Sponsor

Novartis

Generic Drug Name

Vildagliptin Modified Release

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Type 2 diabetes

Study Number

CLAF237B2201

Title

A multi-center, randomized, double-blind study to evaluate the efficacy and long-term safety of vildagliptin modified release (MR) as monotherapy in patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

24-Nov-2008 to 18-Oct-2010

Study Design/Methodology

This was a multi-center, randomized, double-blind, parallel group study, with an adaptive element. After a placebo run-in period, patients were randomized to receive either vildagliptin MR 25 mg qd, MR 50 mg qd, or placebo in a ratio of 1:1:1 for 24 weeks (study period 1).

In a subsequent interim period, patients randomized to vildagliptin MR 25 mg qd or 50 mg qd in period 1 continued on the same dose until dose selection for period 2 (52 weeks) was complete, and patients randomized to placebo in period 1 were switched to sitagliptin 100 mg. Following the interim analysis dose selection, vildagliptin MR 50 mg qd was carried into period 2. Patients who were randomized to vildagliptin MR 50 mg qd continued on the same dose, patients who were randomized to vildagliptin MR 25 mg qd were switched to the MR 50 mg qd dose, and patients who were randomized to placebo were switched to sitagliptin 100 mg qd.

Centres

157 centers in 7 countries: Canada (6), India (6), Malaysia (2), Philippines (3), Romania (5), Slovakia (7) and United States (128).

Publication

Not applicable

Objectives

Primary objective(s): 24 week analysis (Period 1)

- To demonstrate the efficacy of vildagliptin MR (25 mg qd or 50 mg qd) as monotherapy in patients with T2DM.

Secondary objectives(s): 24 week analysis (Period 1)

- To demonstrate the efficacy of vildagliptin MR (25 mg qd or 50 mg qd) as monotherapy in patients with T2DM by testing the hypothesis that the FPG reduction with vildagliptin MR is superior to that of placebo after 24 weeks of treatment.
- To evaluate the safety and tolerability of vildagliptin MR (25 mg qd or 50 mg qd) compared to placebo over 24 weeks of treatment as monotherapy in patients with T2DM.
- To evaluate the body weight change from baseline with vildagliptin MR (25 mg qd or 50 mg qd) compared to placebo after 24 weeks of treatment as monotherapy in patients with T2DM.

Primary objective(s): 76 week analysis (Period 2)

- To demonstrate the long-term safety and tolerability of vildagliptin MR (50mg qd) over the entire study duration as monotherapy in patients with T2DM. This was a secondary objective for the overall study as stated in the protocol.

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

Period 1: Vildagliptin MR 25 mg oral tablets qd or 50 mg oral tablets qd or matching placebo

Period 2: Vildagliptin MR 50 mg oral tablets qd (once daily)

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

Period 2: Sitagliptin 100 mg oral capsules qd (once daily)

Criteria for Evaluation

Primary efficacy variables

HbA_{1c} measured by ion exchange High Performance Liquid Chromatography (HPLC), fasting plasma glucose, and body weight.

Secondary efficacy variables

- FPG
- Body weight

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events, recording of hypoglycemic events, regular monitoring of hematology, blood chemistry and urine parameters, and regular assessments of vital signs, body weight and ECGs.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The primary efficacy variable was change from baseline in HbA_{1c} at Week 24 or at the final visit prior to week 24 if a patient discontinued during study period 1. Superiority of vildagliptin MR (either dose) to placebo for the effect of reducing HbA_{1c} was based on the following null hypotheses and two-sided alternative hypotheses: H_{01}: $\delta_{\text{Vilda MR 25 mg qd}} = \delta_{\text{Placebo}}$ versus H_{01a}: $\delta_{\text{Vilda MR 25 mg qd}} \neq \delta_{\text{Placebo}}$, H_{02}: $\delta_{\text{Vilda MR 50 mg qd}} = \delta_{\text{Placebo}}$ versus H_{02a}: $\delta_{\text{Vilda MR 50 mg qd}} \neq \delta_{\text{Placebo}}$, where δs were the mean change from baseline at Week 24 endpoint in HbA1c in the treatment group indicated. Multiple testing was adjusted for using the Dunnett step-down methodology to maintain an overall two-sided significance level of 0.05. The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment and pooled center as the classification variables and baseline HbA1c as the covariate. The least squares mean (adjusted mean) change from baseline for each treatment group, the difference between two treatment groups and associated two sided 95% confidence interval were obtained from the primary analysis model. The ANCOVA analysis was performed in the FAS population and, as a sensitivity analysis, in the Week 24 PP population. The analysis of the secondary efficacy variables (FPG and body weight) used the same ANCOVA model as specified for the primary efficacy variable HbA1c.

The primary safety conclusion was based on analyses on all data collected during the entire study regardless of rescue medication use. Safety data (including overall AEs, SAEs, death, AEs lead-

ing to discontinuation, pre-defined potential risks of AEs, hypoglycemia, lab abnormality, treatment emergent hepatic enzyme & CPK elevations) collected over the entire study period were summarized by treatment. Similar analyses were also performed on safety data collected during the study period 1.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion:

- Drug-naïve patients with T2DM diagnosed at least 2 months prior to visit 1
- male or female (non-fertile or using a medically approved birth control method)
- age at least 18 years
- HbA_{1c} in the range of ≥ 7.0 and $\leq 10.0\%$
- Body mass index of 22-45 kg/m^2
- FPG < 270 mg/dL (15 mmol/L).

Key exclusion:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
2. FPG ≥ 270 mg/dL (≥ 15.0 mmol/L)
3. Any of the following significant laboratory abnormalities:
   - Clinically significant TSH outside of normal range at visit 1
   - Serum creatinine levels > 2.5 mg/dL (220 µmol/L) at visit 1.
   - Elevated fasting triglycerides > 500 mg/dL at visit 1, confirmed by a repeat measure within 3 working days
   - 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 x ULN and/or direct bilirubin > ULN at visit 1, confirmed by repeat measure within 3 working days
   - Positive Hepatitis B surface antigen (HbsAg)
   - Positive Hepatitis C antibody test (anti-HCV)
   - Clinically significant laboratory abnormalities at the opinion of the investigator
4. Congestive heart failure NYHA class III or IV
5. 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
   - Liver disease, such as cirrhosis, or chronic active hepatitis B or C
   - active substance abuse (including alcohol and alcohol related hepatic disease) within the past 2 years

- hypersensitivity to any of the study drugs or to drugs of similar chemical classes
- malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases

6. Patients taking vildagliptin, other DPP-4 inhibitors, GLP-1 mimetics (e.g. exenatide), GLP-1 analogues (e.g. liraglutide) within 6 months prior to visit 1 whether in a clinical trial or as marketed product.
7. Acute infections which may affect blood glucose control within 4 weeks prior to visit 1.
8. 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 can enter the study at the discretion of the investigator and the sponsor);
   - unstable angina
   - coronary artery bypass surgery or percutaneous coronary intervention
   - stroke
9. 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)
10. Concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study.
11. Any of the following medications:
    - chronic insulin treatment (> 4 weeks of treatment in the absence of an intercurrent illness) or treatment with pramlitide within the past 6 months
    - chronic oral or parenteral corticosteroid treatment (> 7 consecutive days of treatment) within 8 weeks prior to visit 1
    - treatment with class Ia, Ib and Ic or III anti-arrhythmics
    - treatment with growth hormone or similar drugs
    - use of other investigational drugs within 30 days or 5 half-lives of the drug at visit 1, which ever is longer, unless local health authority guidelines mandate a longer period
    - treatment with any drug with a known and frequent toxicity that may interfere with the interpretation of the efficacy and safety data during the study
12. Donation of one unit (500 mL) or more of blood, significant blood loss equaling to at least one unit of blood within the past 2 weeks, or a blood transfusion within the past 8 weeks.
13. Contraindications and warnings according to the country specific label for sitagliptin not listed in the other exclusion criteria.
14. Potentially unreliable patients, and those judged by the investigator to be unsuitable for the study.

Number of Subjects Analysis Population

Population	Vilda MR 25mg/50mg qd N=152 n (%)	Vilda MR 50mg qd N=149 n (%)	Placebo/Sita 100mg qd N=150 n (%)	Total N=451 n (%)
Randomized	152 (100.0)	149 (100.0)	150 (100.0)	451 (100.0)
Safety	152 (100.0)	148 (99.3)	150 (100.0)	450 (99.8)
Full Analysis Set	147 (96.7)	146 (98.0)	148 (98.7)	441 (97.8)
Week 24 Completer Set	126 (82.9)	132 (88.6)	135 (90.0)	393 (87.1)
Number of patients taking rescue medication (%)				
Metformin only	23 (15.1)	24 (16.1)	30 (20.0)	77 (17.1)
Insulin only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metformin and Insulin	4 (2.6)	0 (0.0)	1 (0.7)	5 (1.1)

Percentages are based on the number of patients in the Randomized population.

Demographic and Background Characteristics

Demographic Variable	Vilda MR 25 mg qd N=152	Vilda MR 50 mg qd N=149	Placebo/Sita 100 mg qd N=150	Total N=451
Age (years)				
n	152	149	150	451
Mean	52.6	53.6	55.0	53.7
SD	10.70	11.02	11.37	11.05
Min	27.0	24.0	25.0	24.0
Median	53.0	55.0	55.0	54.0
Max	77.0	86.0	85.0	86.0
Age group				
< 65 years	132 (86.8%)	127 (85.2%)	121 (80.7%)	380 (84.3%)
≥ 65 years	20 (13.2%)	22 (14.8%)	29 (19.3%)	71 (15.7%)
Gender				
Male	80 (52.6%)	81 (54.4%)	82 (54.7%)	243 (53.9%)
Fema e	72 (47.4%)	68 (45.6%	68 (45.3%)	208 (46.)
Race				
Caucasian	89 (58.6%)	85 (57 0%)	8 (5 . %)	257 (57.0%)
Black	8 (5 3%)	11 (7.4%)	11 (7.3%)	30 (6.7%)
Asian (non indian subcontinent)	18 (11.8%)	13 (8.7%)	16 (10.7%)	47 (10.4%)
Asian (indian subcon-tinent)	22 (14.5%)	22 (14.8%)	25 (16.7%)	69 (15.3%)
Hispanic or latino	14 (9.2%)	17 (11.4%)	14 (9.3%)	45 (10.0%)
Japanese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native american	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pacific islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (0.7%)	1 (0.7%)	1 (0.7%)	3 (0.7%)
Height (cm)				
n	151	149	150	450
Mean	166.5	166.0	165.8	166.1

SD	10.58	11.56	10.02	10.72
Min	144.0	141.0	145.0	141.0
Median	167.0	167.0	165.0	166.0
Max	195.0	193.0	190.0	195.0
Body weight (kg)				
n	151	149	150	450
Mean	87.5	88.3	85.9	87.3
SD	21.78	22.98	18.90	21.27
Min	50.0	47.5	52.0	47.5
Median	86.4	86.0	82.3	84.6
Max	140.0	141.8	136.0	141.8
BMI (kg/m^2)				
n	151	149	150	450
Mean	31.3	31.7	31.1	31.3
SD	5.93	6.01	5.43	5.79
Min	22.2	22.1	22.0	22.0
Median	30.8	30.9	30.0	30.6
Max	45.0	45.5	44.8	45.5
BMI group				
< 30 kg/m^2	68 (44.7%)	63 (42.3%)	76 (50.7%)	207 (45.9%)
≥ 30 kg/m^2	83 (54.6%)	86 (57.7%)	74 (49.3%)	243 (53.9%)
≥ 35 kg/m^2	43 (28.3%)	42 (28.2%)	39 (26.0%)	124 (27.5%)

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

Efficacy - Primary Objective Result(s)

ANCOVA results for change from baseline in HbA_{1c} (%) to Week 24 endpoint censored at rescue medication (FAS/Week 24 PP population)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to placebo (SE)	95% CI	p-value
FAS Population						
Vildagliptin MR 25 mg qd	143	7.96 (0.07)	-0.35 (0.09)	-0.23 (0.12)	(-0.51, 0.04)	0.1120
Vildagliptin MR 50 mg qd	141	8.10 (0.08)	-0.66 (0.09)	-0.55 (0.12)	(-0.83, -0.27)	<.0001 *
Placebo	145	8.12 (0.08)	-0.11 (0.09)			
Week 24 PP Population						
Vildagliptin MR 25 mg qd	127	7.94 (0.08)	-0.41 (0.09)	-0.35 (0.13)	(-0.63, -0.07)	0.0119 *
Vildagliptin MR 50 mg qd	130	8.12 (0.08)	-0.64 (0.09)	-0.58 (0.13)	(-0.86, -0.30)	<.0001 *
Placebo	133	8.07 (0.08)	-0.06 (0.09)			

Baseline is defined as the Day 1 measurement or the measurement obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1. Week 24 endpoint is the measurement obtained at the last post-baseline study visit prior to or at scheduled Visit 8 (Week 24) and before the start of rescue medication, regardless of whether it was obtained at a scheduled or unscheduled visit. n is the number of patients with observations at both baseline and Week 24 endpoint.

Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment, pooled center and baseline.

* indicates statistical significance at 5% level using Dunnett's step-down method.

Efficacy - Secondary Objective Results(s):

ANCOVA results for change from baseline in FPG to Week 24 endpoint censored at rescue medication (FAS/Week 24 PP population)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to placebo (SE)	95% CI	p-value
FAS Population						
Vildagliptin MR 25 mg qd	147	9.42 (0.19)	-0.36 (0.20)	-0.47 (0.28)	(-1.02, 0.08)	0.0961
Vildagliptin MR 50 mg qd	146	9.23 (0.21)	-0.52 (0.20)	-0.62 (0.28)	(-1.17, -0.07)	0.0278 *
Placebo	148	9.40 (0.19)	0.10 (0.20)			
Week 24 PP Population						
Vildagliptin MR 25 mg qd	128	9.33 (0.20)	-0.45 (0.21)	-0.77 (0.29)	(-1.33, -0.20)	0.0078 *
Vildagliptin MR 50 mg qd	131	9.20 (0.22)	-0.41 (0.21)	-0.73 (0.28)	(-1.29, -0.17)	0.0107 *
Placebo	135	9.38 (0.20)	0.32 (0.20)			

Baseline is defined as the Day 1 measurement or the measurement obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1. Week 24 endpoint is the measurement obtained at the last post-baseline study visit prior to or at scheduled Visit 8 (Week 24) and before the start of rescue medication, regardless of whether it was obtained at a scheduled or unscheduled visit. n is the number of patients with observations at both baseline and Week 24 endpoint.

Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment, pooled center and baseline.

* indicates statistical significance at 5% level.

ANCOVA results for change from baseline in body weight (kg) to Week 24 endpoint (FAS population)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to placebo (SE)	95% CI	p-value
Vildagliptin MR 25 mg qd	147	88.29 (1.92)	-1.18 (0.47)	0.08 (0.65)	(-1.21, 1.36)	0.9085
Vildagliptin MR 50 mg qd	146	87.43 (1.90)	-0.45 (0.48)	0.81 (0.66)	(-0.48, 2.10)	0.2176
Placebo	148	85.67 (1.54)	-1.26 (0.47)			

Baseline is defined as the Day 1 measurement or the measurement obtained at an earlier visit (scheduled or un-scheduled) which was closest to Day 1. Week 24 endpoint is the measurement obtained at the last post-baseline study visit prior to or at scheduled Visit 8 (Week 24) and before the start of rescue medication, regardless of whether it was obtained at a scheduled or unscheduled visit. n is the number of patients with observations at both baseline and Week 24 endpoint.

Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p-values were from an ANCOVA model containing terms for treatment, pooled center and baseline.

* indicates statistical significance at 5% level.

Safety Results (76 week)

Number (%) of patients with AEs during the entire study period by primary system organ class (Safety population)

Primary system organ class	Vilda MR 25mg/50mg qd N=152 n (%)	Vilda MR 50mg qd N=148 n (%)	Placebo/Sita 100mg qd N=150 n (%)
Any Primary system organ class	97 (63.8)	99 (66.9)	101 (67.3)
Blood and lymphatic system disorders	1 (0.7)	1 (0.7)	8 (5.3)
Cardiac disorders	5 (3.3)	5 (3.4)	5 (3.3)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	1 (0.7)
Ear and labyrinth disorders	5 (3.3)	4 (2.7)	5 (3.3)
Endocrine disorders	1 (0.7)	0 (0.0)	0 (0.0)
Eye disorders	7 (4.6)	9 (6.1)	5 (3.3)
Gastrointestinal disorders	33 (21.7)	35 (23.6)	33 (22.0)
General disorders and administration site conditions	23 (15.1)	18 (12.2)	24 (16.0)
Hepatobiliary disorders	2 (1.3)	1 (0.7)	3 (2.0)
Immune system disorders	1 (0.7)	2 (1.4)	4 (2.7)
Infections and infestations	62 (40.8)	62 (41.9)	57 (38.0)
Injury, poisoning and procedural complications	23 (15.1)	19 (12.8)	17 (11.3)
Investigations	8 (5.3)	6 (4.1)	11 (7.3)
Metabolism and nutrition disorders	13 (8.6)	13 (8.8)	11 (7.3)
Musculoskeletal and connective tissue disorders	36 (23.7)	25 (16.9)	30 (20.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.0)	5 (3.4)	1 (0.7)
Nervous system disorders	22 (14.5)	26 (17.6)	29 (19.3)
Psychiatric disorders	9 (5.9)	10 (6.8)	8 (5.3)
Renal and urinary disorders	9 (5.9)	5 (3.4)	13 (8.7)
Reproductive system and breast disorders	4 (2.6)	5 (3.4)	5 (3.3)
Respiratory, thoracic and mediastinal disorders	15 (9.9)	31 (20.9)	19 (12.7)
Skin and subcutaneous tissue disorders	19 (12.5)	19 (12.8)	13 (8.7)
Social circumstances	0 (0.0)	0 (0.0)	1 (0.7)
Vascular disorders	13 (8.6)	22 (14.9)	18 (12.0)

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.

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

Preferred term	Vilda MR 25mg/50mg qd N=152 n (%)	Vilda MR 50mg qd N=148 n (%)	Placebo/Sita 100mg qd N=150 n (%)
Any Preferred term	97 (63.8)	99 (66.9)	101 (67.3)
Upper respiratory tract infection	20 (13.2)	14 (9.5)	17 (11.3)
Nasopharyngitis	15 (9.9)	10 (6.8)	8 (5.3)
Hypertension	11 (7.2)	19 (12.8)	16 (10.7)
Back pain	10 (6.6)	5 (3.4)	8 (5.3)
Diarrhoea	8 (5.3)	10 (6.8)	8 (5.3)
Pain in extremity	8 (5.3)	2 (1.4)	7 (4.7)
Pyrexia	8 (5.3)	8 (5.4)	7 (4.7)
Dizziness	7 (4.6)	6 (4.1)	10 (6.7)
Nausea	7 (4.6)	2 (1.4)	4 (2.7)
Sinusitis	7 (4.6)	8 (5.4)	11 (7.3)

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 Vildagliptin MR 25mg/50mg qd group.

Serious Adverse Events and Deaths

Preferred Term	Vilda MR 25mg/50mg qd N=152 n (%)	Vilda MR 50mg qd N=148 n (%)	Placebo/Sita 100mg qd N=150 n (%)
Deaths	1 (0.7)	0 (0.0)	0 (0.0)
SAEs	8 (5.3)	10 (6.8)	12 (8.0)
Discontinuation of study drug due to AEs	4 (2.6)	1 (0.7)	6 (4.0)
AEs causing dose adjustment or study drug interruption	8 (5.3)	12 (8.1)	6 (4.0)
Clinically significant CCV AEs	3 (2.0)	4 (2.7)	6 (4.0)
Clinically significant hepatic AEs	1 (0.7)	0 (0.0)	2 (1.3)
Clinically significant SVEM AEs	4 (2.6)	1 (0.7)	2 (1.3)

These categories are not mutually exclusive.

1 patient died during the study: This male patient had an active medical history of chronic atrial fibrillation and he died form progression of chronic atrial fibrillations, it was not suspected to study medication list.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report 03 June 2011
Date Inclusion on Novartis Clinical Trial Results Database 28 September 2011
Date of Latest Update 26 September 2011