPS was also performed to assess the robustness of the conclusion.
Other efficacy variables (FPG, predefine responder analysis, insulin resistance and sensitivity parameters from oGTT) were analyzed using a similar model as the primary efficacy endpoint, but in the FAS only. Safety data and laboratory data were summarized by treatment as appropriate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion

- Confirmed diagnosis of T2DM by standard criteria.
- Treatment with stable, once or twice daily doses (maximum dose of 1 unit/kg/day) of basal long-acting, intermediate-acting-acting insulin alone or in pre-mixed combination with rapid-acting or short-acting insulin for at least 12 weeks prior to Visit 1. Stable is defined as ±10% of the Visit 1 dose during the previous 12 weeks.
- Patients receiving metformin must be on a stable dose of metformin (at least 1500 mg daily or a maximally tolerated dose) for at least 12 weeks prior to Visit 1.
- HbA_{1c} ≥7.5 to ≤11% at Visit 1
- Age: ≥18 to ≤80 years old at Visit 1
- BMI ≥22 to ≤40 kg/m^2 at Visit 1.
- Males or females
- Females must be non-fertile or females of childbearing potential must use a medically approved birth control method based on local regulations
- Agreement to maintain the stable dose of insulin (±10% of Visit 1 dose) and metformin, if applicable, throughout the study.
- Agreement to continue current diet and exercise regime throughout the duration of the study, unless otherwise instructed by the investigator

Exclusion:

- Use of rapid or short acting insulin except in pre-mixed formulations with intermediate or long-acting insulin, insulin administration more frequently than twice-daily, or total insulin dose >1 unit/kg/day.
- Use of weight control products including weight-loss medications
- DPP-4 inhibitors, GLP-1 analogues/mimetics, Oral Anti-diabetic Agents (OADs) except metformin within the previous 6 months
- Chronic oral (>7 consecutive days), parenteral or intra-articular corticosteroid treatment

within 8 weeks

- Type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes (e.g., Cushing's syndrome or acromegaly-associated diabetes).
- Hepatic disorders
- Clinically significant renal dysfunction
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) at Visit 1, confirmed by repeat measure within 3 working days
- Total bilirubin > 2 xULN and/or direct bilirubin > 1 x ULN confirmed by repeat measure within 3 working days
- Positive Hepatitis B surface antigen (HbsAg)
- Positive Hepatitis C antibody test (anti-HCV)

Participant Flow (Randomized Set)

Disposition Reason	Vilda* 50mg bid N=228 n (%)	Placebo N=221 n (%)	Total N=449 n (%)
Completed	208 (91.2)	191 (86.4)	399 (88.9)
Discontinued	20 (8.8)	30 (13.6)	50 (11.1)
Administrative problems	1 (0.4)	1 (0.5)	2 (0.4)
Adverse event(s)	9 (3.9)	4 (1.8)	13 (2.9)
Death	0 (0.0)	1 (0.5)	1 (0.2)
Lost to follow-up	0 (0.0)	7 (3.2)	7 (1.6)
Patient withdrew consent	8 (3.5)	12 (5.4)	20 (4.5)
Protocol deviation	2 (0.9)	5 (2.3)	7 (1.6)

*Vildagliptin

Baseline Characteristics (Randomized Set)

Demographic Variable	Vilda* 50mg bid N=228	Placebo N=221	Total N=449
Age (Yrs)			
n	228	221	449
Mean	59.3	59.1	59.2
SD	9.85	10.08	9.95
Min	30.0	30.0	30.0
Median	60.0	60.0	60.0
Max	80.0	80.0	80.0
Age group			
< 65 yrs	160 (70.2%)	154 (69.7%)	314 (69.9%)
>=65 yrs	68 (29.8%)	67 (30.3%)	135 (30.1%)
< 75 yrs	210 (92.1%)	209 (94.6%)	419 (93.3%)
>=75 yrs	18 (7.9%)	12 (5.4%)	30 (6.7%)
Sex			
Female	119 (52.2%)	106 (48.0%)	225 (50.1%)
Male	109 (47.8%)	115 (52.0%)	224 (49.9%)
Race			
Asian	87 (38.2%)	86 (38.9%)	173 (38.5%)
Caucasian	116 (50.9%)	116 (52.5%)	232 (51.7%)
Other	25 (11.0%)	19 (8.6%)	44 (9.8%)
Ethnicity			
Hispanic/Latino	25 (11.0%)	24 (10.9%)	49 (10.9%)
Indian (Indian subcontinent)	62 (27.2%)	61 (27.6%)	123 (27.4%)
Chinese	24 (10.5%)	24 (10.9%)	48 (10.7%)

Other	117 (51.3%)	112 (50.7%)	229 (51.0%)
Height (cm)			
n	228	221	449
Mean	163.7	164.6	164.2
SD	9.91	10.32	10.12
Min	139.0	142.0	139.0
Median	164.5	165.0	165.0
Max	191.0	198.0	198.0
Body weight (kg)			
n	228	221	449
Mean	77.9	78.9	78.4
SD	16.24	16.69	16.45
Min	44.5	45.0	44.5
Median	75.3	76.1	76.0
Max	132.0	131.1	132.0
BMI (kg/m^2)			
n	228	221	449
Mean	28.9	29.0	28.9
SD	4.38	4.58	4.47
Min	21.1	22.0	21.1
Median	28.1	28.1	28.1
Max	40.1	39.8	40.1
BMI group			
<30 (kg/m^2)	138 (60.5%)	139 (62.9%)	277 (61.7%)
>=30(kg/m^2)	90 (39.5%)	82 (37.1%)	172 (38.3%)
>=35(kg/m^2)	23 (10.1%)	28 (12.7%)	51 (11.4%)
Demography information is collected on the day of the screening measurement (Week -2, Visit 1). *Vildagliptin			

Outcome measures

Primary Outcome Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to study endpoint (Full Analysis Set)

				Difference in adjusted mean change (Vilda-Placebo)**		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**(95% CI)**	**P-Value**
Full-analysis set						
Vilda** 50mg bid	221	8.80 (0.07)	-0.77 (0.08)	-0.72 (0.10)	(-0.92 , -0.52)	<0.001*
Placebo	215	8.84 (0.07)	-0.05 (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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24).

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, Hba1c at baseline, metformin use (not required for metformin use subgroups), insulin type and pooled centers.

Primary analysis is based on FAS.

* indicates statistical significance according to the hierarchical test procedure.

**Vildagliptin

Secondary Outcome Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to study endpoint (Full Analysis Set)

				Difference in adjusted mean change (Vilda**-Placebo)		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**(95% CI)**	**P-Value**
Full-analysis set (Insulin + met)						
Vilda** 50mg bid	133	8.78 (0.08)	-0.98 (0.09)	-0.63 (0.12)	(-0.86 , -0.39)	<0.001*
Placebo	134	8.80 (0.08)	-0.35 (0.09)			
Full-analysis set (Insulin)						
Vilda** 50mg bid	88	8.84 (0.12)	-0.60 (0.19)	-0.84 (0.19)	(-1.21 , -0.47)	<0.001*
Placebo	81	8.90 (0.11)	0.24 (0.20)			

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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24).

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, Hba1c at baseline, metformin use (not required for metformin use subgroups), insulin type and pooled centers.

Primary analysis is based on FAS.

* indicates statistical significance according to the hierarchical test procedure.

** Vildagliptin

ANCOVA results for change in FPG (mmol/L) from baseline to study endpoint by treatment (Full analysis set)

				Difference in adjusted mean change (Vilda**-Placebo)		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**(95% CI)**	**P-Value***
Full-analysis set						
Vilda** 50mg bid	222	9.84 (0.20)	-0.77 (0.24)	-0.59 (0.30)	(-1.18 , 0.00)	0.050
Placebo	215	9.50 (0.20)	-0.18 (0.25)			
Full-analysis set (Insulin + met)						
Vilda** 50mg bid	134	9.86 (0.24)	-0.98 (0.25)	-0.21 (0.33)	(-0.86 , 0.43)	0.521
Placebo	134	9.30 (0.24)	-0.77 (0.25)			
Full-analysis set (Insulin)						
Vilda** 50mg bid	88	9.80 (0.36)	-0.75 (0.59)	-1.07 (0.57)	(-2.19 , 0.05)	0.060
Placebo	81	9.84 (0.35)	0.32 (0.62)			

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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24.

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, FPG at baseline, metformin use (not required for metformin use subgroups) insulin type and pooled centers.

* indicates statistical significance at 5% level.

** Vildagliptin

Number of patients who responded at study endpoint by treatment (Full Analysis Set and Full Analysis Set by concomitant metformin use)

Full Analysis Set	**Vilda** 50mg bid N=224 n (%)**	**Placebo N=216 n (%)**	**p-value***
N'[1]	221 (100.0)	215 (100.0)	
Responder Criterion			
At least one criterion met	49 (22.2)	12 (5.6)	<0.001
HbA_{1c} < 7% [2]	49/221 (22.2)	11/214 (5.1)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	16 55 (29.1)	5/52 (9.6)	0.011
HbA_{1c} ≤ 6.5% [2]	17/221 (7.7)	5/215 (2.3)	0.010
Full Analysis Set Concomitant metformin use: yes	**Vilda** 50mg bid N=136 n (%)**	**Placebo N=135 n (%)**	**p-value***
N'[1]	133 (100.0)	134 (100.0)	
Respo der Criterion			
At least one crite ion met	28 (21.1)	7 (5.2)	<0.001
HbA_{1c} < 7% [2]	28/133 (21.1)	7/134 (5.2)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	8/30 (26.7)	2/34 (5.9)	0.036
HbA_{1c} ≤ 6.5% [2]	13/133 (9.8)	2/134 (1.5)	0.003
Full Analysis Set Concomitant metform n use: no	**Vilda** 50mg bid N=88 n (%)**	**Placebo N=81 n (%)**	**p-value***
N'[1]	88 (100.0)	81 (100.0)	
Responder Criterion			
At least one criterion met	21 (23.9)	5 (6.2)	0.001
HbA_{1c} < 7% [2]	21/88 (23.9)	4/80 (5.0)	<0.001
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	/25 (32.0)	3/18 (16.7)	0.309
HbA_{1c} ≤ 6.5% [2]	4/88 (4.5)	3/81 (3.7)	>0.999

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. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 24.

* Chi-square test for Vilda 50mg bid vs. Placebo.

[1]) Number of patients with both baseline and endpoint HbA_{1c} measurements,which is used as denominator unless specified otherwise.

[2]) Denominator includes only patients with baseline $HbA_{1c} \geq 7\%$ (> 6.5%) and endpoint HbA_{1c} measurement.

[3]) Denominator includes only patients with 7% ≤ baseline HbA1c ≤ 8% and endpoint HbA1c measurement.$HbA_{1c} \leq 6.5\%$

** Vildagliptin

Safety Results

Number (%) of patients with AEs by primary system organ class (Safety set)

Primary system organ class	Vilda* 50mg bid N=227 n (%)	Placebo N=221 n (%)
Any primary system organ class	131 (57.7)	105 (47.5)
Blood and lymphatic system disorders	4 (1.8)	1 (0.5)
Cardiac disorders	10 (4.4)	8 (3.6)
Congenital, familial and genetic disorders	1 (0.4)	0 (0.0)
Ear and labyrinth disorders	3 (1.3)	0 (0.0)
Eye disorders	13 (5.7)	9 (4.1)
Gastrointestinal disorders	31 (13.7)	16 (7.2)
General disorders and administration site conditions	30 (13.2)	28 (12.7)
Hepatobiliary disorders	2 (0.9)	1 (0.5)
Immune system disorders	0 (0.0)	1 (0.5)
Infections and infestations	51 (22.5)	32 (14.5)
Injury, poisoning and procedural complications	8 (3.5)	8 (3.6)
Investigations	10 (4.4)	8 (3.6)
Metabolism and nutrition disorders	28 (12.3)	22 (10.0)
Musculoskeletal and connective tissue disorders	25 (11.0)	23 (10.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (1.3)	0 (0.0)
Nervous system disorders	42 (18.5)	34 (15.4)
Psychiatric disorders	12 (5.3)	4 (1.8)
Renal and urinary disorders	1 (0.4)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	10 (4.4)	9 (4.1)
Skin and subcutaneous tissue disorders	31 (13.7)	32 (14.5)
Vascular disorders	4 (1.8)	3 (1.4)

Primary system organ classes are presented 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.

Coded using MedDRA version 14.0

* Vildagliptin

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

Preferred term	Vilda* 50mg bid N=227 n (%)	Placebo N=221 n (%)
Any preferred term	131 (57.7)	105 (47.5)
Hyperhidrosis	26 (11.5)	28 (12.7)
Hypoglycaemia	19 (8.4)	16 (7.2)
Dizziness	18 (7.9)	19 (8.6)
Tremor	16 (7.0)	11 (5.0)
Upper respiratory tract infection	16 (7.0)	7 (3.2)
Diarrhoea	10 (4.4)	4 (1.8)
Headache	9 (4.0)	4 (1.8)
Vision blurred	9 (4.0)	2 (0.9)
Asthenia	8 (3.5)	10 (4.5)
Cough	7 (3.1)	4 (1.8)
Hunger	7 (3.1)	7 (3.2)
Blood glucose decreased	6 (2.6)	6 (2.7)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category.
Preferred terms are sorted by descending order of incidence in the Vilda 50mg bid group.
* Vildagliptin

Serious Adverse Events and Deaths

Event category	Vilda* 50mg bid N=227 n (%)	Placebo N=221 n (%)
Deaths	0 (0.0)	1 (0.5)
SAEs	9 (4.0)	9 (4.1)
Discontinuation due to AEs	9 (4.0)	5 (2.3)
AEs causing dose adjustment or study drug interruption	4 (1.8)	1 (0.5)
AEs of predefined risk	56 (24.7)	38 (17.2)

* Vildagliptin

Number of patients experiencing hypoglycemic events during the randomized double-blind period by event profile and treatment (Safety Set)

	Vilda** 50mg bid N=227 n (%)	Placebo N=221 n (%)	p-Value*
Number (%) of patients with at least one hypoglycemic event	19 (8.4)	16 (7.2)	0.656

Number (%) of patients with			
one hypoglycemic event	14 (6.2)	10 (4.5)	
two hypoglycemic events	1 (0.4)	1 (0.5)	
>2 hypoglycemic events	4 (1.8)	5 (2.3)	
Number (%) of patients who discontinued due to hypoglycemic events	1 (0.4)	0 (0.0)	
Number (%) of patients with grade 2 hypoglycemic events	2 (0.9)	1 (0.5)	
Number (%) of patients with suspected grade 2 hypoglycemic events	0 (0.0)	1 (0.5)	
Number (%) of patients with severe hypoglycemic events	2 (0.9)	2 (0.9)	>0.999

* indicates statistical significance at 5% level.

Chi-squared test was used to compare the number of patients with at least one hypoglycemic event. The Fisher exact test was used to compare the number of patients with severe events.

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), c) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and no plasma glucose measurement is available (suspected grade 2).

** Vildagliptin

Date of Clinical Trial Report

26 Jan 2012

Date Inclusion on Novartis Clinical Trial Results Database

12 OCT 2012

Date of Latest Update

10 OCT 2012