Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Investigational

Study Number

CLAF237A2354

Title

A multicenter, double-blind, randomized, active-controlled study to assess the efficacy of 24 weeks treatment with vildagliptin 50 mg bid to pioglitazone 30 mg qd as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy followed by a 28-weeks, single-blind period to further assess the safety of each treatment combination

Phase of Development

Phase III

Study Start/End Dates

29 September 2005 to 19 September 2007

Study Design/Methodology

This was a multicenter, randomized, double-blind, active-controlled trial. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (HbA_{1c} 7.5-11%) were included in the trial (patients treated with metformin for at least 3 months and had been at a stable dose of at least 1500 mg daily for a minimum of 4 weeks were eligible to participate in the trial) Eligible patients were randomized in a 1:1 ratio to receive vildagliptin 50 mg twice daily (bid) or pioglitazone 30 mg once daily (qd) in addition to their continued metformin treatment.

Patients were randomized at Baseline (Day 1) and treated for 52 weeks, inclusive of 24 weeks of double-blind treatment followed by 28 weeks of single-blind treatment, during which time the Investigator and patient remained blinded to treatment. Analysis of the primary end point at Week 24 lead to unblinding of Novartis personnel for the remaining 28 weeks of the study.

Centres

170 centers: Austria (3), Australia (5), Germany (37), Great Britain (28), Italy (14), South Africa(4), Spain (31), Switzerland (10), United States (38)

Publication

Objectives

Primary Objective

- To demonstrate the efficacy of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the HbA_{1c} reduction with vildagliptin is not inferior to that with pioglitazone at Week 24.

Secondary objectives

- To demonstrate the safety of vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by showing that add-on therapy with vildagliptin to metformin has a favorable adverse event (AE) profile (including peripheral edema) compared with pioglitazone at Week 24.
- To demonstrate the efficacy of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that fasting plasma glucose (FPG) reduction with vildagliptin is not inferior to that with pioglitazone at Week 24.
- To demonstrate the efficacy of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by showing that responder rates with vildagliptin are similar to those with pioglitazone at Week 24.
- To demonstrate the ancillary clinical benefits of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that vildagliptin has a favorable effect on body weight relative to pioglitazone at Week 24.
- To assess the long term safety of vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by showing that add-on therapy with vildagliptin has a favorable adverse event profile at Week 52.

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

Vildagliptin 50 mg bid (added to metformin ≥ 1500 mg qd), taken orally

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

Pioglitazone 30 mg qd (added to metformin ≥ 1500 mg qd)

Criteria for Evaluation

Primary Efficacy Parameter

The primary efficacy variable was HbA_{1c}, measured by National Glycohemoglobin Standardization Program (NGSP), specifically, ion exchange High Performance Liquid Chromatography (HPLC).

Secondary Efficacy Parameters

The secondary efficacy variables were:

1. fasting plasma glucose (FPG)
2. body weight
3. responder rates
    - Endpoint HbA_{1c} <= 6.5%
    - Endpoint HbA_{1c} <= 7.0%
    - HbA_{1c} absolute reduction from baseline at endpoint >= 1.0%
    - HbA_{1c} absolute reduction from baseline at endpoint >= 0.7%
    - HbA_{1c} absolute reduction from baseline at endpoint >= 0.5%

Safety and tolerability

Safety assessments included monitoring and recording all adverse events (AEs), serious adverse events (SAEs) and pregnancies; regular monitoring of hematology, blood chemistry, and urine (performed at a central laboratory); and regular assessments of vital signs, ECG, physical condition, and body weight. Severity and relationship to study drug were recorded for all AEs and SAEs.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The primary hypothesis tested was the non-inferiority of vildagliptin 50 mg bid over pioglitazone 30 mg qd for the effect of reducing HbA_{1c}, with the primary efficacy variable being absolute change from baseline in HbA_{1c} at Week 24. Secondary efficacy variables included change from baseline HbA_{1c} at Week 52 and change from baseline in FPG, body weight, and responder rates at Weeks 24 and 52.

Change from baseline in primary and secondary endpoints was analyzed using analysis of covariance (ANCOVA) model with treatment group and pooled center as classification variables and baseline value as a covariate. The primary hypothesis was based on the per protocol (PP) population with additional sensitivity analyses performed on the intent to treat (ITT) population. Secondary efficacy endpoints were analyzed in the same manner. The percentage of patients meeting each of the responder criteria in each treatment group was summarized and compared between treatment groups using a Chi-square test in both PP and ITT populations.

The hypothesis testing procedure was carried out through a confidence interval approach. The null hypothesis was rejected and non-inferiority established if the upper limit of the confidence interval did not exceed 0.4%; if the upper limit did not exceed 0.4%, then the non-inferiority of vildagliptin was established at that margin. The 95% confidence intervals were derived from least squares mean (LS-mean) changes from baseline ('adjusted mean') of each treatment group. Treatment comparisons in secondary endpoints were made at an individual two-sided significance level of 5%. Demographic and background data as well as safety data were summarized by treatment group. Safety analyses were conducted on the safety (SAF) population.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population consisted of male and female adult patients, age 18 to 77 years, with body mass index (BMI) ranging from 22 to 45 kg/m^2, whose type 2 diabetes was inadequately controlled (HbA_{1c}, 7.5-11% and FPG < 270 mg/dL (15 mmol/L) at Visit 1) on prior metformin

monotherapy at a dose of at least 1500 mg per day. Patients must have agreed to maintain the same dose of metformin throughout the study, been able to comply with all study requirements, and provided written informed consent to participate in the study.

Exclusion criteria were: pregnant or lactating female; a history of type 1 diabetes, diabetes that is a result of pancreatic injury or secondary forms of diabetes; acute metabolic diabetic complications within past 6 months; evidence of significant diabetic complications; acute infections, which may affect blood glucose control within the past 4 weeks; Torsades de Pointes, ventricular tachycardia, ventricular fibrillation; percutaneous coronary intervention in the past 3 months; myocardial infarction, coronary artery bypass surgery, unstable angina and stroke within the past 6 months; congestive heart failure (NYHY class I-IV), second degree AV block (Mobitz I and II), third degree AV block, prolonged QT_c; 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; significant renal dysfunction; acromegaly or treatment with growth hormone; concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study ;donation of one unit (500 ml) or more of blood; contraindications and warnings according to the country specific label for metformin or pioglitazone; known sensitivity to pioglitazone, rosiglitazone or similar drugs; treatment with any oral anti-diabetic other than metformin within 3 months prior visit 1; chronic insulin treatment within the past 6 months; chronic oral or parenteral corticosteroid treatment within the past 8 weeks; treatment with class 1a, Ib and Ic or III anti-arrhythmics; thyroid hormone replacement if the dosage has been stable for at least 3 months; use of other investigational drugs at visit 1; treatment with any drug with a known and frequent toxicity to a major organ system within the past 3 months (e.g.cytostatic drugs); significant laboratory abnormalities; history of active substance abuse (including alcohol) within past 2 years; potentially unreliable patients, and those judged by the investigator to be unsuitable for the study.

Number of Subjects

	Vilda 50 mg bid	Pio 30 mg qd	Total	
Planned n	588	588	1176	
Randomized n	295	281	576	
Randomized population (RAN) n (%)	295 (100%)	281 (100%)	576 (100%)	
Safety population (SAF) n (%)	295 (100%)	280 (99.6%)	575 (99.8%)	
Intent to Treat population (ITT) n (%)	293 (99.3%)	277 (98.6%)	570 (99.0%)	
Completed n (%)	242 (82.0%)	226 (80.4%)	468 (81.3%)	
Withdrawn n (%)	53 (18.0%)	55 (19.6%)	108 (18.8%)	
Withdrawn due to adverse events n (%)	11 (3.7%)	16 (5.7%)	27 (4.7%)	
Withdrawn due to lack of efficacy n (%)	16 (5.4%)	12 (4.3%)	28 (4.9%)	
Withdrawn for other reasons n (%)	26 (8.8%)	27 (9.6%)	55 (9.2%)	

Demographic and Background Characteristics

	Vilda 50 mg bid	Pio 30 mg qd	Total	
N (Randomized)	295	281	576	
Females : males	182:113	180:101	362:214	
Mean age, years (SD)	56.3 (9.32)	57.0 (9.65)	56.6 (9.48)	
Mean body weight, kg (SD)	91.8 (19.48)	91.2 (16.93)	91.5 (17.73)	
Mean BMI, kg/m^2 (SD)	32.2 (5.57)	32.1 (5.14)	32.1 (5.36)	
Race				
Caucasian n (%)	243 (82.4%)	230 (81.9%)	473 (82.1%)	
Black n (%)	9 (3.1%)	7 (2.5%)	16 (2.8%)	
Asian n (%)	16 (5.5%)	13 (4.6%)	29 (5.0%)	
Hispanic of Latino n (%)	25 (8.5%)	29 (10.3%)	54 (9.4%)	
Other n (%)	2 (0.7%)	2 (0.7%)	4 (0.7%)	
Mean HbA_{1c} % (SD)	8.4 (0.95)	8.4 (0.93)	8.4 (0.94)	
Mean FPG, mmol/L (SD)	10.9 (2.62)	11.0 (2.68)	11.0 (2.65)	
Mean duration of diabetes, years (SD)	6.4 (4.93)	6.4 (5.20)	6.4 (5.06)	
Mean metformin usage, months (SD)	42.4 (41.36)	44.3 (44.66)	43.3 (42.97)	

Primary Efficacy Result(s)

Change in HbA_{1c} from baseline to Week 24 Endpoint (ITT and PP populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change at endpoint (SE)	Mean difference to comparator (SE)	95% CI
ITT population					
Vilda 50 mg bid + Met	293	8.44 (0.06)	-0.84 (0.05)	0.04 (0.08)	(-0.12,0.19)
Pio 30 mg qd + Met	277	8.43 (0.06)	-0.87 (0.06)		
Per protocol (PP) population					
Vilda 50 mg bid + Met	264	8.41 (0.06)	-0.88 (0.05)	0.10 (0.08)	(-0.05,0.26)
Pio 30 mg qd + Met	246	8.40 (0.06)	-0.98 (0.06)		

Secondary Efficacy Results

Change in FPG (mmol/L) from baseline to Week 24 endpoint (ITT and PP populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to comparator (SE)	95% CI
ITT population					
Vilda 50 mg bid + Met	293	10.89 (0.15)	-1.18 (0.13)	0.70 (0.19)	(0.33,1.08)
Pio 30 mg qd + Met	276	11.04 (0.16)	-1.89 (0.14)		
Per protocol population					
Vilda 50 mg bid + Met	264	10.95 (0.16)	-1.35 (0.13)	0.72 (0.19)	(0.34,1.09)
Pio 30 mg qd + Met	246	10.98 (0.17)	-2.07 (0.14)		

Number of responders at Week 24 Endpoint (ITT and PP populations)

	Vilda 50 mg bid + Met n (%)	Pio 30 mg qd + Met n (%)	p-value
ITT population	N=293	N=277	
N	293 (100)	277 (100)	
Responder criterion			
At least one criterion met	200 (68.3)	197 (71.1)	0.458
HbA_{1c} < 7%	73/285 (25.6)	89/273 (32.6)	0.069
HbA_{1c} <= 6.5%	53/293 (18.1)	46/277 (16.6)	0.641
Reduction of $HbA_{1c} \geq 1\%$	131 (44.7)	129 (46.6)	0.656
Reduction of $HbA_{1c} \geq 0.7\%$	173 (59.0)	166 (59.9)	0.830
Reduction of $HbA_{1c} \geq 0.5\%$	197 (67.2)	194 (70.0)	0.472
Per protocol (PP) population	N=264	N=246	
N	264 (100)	246 (100)	
Responder criterion			
At least one criterion met	188 (71.2)	185 (75.2)	0.310
HbA_{1c} < 7%	69/256 (27.0)	87/242 (36.0)	0.030
HbA_{1c} <= 6.5%	52/264 (19.7)	44/246 (17.9)	0.601
Reduction of $HbA_{1c} \geq 1\%$	126 (47.7)	124 (50.4)	0.545
Reduction of $HbA_{1c} \geq 0.7\%$	163 (61.7)	157 (63.8)	0.628

Reduction of $HbA_{1c} \geq 0.5\%$	185 (70.1)	182 (74.0)	0.326

Change in body weight (kg) from baseline to Week 24 endpoint (PP population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to comparator (SE)	95% CI	p-value
Vilda 50 mg bid + Met	264	91.59 (1.14)	0.31 (0.18)	-1.60 (0.26)	(-2.10,-1.10)	<0.001
Pio 30 mg qd + Met	246	92.00 (1.10)	1.91 (0.19)			

Safety Results

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

Primary system organ class	Week 24 Vilda 50 mg bid + Met N=295 n (%)	Week 52 Vilda 50 mg bid + Met N=295 n (%)	Week 24 Pio 30 mg qd + Met N=280 n (%)	Week 52 Pio 30 mg qd + Met N=280 n (%)
Any primary system organ class	177 (60.0)	200 (67.8)	158 (56.4)	191 (68.2)
Blood and lymphatic system disorders	3 (1.0)	5 (1.7)	2 (0.7)	2 (0.7)
Cardiac disorders	11 (3.7)	14 (4.7)	7 (2.5)	11 (3.9)
Congenital, familial and genetic disorders	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	6 (2.0)	7 (2.4)	1 (0.4)	3 (1.1)
Endocrine disorders	Not reported	1 (0.3)	Not reported	1 (0.4)
Eye disorders	9 (3.1)	10 (3.4)	4 (1.4)	8 (2.9)
Gastrointestinal disorders	47 (15.9)	59 (20.0)	25 (8.9)	41 (14.6)
General disorders and administration site conditions	43 (14.6)	56 (19.0)	31 (11.1)	52 (18.6)
Hepatobiliary disorders	1 (0.3)	1 (0.3)	3 (1.1)	3 (1.1)
Immune system disorders	0 (0.0)	2 (0.7)	3 (1.1)	3 (1.1)
Infections and infestations	54 (18.3)	86 (29.2)	56 (20.0)	92 (32.9)
Injury, poisoning and procedural complications	17 (5.8)	27 (9.2)	10 (3.6)	22 (7.9)
Investigations	3 (1.0)	7 (2.4)	11 (3.9)	15 (5.4)
Metabolism and nutrition disorders	8 (2.7)	11 (3.7)	10 (3.6)	13 (4.6)
Musculoskeletal and connective tissue disorders	37 (12.5)	54 (18.3)	30 (10.7)	57 (20.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	5 (1.7)	3 (1.1)	6 (2.1)
Nervous system disorders	39 (13.2)	48 (16.3)	32 (11.4)	48 (17.1)
Psychiatric disorders	15 (5.1)	17 (5.8)	13 (4.6)	17 (6.1)
Renal and urinary disorders	5 (1.7)	7 (2.4)	7 (2.5)	12 (4.3)
Reproductive system and breast disorders	6 (2.0)	8 (2.7)	7 (2.5)	11 (3.9)
Respiratory, thoracic and mediastinal disorders	12 (4.1)	18 (6.1)	16 (5.7)	23(8.2)
Skin and subcutaneous tissue disorders	24 (8.1)	34 (11.5)	17 (6.1)	31 (11.1)
Surgical and medical procedures	Not reported	0 (0.0)	Not reported	2 (0.7)
Vascular disorders	11 (3.7)	14 (4.7)	10 (3.6)	12 (4.3)

10 Most Frequently Reported AEs Overall by Preferred Term n (%) at Week 24

Preferred term	Vilda 50 mg bid + Met N=295 n (%)	Pio 30 mg qd + Met N=280 n (%)
- Any Preferred Term	177 (60.0)	158 (56.4)
Oedema peripheral	26 (8.8)	17 (6.1)
Headache	16 (5.4)	14 (5.0)
Dizziness	14 (4.7)	7 (2.5)
Nasopharyngitis	12 (4.1)	13 (4.6)
Diarrhoea	10 (3.4)	8 (2.9)
Pain in extremity	7 (2.4)	6 (2.1)
Hypertension	6 (2.0)	8 (2.9)
Cough	4 (1.4)	10 (3.6)
Back pain	10 (3.4)	3 (1.1)
Constipation	9 (3.1)	3 (1.1)

10 Most Frequently Reported AEs Overall by Preferred Term n (%) at Week 52

Preferred term	Vilda 50 mg bid + Met N=295 n (%)	Pio 30 mg qd + Met N=280 n (%)
Any primary system organ class	200 (67.8)	191 (68.2)
Oedema peripheral	32 (10.8)	31 (11.1)
Headache	19 (6.4)	17 (6.1)
Nasopharyngitis	16 (5.4)	20 (7.1)
Back pain	15 (5.1)	15 (5.4)
Dizziness	15 (5.1)	11 (3.9)
Diarrhoea	14 (4.7)	14 (5.0)
Arthralgia	12 (4.1)	9 (3.2)
Pain in extremity	10 (3.4)	11 (3.9)
Influenza	9 (3.1)	9 (3.2)

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

Preferred term	Week 24 Vilda 50 mg bid + Met N=295 n (%)	Week 52 Vilda 50 mg bid + Met N=295 n (%)	Week 24 Pio 30 mg qd + Met N=280 n (%)	Week 52 Pio 30 mg qd + Met N=280 n (%)
Deaths	0	0	0	0
SAEs	6 (2.0)	12 (4.1)	13 (4.6)	25 (8.9)
Discontinuation due to AEs	9 (3.1)	12 (4.1)	9 (3.2)	16 (5.7)
AEs causing dose adjustment or study drug interruption	12 (4.1)	18 (6.1)	13 (4.6)	16 (5.7)
Clinically significant CCV AEs	2 (0.7)	2 (0.7)	4 (1.4)	6 (2.1)
Clinically significant IM AEs	3 (1.0)	4 (1.4)	0 (0)	0
Other clinically significant AEs	68 (23.0)	86 (29.2)	60 (21.5)	79 (28.2)

Number (%) of patients with SAEs by preferred term

Preferred term	Week 24 Vilda 50 mg bid + Met N=295 n (%)	Week 52 Vilda 50 mg bid + Met N=295 n (%)	Week 24 Pio 30 mg qd + Met N=280 n (%)	Week 52 Pio 30 mg qd + Met N=280 n (%)
Any SAE	6(2.0)	12(4.1)	13(4.6)	25(8.9)
Asthmatic crisis	Not reported	1(0.3)	Not reported	0(0.0)
Basal ganglion degeneration	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Bile duct stone	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Blister	Not reported	1(0.3)	Not reported	0(0.0)
Breast cancer	Not reported	1(0.3)	Not reported	0(0.0)
Cholelithiasis	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Coronary artery stenosis	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Fall	1(0.3)	1(0.3)	0(0.0)	2(0.7)
Ischaemia	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Leukocytoclastic vasculitis	Not reported	1(0.3)	Not reported	0(0.0)
Muscular weakness	Not reported	1(0.3)	Not reported	0(0.0)
Nephrolithiasis	Not reported	1(0.3)	Not reported	2(0.7)
Paraesthesia	Not reported	1(0.3)	Not reported	0(0.0)
Post procedural haemorrhage	1(0.3)	1(0.3)	0(0.0)	0(0.0)

Rib fracture	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Transient ischaemic attack	Not reported	1(0.3)	Not reported	1(0.4)
Urinary retention	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Urticaria	Not reported	1(0.3)	Not reported	0(0.0)
Uterine leiomyoma	1(0.3)	1(0.3)	0(0.0)	0(0.0)
Adenocarcinoma	Not reported	0(0.0)	Not reported	1(0.4)
Angina pectoris	Not reported	0(0.0)	Not reported	1(0.4)
Aphasia	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Appendicitis	Not reported	0(0.0)	Not reported	1(0.4)
Arterial occlusive disease	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Atrioventricular block	Not reported	0(0.0)	Not reported	1(0.4)
Bladder cancer	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Bladder spasm	Not reported	0(0.0)	Not reported	1(0.4)
Bundle branch block left	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Calculus bladder	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Calculus urinary	Not reported	0(0.0)	Not reported	1(0.4)
Cerebrovascular accident	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Coronary artery disease	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Diabetic foot	Not reported	0(0.0)	Not reported	1(0.4)
Dysphagia	Not reported	0(0.0)	Not reported	1(0.4)
Hemiparesis	Not reported	0(0.0)	Not reported	1(0.4)
Humerus fracture	Not reported	0(0.0)	Not reported	1(0.4)
Malignant melanoma	Not reported	0(0.0)	Not reported	1(0.4)
Mitral valve calcification	Not reported	0(0.0)	Not reported	1(0.4)
Multiple myeloma	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Oesophageal carcinoma	Not reported	0(0.0)	Not reported	1(0.4)
Peyronie’s disease	0(0.0)	Not reported	1(1.4)	Not reported
Renal colic	Not reported	0(0.0)	Not reported	1(0.4)
Skin ulcer	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Spinal fracture	Not reported	0(0.0)	Not reported	1(0.4)
Supraventricular tachycardia	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Syncope	0(0.0)	0(0.0)	2(0.7)	1(0.4)
Transient Ischemic Attack	0(0.0)	Not reported	1(0.4)	Not reported
Thrombotic stroke	Not reported	0(0.0)	Not reported	1(0.4)

Uterine polyp	Not reported	0(0.0)	Not reported	1(0.4)
Wrist fracture	Not reported	0(0.0)	Not reported	1(0.4)

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

12 December 2008

Date Inclusion on Novartis Clinical Trial Results Database

29 July 2008

Date of Latest Update

20 October 2009