Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Type 2 diabetes

Study Number
CLAF237A2398

Title A Multi-center, Randomized, Double-Blind, Active Controlled Study to Compare the Effect of 24 Weeks Treatment with Vildagliptin 100 mg qd or Metformin 1500 mg daily in Elderly Drug Naïve Patients with Type 2 Diabetes

Phase of Development
Phase IIIb

Study Start/End Dates
14-Sep-2006 to 29-May-2008

Study Design/Methodology

This was a 24-week, multicenter, randomized, double-blind, active-controlled, parallel-group study. Elderly (aged from 65 years to the upper age limit recommended by local prescribing information for metformin) drug-naïve patients with type 2 diabetes (HbA1c 7-9%) were included in the trial. Following a 2-week screening period, eligible patients were randomized in a ratio of 1 : 1 to receive vildagliptin 100 mg daily (given as a once-daily dose) or metformin titrated to 1500 mg daily (given as divided doses, 1000 mg in the morning and 500 mg in the evening) for 24 weeks of active treatment. Dose adjustments of study medication were not allowed; patients who were unable to tolerate 1500 mg daily metformin were to be discontinued from the study.

Centers

A total of 141 centers in 14 countries screened at least 1 patient (number of centers in brackets): Austria (10), Canada (4), Estonia (6), Germany (17), Hungary (3), Italy (7), Republic of Korea (9), Latvia (5), Norway (9), Russia (10), Spain (20),Taiwan (10), USA (28) and Venezuela (3). A total of 113 centers in 14 countries randomized at least 1 patient (number of centers in brackets): Austria (6), Canada (3), Estonia (5), Germany (14), Hungary (3), Italy (6), Republic of Korea (8), Latvia (3), Norway (9), Russia (9), Spain (16), Taiwan (9), USA (19) and Venezuela (3).

Outcome Measures

Primary objective:
1. To demonstrate the efficacy of vildagliptin in elderly drug naïve patients with type 2 diabetes by testing the hypothesis that the hemoglobin A_{1c} (HbA_{1c}) reduction with vildagliptin 100 mg qd is not inferior to that with metformin 1500 mg daily after 24 weeks of treatment.

Secondary objectives:

1. To evaluate the general safety and tolerability of vildagliptin 100 mg qd in elderly drug naïve patients with type 2 diabetes after 24 weeks of treatment.

2. To demonstrate that vildagliptin 100 mg qd has a better gastrointestinal tolerability to metformin in elderly drug naïve patients with type 2 diabetes after 24 weeks of treatment.

3. To evaluate the responder rates with vildagliptin 100 mg qd in elderly drug naïve patients with type 2 diabetes after 24 weeks of treatment.

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

Patients were assigned to doubleblind treatment of either vildagliptin 100 mg qd or metformin 1500 mg daily, in a ratio of 1:1 using a double-dummy technique.

Vildagliptin 100 mg or matching placebo was taken before the morning meal. Metformin 500mg tablets or matching placebo were taken and uptitrated as follows: at week 1, one tablet before the morning meal; at week 2, one tablet before the morning meal and one tablet before the evening meal; at weeks 3 to 24, two tablets before the morning meal and one tablet before the evening meal.

Statistical Methods

The primary efficacy variable was the change from baseline in HbA_{1c} at Week 24 or at the final visit with HbA_{1c} measurement for those patients who did not have a Week 24 HbA_{1c} measurement (the last observation carried forward (LOCF) approach). The test for the non-inferiority of vildagliptin to metformin was primarily based on the following null hypothesis and one-sided alternative hypothesis:

H_o: $\delta_{vilda} \geq \delta_{met} + 0.4\%$ versus H_a: $\delta_{vilda} < \delta_{met} + 0.4\%$ where δ_{vilda} and δ_{met} are the mean change from baseline for vildagliptin and metformin, respectively.

An analysis of covariance (ANCOVA) model was fitted including terms for treatment and pooled center as the classification variable and baseline HbA_{1c} as the covariate. The least squares mean (adjusted mean) change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (vildagliptin – metformin), and the two-sided 95% confidence interval for the difference were obtained from the primary analysis model. The null hypothesis was to be rejected and non-inferiority established if the upper limit of the confidence interval does not exceed 0.4%. Furthermore, if the upper limit does not exceed 0.3% the non-inferiority of vildagliptin to metformin was also to be established at a 0.3% margin. The analysis of the primary efficacy variable using the ITT population was the primary basis of conclusion. The analysis based on the PP population was also performed to assess the robustness of the conclusion.

The analysis of the secondary and exploratory efficacy variables used the same ANCOVA model as specified for the primary efficacy variable. Analyses were done in the ITT population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Age in the range of 65 years to the upper age limit recommended by local prescribing information for metformin.

2. Drug naïve patients with T2DM. Drug naïve patients are defined as subjects who were never treated with an oral antidiabetic agent or subjects who have not taken any oral antidiabetic agent for at least 12 weeks prior to study entry (Visit 1) and if they have received oral antidiabetic agents then never for > 3 months at any time in the past.

3. Body mass index (BMI) in the range of 22-40 kg/m2 inclusive at visit 1.

4. HbA1c in the range of 7 to 9% inclusive at visit 1.

5. FPG < 270 mg/dL (15 mmol/L) at visit 1 (measurement may have been repeated once to confirm FPG value).

6. Agreement to maintain prior diet and exercise habits during the full course of the study.

7. Written informed consent to participate in the study.

8. Ability to comply with all study requirements.

Exclusion criteria

1. 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) within the past 6 months.
2. Acute infections which may affect blood glucose control within 4 weeks prior to visit 1 and other concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study.
3. Any of the following within the past 6 months:
   - myocardial infarction (MI) (if the visit 1 ECG reveals patterns consistent with a MI and the date of the event cannot be determined, then the patient could enter the study at the discretion of the investigator and the sponsor);
   - coronary artery bypass surgery or percutaneous coronary intervention;
   - Unstable angina or stroke.
4. Congestive heart failure requiring pharmacologic treatment.
5. 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 ms)
6. Liver disease such as cirrhosis or chronic active hepatitis.

7. Treatment with class Ia, Ib and Ic or III anti-arrhythmics.
8. Any of the following significant laboratory abnormalities:
    - ALT, AST > 2 times the upper limit of normal (ULN) at visit 1, confirmed by a repeat measure within 3 working days.
    - Total bilirubin > 2 times ULN and direct bilirubin > ULN at visit 1, confirmed by a repeat measure within 3 working days
    - A positive Hepatitis B test (surface antigen, HBsAg).
    - A 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 at visit 1.
    - Clinically significant laboratory abnormalities, confirmed by repeat measurement, other than hyperglycemia, hyperinsulinemia, and glycosuria at visit 1.
    - Fasting triglycerides > 700 mg/dL (7.9 mmol/L) at visit 1.

Other protocol defined inclusion/exclusion criteria applied

Participant Flow

Disposition Reason	Vilda 100 mg qd N=169	Met 1500 mg daily N=166	Total N=335
Completed	142 (84.0%)	140 (84.3%)	282 (84.2%)
Discontinued	27 (16.0%)	26 (15.7%)	53 (15.8%)
Abnormal laboratory value(s)	2 (1.2%)	0 (0.0%)	2 (0.6%)
Adverse event(s)	6 (3.6%)	13 (7.8%)	19 (5.7%)
Death	1 (0.6%)	0 (0.0%)	1 (0.3%)
Lost to follow-up	3 (1.8%)	3 (1.8%)	6 (1.8%)
Patient withdrew consent	13 (7.7%)	8 (4.8%)	21 (6.3%)
Protocol violation	1 (0.6%)	0 (0.0%)	1 (0.3%)
Unsatisfactory therapeutic effect	1 (0.6%)	2 (1.2%)	3 (0.9%)

Baseline Characteristics

Demographic variable	Vilda 100 mg qd N=169	Met 1500 mg daily N=166	Total N=335
Age (years)			
Mean ± SD	71.6 ± 5.22	70.2 ± 5.08	70.9 ± 5.19
Median	71.0	69.0	70.0
Min, Max	65.0, 93.0	65.0, 89.0	65.0, 93.0
Sex			
Male	75 (44.4%)	88 (53.0%)	163 (48.7%)
Female	94 (55.6%)	78 (47.0%)	172 (51.3%)
Race			
Caucasian	123 (72.8%)	117 (70.5%)	240 (71.6%)
Asian (non Indian subcontinent)	32 (18.9%)	36 (21.7%)	68 (20.3%)
Hispanic or Latino	13 (7.7%)	10 (6.0%)	23 (6.9%)
Black	1 (0.6%)	1 (0.6%)	2 (0.6%)
Japanese	0 (0.0%)	1 (0.6%)	1 (0.3%)
Other	0 (0.0%)	1 (0.6%)	1 (0.3%)
Height (cm)			
Mean ± SD	163.1 ± 10.23	164.7 ± 10.46	163.9 ± 10.36
Median	162.0	165.0	164.0
Min, Max	144.0, 191.0	140.0, 193.0	140.0, 193.0
Body weight (kg)			
Mean ± SD	79.8 ± 16.72	80.2 ± 17.41	80.0 ± 17.04
Median	77.0	77.2	77.1
Min, Max	48.5, 145.2	50.0, 127.0	48.5, 145.2
BMI (kg/m^2)			
Mean ± SD	29.8 ± 4.44	29.4 ± 4.57	29.6 ± 4.51
Median	29.3	28.5	28.9
Min, Max	21.6, 41.0	22.0, 39.9	21.6, 41.0
BMI group			
< 30 (kg/m**2)	97 (57.4%)	100 (60.2%)	197 (58.8%)
≥ 30(kg/m**2)	72 (42.6%)	66 (39.8%)	138 (41.2%)
≥ 35 (kg/m**2)	22 (13.0%)	23 (13.9%)	45 (13.4%)

Demography information is collected on the day of the screening measurement (Week -2, Visit 1).

Outcome measures results

Primary Outcome measure

Change in baseline hemoglobin A1c (HbA1c) after 24 weeks

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met 1500 mg daily (SE)	95% CI
ITT population[§]					
Vilda 100 mg qd	159	7.78 (0.05)	-0.64 (0.07)	0.11 (0.09)	(-0.08, 0.29)*
Met 1500 mg daily	161	7.71 (0.04)	-0.75 (0.07)		
Per Protocol population					
Vilda 100 mg qd	140	7.80 (0.05)	-0.67 (0.07)	0.19 (0.09)	(0.01, 0.38)*
Met 1500 mg daily	136	7.69 (0.05)	-0.86 (0.07)		

Baseline is the measurement obtained on Day 1, or on a 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.

§ Primary basis of conclusion

* Indicates non-inferiority to comparator at the one-sided 2.5% alpha level. Non-inferiority margin is 0.4%.

Secondary Outcome Measure

Number (%) of patients who responded at endpoint (ITT population)

	Vilda 100 mg qd n (%)	Met 1500 mg daily n (%)	p-value*
	N=159	N=164	
N[1]	159 (100.0)	161 (100.0)	
At least one criterion met	113 (71.1)	117 (72.7)	0.750
HbA_{1c} < 7% [2]	74/151 (49.0)	91/149 (61.1)	0.036
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	49/85 (57.6)	70/99 (70.7)	0.065
HbA_{1c} ≤ 6.5% [2]	45/159 (28.3)	49/160 (30.6)	0.649
Reduction of HbA_{1c} ≥ 1% [1]	51 (32.1)	65 (40.4)	0.123
Reduction of HbA_{1c} ≥ 0.7% [1]	86 (54.1)	96 (59.6)	0.317
Reduction of HbA_{1c} ≥ 0.5% [1]	107 (67.3)	109 (67.7)	0.938

Baseline is the measurement obtained on Day 1, or on a 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 vs metformin 1500 mg daily.

[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} ≥ 7% (> 6.5%) and endpoint HbA_{1c} measurement.

[3] Denominator includes only patients with 7% < baseline HbA_{1c} ≤ 8% and endpoint HbA_{1c} measurement.

Gastrointestinal tolerability after 24 weeks of treatment

Preferred term	Vilda 100 mg qd N=167 n (%)	p-value*	Met 1500 mg daily N=165 n (%)
-Any GI event	25 (15.0)	0.028	41 (24.8)
Abdominal discomfort	2 (1.2)		1 (0.6)
Abdominal distension	1 (0.6)		1 (0.6)
Abdominal pain	1 (0.6)		3 (1.8)
Abdominal pain upper	5 (3.0)		5 (3.0)
Aphthous stomatitis	1 (0.6)		0 (0.0)
Colitis	0 (0.0)		1 (0.6)
Constipation	5 (3.0)		1 (0.6)
Dental caries	1 (0.6)		0 (0.0)
Diarrhoea	5 (3.0)		22 (13.3)
Dry mouth	1 (0.6)		0 (0.0)
Dyspepsia	0 (0.0)		2 (1.2)
Epigastric discomfort	1 (0.6)		0 (0.0)
Eructation	1 (0.6)		0 (0.0)
Flatulence	0 (0.0)		3 (1.8)
Frequent bowel movements	0 (0.0)		1 (0.6)
Gastritis	0 (0.0)		1 (0.6)
Gastrointestinal disorder	1 (0.6)		0 (0.0)
Gastrooesophageal reflux disease	0 (0.0)		1 (0.6)
Haemorrhoids	0 (0.0)		1 (0.6)
Mouth ulceration	0 (0.0)		1 (0.6)
Nausea	5 (3.0)		9 (5.5)
Oesophagitis	0 (0.0)		1 (0.6)
Stomach discomfort	0 (0.0)		1 (0.6)
Toothache	0 (0.0)		1 (0.6)

GI = Gastrointestinal
Preferred terms are sorted alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
* Fisher's exact test for Vilda 100 mg qd vs Met 1500 mg daily.

Safety

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

Primary system organ class	Vilda 100 mg qd N=167 n (%)	Met 1500 mg daily N=165 n (%)
Any primary system organ class	74 (44.3)	83 (50.3)
Blood and lymphatic system disorders	3 (1.8)	2 (1.2)
Cardiac disorders	6 (3.6)	4 (2.4)
Ear and labyrinth disorders	4 (2.4)	2 (1.2)
Endocrine disorders	2 (1.2)	0 (0.0)
Eye disorders	8 (4.8)	3 (1.8)
Gastrointestinal disorders	25 (15.0)	41 (24.8)
General disorders and administration site conditions	9 (5.4)	7 (4.2)
Hepatobiliary disorders	1 (0.6)	0 (0.0)
Infections and infestations	21 (12.6)	25 (15.2)
Injury, poisoning and procedural complications	4 (2.4)	4 (2.4)
Investigations	1 (0.6)	1 (0.6)
Metabolism and nutrition disorders	2 (1.2)	4 (2.4)
Musculoskeletal and connective tissue disorders	18 (10.8)	18 (10.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2)	1 (0.6)
Nervous system disorders	10 (6.0)	16 (9.7)
Psychiatric disorders	9 (5.4)	1 (0.6)
Renal and urinary disorders	1 (0.6)	5 (3.0)
Respiratory, thoracic and mediastinal disorders	5 (3.0)	9 (5.5)
Skin and subcutaneous tissue disorders	7 (4.2)	13 (7.9)
Vascular disorders	7 (4.2)	10 (6.1)

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

Number (%) of patients with serious or clinically significant AEs (Safety population)

Preferred Term	Vilda 100 mg qd N=167 n (%)	Met 1500 mg daily N=165 n (%)
Deaths	1 (0.6)	0 (0.0)
SAEs	5 (3.0)	6 (3.6)
Discontinuation of study drug due to AEs	7 (4.2)	13 (7.9)
AEs causing dose adjustment or study drug interruption	6 (3.6)	4 (2.4)

Other Relevant Findings

No other important or notable findings were reported in this study.

Date of Clinical Trial Report

02 FEB 2009

Date of inclusion on Novartis Clinical Trial Results Database 13 MAY 2009
Date of Latest Update 25 JUN 2012