Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Investigational

Study Number

CLAF237A2301

Title

A multicenter, randomized, double-blind study to compare the effects of 24 weeks treatment with LAF237 (50 mg qd, 50 mg bid or 100 mg qd) to placebo in drug naïve patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

5 Apr 2004 to 6 Oct 2005

Study Design/Methodology

This was a multicenter, randomized, double-blind, placebo controlled study. Drug naive patients with type 2 diabetes (HbA_{1c} 7.5-10%) were randomized to vildagliptin 50 mg daily (qd), vildagliptin 50 mg twice daily (bid), vildagliptin 100 mg qd or placebo in a ratio of 1:1:1:1 and treated for 24 weeks.

Centres

134 centers in 3 countries: US (122), Russia (9), Tunisia (3)

Publication

Dejager S, Razac S, Foley J, Schweizer A Vildagliptin in drug-naïve patients with type 2 diabetes: a 24-week, double-blind, randomized, placebo-controlled, multiple-dose study. Horm Metab Res 2007; 39:218-223

http://www.ncbi.nlm.nih.gov/pubmed/17373638?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Objectives

Primary outcome/efficacy objective(s)

To evaluate the efficacy of vildagliptin in patients with type 2 diabetes by measuring change in hemoglobin A_{1c} (HbA_{1c}) after 24 weeks of treatment.

Secondary outcome/efficacy objective(s)

- Change from baseline in fasting plasma glucose (FPG) at 24 weeks
- Patients with endpoint HbA1c <7% after 24 weeks
- Patients with reduction in HbA1c = 0.7% after 24 weeks
- Change from baseline in body weight at 24 weeks
- Change from baseline in fasting lipids at 24 weeks

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

Vildagliptin 50 mg and 100 mg tablets dosed 50 mg qd, 50 mg bid and 100 mg qd, for oral administration

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

Placebo tablets dosed in the same manner as vildagliptin

Criteria for Evaluation

Primary efficacy:

The primary efficacy variable was HbA_{1c} measured by High Performance Liquid Chromatography (HPLC).

Secondary efficacy:

The secondary efficacy variables included: FPG; fasting lipids (triglycerides, total cholesterol, calculated low density lipoproteins (LDL), high density lipoproteins (HDL), calculated very low density lipoproteins (VLDL), calculated non-HDL); body weight; beta-cell function measures ; insulin resistance measures ; responder rates: 1. Endpoint HbA_{1c} < 7%, 2. Endpoint HbA_{1c} = 6.5%, 3. HbA_{1c} absolute reduction from baseline at endpoint = 1%, 4. HbA_{1c} absolute reduction from baseline at endpoint = 0.7%, 5. HbA_{1c} absolute reduction from baseline at endpoint = 0.5%; and prandial efficacy parameters including area under the 0-4 hour prandial curve ($AUC_{0\text{-}4hr}$) for plasma glucose, insulin and C-peptide, adjusted $AUC_{0\text{-}4hr}$ for plasma glucose, insulin and C-peptide, peak prandial excursion of glucose, and 2-hr absolute glucose level following a standard meal challenge, in a subset of patients.

Safety/tolerability:

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events (with their severity and relationship to study drug), and pregnancies, recording of hypoglycemic events, the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, body weight, and ECGs.

Pharmacology:

Blood samples for measurement of plasma levels of vildagliptin were collected during the Week 24 meal test.

Other:

Not applicable

Statistical Methods

The primary hypotheses tested were the superiority of vildagliptin 50 mg qd, or 50 mg bid, or 100 mg qd over placebo for the effect of reducing HbA_{1c} after 24 weeks of treatment. 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 primary hypothesis was based on the primary intent-to-treat (ITT) population with additional sensitivity analyses performed on the per protocol, sensitivity ITT and incorrectly randomized populations. The sensitivity ITT population consisted of all patients in the primary ITT and incorrectly randomized populations and patients with no valid HbA_{1c} assessment at baseline. Critical secondary endpoints were also analyzed for all four populations. Other secondary endpoints were analyzed for the primary and sensitivity ITT populations. The estimated treatment difference (vildagliptin - placebo) and its 95% confidence interval were derived from the least square mean change from baseline ('adjusted mean') of each treatment group. The Hochberg step-up procedure was used to maintain an overall two-sided 5% significance level for the HbA_{1c} and FPG analyses. Treatment comparisons in other secondary efficacy variables were made at an individual two-sided 5% significance level. Demographic and background data as well as safety data were summarized by treatment group.

Study Population: Inclusion/Exclusion Criteria and Demographics

The population consisted of male or female (non-fertile or of childbearing potential using a medically approved birth control method) drug-naïve patients with type 2 diabetes, aged 18-80 years, body mass index of 22-45 kg/m^2, HbA_{1c} 7.5-10% inclusive, and FPG < 270 mg/dL (15 mmol/L).

Exclusion criteria included pregnant or lactating female; a history of type 1 diabetes, any secondary forms of diabetes; acute metabolic diabetic complications within past 6 months; acute infections which may affect blood glucose control within the past 4 weeks; a series of cardiac-related conditions (Torsades de Pointes, ventricular tachycardia or fibrillation; percutaneous coronary intervention in the past 3 months; myocardial infarction, coronary artery bypass surgery, or unstable angina within the past 6 months; congestive heart failure NYHA class III or IV; second or third degree AV block, and prolonged QTc); treatment with class Ia, Ib, Ic, or III anti-arrhythmics; any of the following significant laboratory abnormalities: ALT, AST greater than three times the upper limit of the normal range, direct bilirubin greater than 1.3 times the upper limit of the normal range, serum creatinine levels > 2.5 mg/dL (220 µmol/L), clinically significant abnormal TSH, and fasting triglycerides > 700 mg/dL (> 7.9 mmol/L).

Number of Subjects

	Vildagliptin 50mg qd	Vildagliptin 50mg bid	Vildagliptin 100mg qd	Placebo
Planned N	144	144	144	145
Randomised n	163	152	157	160
Completed n (%)	130 (79.8)	128 (84.2)	134 (85.4)	119 (74.4)
Withdrawn n (%)	33 (20.2)	24 (15.8)	23 (14.6)	41 (25.6)
Included in the primary analysis n (%)	104 (63.8)	90 (59.2)	92 (58.6)	94 (58.8)
Withdrawn due to adverse events n (%)	3 (1.8)	2 (1.3)	6 (3.8)	6 (3.8)
Withdrawn due to lack of efficacy n (%)	6 (3.7)	6 (3.9)	2 (1.3)	15 (9.4)
Withdrawn for other reasons n (%)	24 (14.7)	16 (10.6)	15 (9.5)	20 (12.5)

Demographic and Background Characteristics

	Vildagliptin 50mg qd	Vildagliptin 50mg bid	Vildagliptin 100mg qd	Placebo
N (Primary ITT)	104	90	92	94
Females:males (%)	59% : 41%	53% : 47%	47% : 53%	52% : 48%
Mean age, years (SD)	55.3 (11.38)	52.8 (9.64)	53.6 (10.80)	52.2 (11.22)
Mean weight, kg (SD)	93.4 (20.23)	95.1 (17.18)	93.9 (21.46)	92.5 (18.95)
Race White n (%) Black n (%) Asian (Indian subcontinent) n (%) Asian (non-Indian subcontinent) n (%) Hispanic or Latino Other n (%)	 76 (73.1) 10 (9.6) 1 (1.0) 1 (1.0) 14 (13.5) 2 (2.0)	 66 (73.3) 9 (10.0) 0 (0) 1 (1.1) 12 (13.3) 2 (2.2)	 70 (76.1) 4 (4.3) 1 (1.1) 3 (3.3) 14 (15.2) 0 (0)	 65 (69.1) 12 (12.8) 2 (2.1) 3 (3.2) 11 (11.7) 1 (1.1)
Mean HbA1c % (SD)	8.2 (0.79)	8.6 (0.83)	8.4 (0.80)	8.4 (0.80)
Mean duration of diabetes –yrs (SD)	2.1 (3.56)	2.1 (3.3)	2.4 (4.24)	1.6 (2.48)

Primary Efficacy Result(s)

Change in hemoglobin A_{1c} (HbA_{1c}) after 24 weeks of treatment

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Placebo (SE)	95% CI	p-value
Primary ITT population						
Vilda 50mg qd	104	8.23 (0.08)	-0.78 (0.12)	-0.48 (0.17)	(-0.82,-0.14)	0.006 *
Vilda 50mg bid	90	8.56 (0.09)	-0.79 (0.13)	-0.49 (0.18)	(-0.84,-0.14)	0.006 *
Vilda 100mg qd	92	8.41 (0.08)	-0.88 (0.13)	-0.58 (0.18)	(-0.93,-0.23)	0.001 *
Placebo	94	8.40 (0.08)	-0.30 (0.13)			

Secondary efficacy result(s)

	Vildagliptin 50mg qd	Vildagliptin 50mg bid	Vildagliptin 100mg qd	Placebo
Number (%) of patients who responded at endpoint, Primary ITT population				
HbA1c < 7%	44 (42.7)	35 (39.3)	37 (40.2)	24 (25.5)
P Value	0.011	0.046	0.033	
Reduction in HbA1c = 0.7%	62 (59.6)	59 (65.6)	61 (66.3)	39 (41.5)
P value	0.011	0.001	<0.001	

Mean change in fasting plasma glucose (mmol/L) from baseline to endpoint

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to comparator (SE)	95% CI	p-value
Primary ITT population						
Vilda 50mg qd	103	9.79 (0.23)	-0.96 (0.25)	-0.82 (0.36)	(-1.52,-0.12)	0.021
Vilda 50mg bid	90	10.08 (0.24)	-0.75 (0.27)	-0.62 (0.37)	(-1.34,0.10)	0.093
Vilda 100mg qd	92	9.92 (0.24)	-0.83 (0.27)	-0.70 (0.37)	(-1.42,0.02)	0.058
Placebo	94	9.86 (0.26)	-0.14 (0.26)			

Percent change in fasting lipid parameters at endpoint (Primary ITT population)

Parameter	Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Placebo (SE)	95% CI	p-value
Triglycerides	Vilda 50mg qd	101	2.34 (0.19)	-2.58 (4.54)	-4.92 (6.55)	(-17.80,7.96)	0.453
(mmol/L)	Vilda 50mg bid	89	2.20 (0.12)	-4.88 (4.87)	-7.22 (6.73)	(-20.45,6.01)	0.284
	Vilda 100mg qd	91	2.43 (0.16)	-4.40 (4.86)	-6.74 (6.72)	(-19.95,6.48)	0.317
	Placebo	92	2.85 (0.34)	2.34 (4.87)			
Total cholesterol	Vilda 50mg qd	101	5.15 (0.12)	-1.37 (1.55)	-2.43 (2.22)	(-6.79,1.93)	0.274
(mmol/L)	Vilda 50mg bid	89	5.46 (0.12)	-3.46 (1.65)	-4.52 (2.28)	(-9.00,-0.05)	0.048 *
	Vilda 100mg qd	91	5.25 (0.12)	-1.68 (1.65)	-2.74 (2.28)	(-7.22,1.74)	0.230
	Placebo	92	5.34 (0.15)	1.06 (1.65)			
LDL cholesterol	Vilda 50mg qd	94	3.06 (0.11)	0.57 (2.44)	-2.36 (3.55)	(-9.34,4.63)	0.507
(mmol/L)	Vilda 50mg bid	86	3.21 (0.12)	-1.84 (2.57)	-4.77 (3.61)	(-11.88,2.34)	0.188
	Vilda 100mg qd	84	3.08 (0.09)	0.26 (2.63)	-2.66 (3.64)	(-9.83,4.51)	0.466
	Placebo	81	3.12 (0.11)	2.93 (2.68)			
HDL cholesterol	Vilda 50mg qd	101	1.19 (0.03)	0.89 (1.78)	-4.99 (2.56)	(-10.02,0.04)	0.052
(mmol/L)	Vilda 50mg bid	89	1.23 (0.03)	3.74 (1.91)	-2.14 (2.63)	(-7.31,3.03)	0.416
	Vilda 100mg qd	91	1.14 (0.03)	4.83 (1.92)	-1.05 (2.63)	(-6.23,4.13)	0.690
	Placebo	92	1.16 (0.03)	5.88 (1.90)			
non-HDL cholesterol	Vilda 50mg qd	101	3.96 (0.11)	-1.14 (2.01)	-1.57 (2.88)	(-7.23,4.10)	0.587
(mmol/L)	Vilda 50mg bid	89	4.23 (0.12)	-4.41 (2.14)	-4.84 (2.95)	(-10.64,0.97)	0.102
	Vilda 100mg qd	91	4.12 (0.11)	-2.30 (2.14)	-2.73 (2.96)	(-8.54,3.08)	0.356
	Placebo	92	4.18 (0.15)	0.43 (2.14)			
VLDL cholesterol	Vilda 50mg qd	94	0.91 (0.04)	-5.76 (3.74)	-4.20 (5.46)	(-14.95,6.54)	0.442
(mmol/L)	Vilda 50mg bid	86	0.95 (0.05)	-4.49 (3.95)	-2.93 (5.56)	(-13.88,8.02)	0.599
	Vilda 100mg qd	84	0.96 (0.04)	-9.84 (4.04)	-8.28 (5.62)	(-19.34,2.77)	0.141
	Placebo	81	0.87 (0.04)	-1.56 (4.13)			

Change in body weight (kg) from baseline to endpoint (Primary ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Placebo (SE)	95% CI	p-value
Vilda 50mg qd	103	92.98 (1.99)	-1.80 (0.37)	-0.40 (0.53)	(-1.44,0.64)	0.446
Vilda 50mg bid	90	94.43 (1.79)	-0.28 (0.40)	1.11 (0.54)	(0.04,2.18)	0.041 *
Vilda 100mg qd	92	93.55 (2.22)	-0.84 (0.40)	0.55 (0.54)	(-0.52,1.62)	0.311
Placebo	94	92.37 (1.93)	-1.40 (0.39)			

Safety Results

Adverse Events by System Organ Class

Primary system organ class	Vilda 50mg qd N=162 n (%)	Vilda 50mg bid N=151 n (%)	Vilda 100mg qd N=155 n (%)	Placebo N=157 n (%)
Any primary system organ class	108 (66.7)	94 (62.3)	111 (71.6)	97 (61.8)
Blood & lymphatic system disorders	1 (0.6)	1 (0.7)	2 (1.3)	0 (0.0)
Cardiac disorders	3 (1.9)	6 (4.0)	7 (4.5)	0 (0.0)
Congenital, familial & genetic dis.	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	2 (1.2)	3 (2.0)	3 (1.9)	1 (0.6)
Endocrine disorders	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
Eye disorders	4 (2.5)	10 (6.6)	3 (1.9)	6 (3.8)
Gastrointestinal disorders	19 (11.7)	25 (16.6)	20 (12.9)	22 (14.0)
General dis. & admin. site conditions	17 (10.5)	17 (11.3)	18 (11.6)	16 (10.2)
Hepatobiliary disorders	1 (0.6)	0 (0.0)	2 (1.3)	2 (1.3)
Immune system disorders	4 (2.5)	0 (0.0)	3 (1.9)	2 (1.3)
Infections and infestations	46 (28.4)	46 (30.5)	43 (27.7)	46 (29.3)
Injury, poisoning & procedural compl.	8 (4.9)	15 (9.9)	12 (7.7)	8 (5.1)
Investigations	7 (4.3)	6 (4.0)	13 (8.4)	4 (2.5)
Metabolism & nutrition disorders	10 (6.2)	3 (2.0)	7 (4.5)	9 (5.7)
Musculoskel. & connective tissue dis.	24 (14.8)	17 (11.3)	20 (12.9)	22 (14.0)
Neoplasms benign, malign. & unspec.	1 (0.6)	0 (0.0)	0 (0.0)	4 (2.5)
Nervous system disorders	29 (17.9)	26 (17.2)	31 (20.0)	27 (17.2)
Pregnancy, puerperium & perinatal	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Psychiatric disorders	3 (1.9)	9 (6.0)	2 (1.3)	5 (3.2)
Renal and urinary disorders	5 (3.1)	5 (3.3)	5 (3.2)	5 (3.2)
Reproductive syst. & breast disorders	4 (2.5)	1 (0.7)	3 (1.9)	4 (2.5)
Resp., thoracic & mediast. disorders	14 (8.6)	8 (5.3)	14 (9.0)	10 (6.4)
Skin & subcutaneous tissue disorders	14 (8.6)	10 (6.6)	15 (9.7)	12 (7.6)
Vascular disorders	8 (4.9)	3 (2.0)	10 (6.5)	3 (1.9)

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

Preferred term	Vilda 50mg qd N=162 n (%)	Vilda 50mg bid N=151 n (%)	Vilda 100mg qd N=155 n (%)	Placebo N=157 n (%)
Any Preferred term	108 (66.7)	94 (62.3)	111 (71.6)	97 (61.8)
Dizziness	8 (4.9)	13 (8.6)	10 (6.5)	8 (5.1)
Nasopharyngitis	14 (8.6)	13 (8.6)	13 (8.4)	13 (8.3)
Upper resp. tract infection	3 (1.9)	10 (6.6)	7 (4.5)	6 (3.8)
Headache	10 (6.2)	9 (6.0)	8 (5.2)	10 (6.4)
Diarrhea	3 (1.9)	6 (4.0)	2 (1.3)	5 (3.2)
Back pain	5 (3.1)	5 (3.3)	6 (3.9)	2 (1.3)
Fatigue	5 (3.1)	5 (3.3)	3 (1.9)	4 (2.5)
Hyperhidrosis	6 (3.7)	5 (3.3)	2 (1.3)	2 (1.3)
Vision blurred	3 (1.9)	5 (3.3)	3 (1.9)	1 (0.6)
Arthralgia	4 (2.5)	4 (2.6)	4 (2.6)	2 (1.3)

Serious Adverse Events and Deaths

	Vilda 50mg qd N=162 n (%)	Vilda 50mg bid N=151 n (%)	Vilda 100mg qd N=155 n (%)	Placebo N=157 n (%)
Deaths*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)*
SAEs	8 (4.9)	6 (4.0)**	3 (1.9)	5 (3.2)
AEs leading to discontinuation	3 (1.9)	2 (1.3)	6 (3.9)	7 (4.5)
AEs causing dose adjustment or study drug interruption	5 (3.1)	3 (2.0)	5 (3.2)	5 (3.2)
Clinically significant CCV AEs	2 (1.2)	4 (2.6)	2 (1.3)	1 (0.6)
Clinically significant IM AEs	1 (0.6)	0(0.0)	1 (0.6)	1 (0.6)
Other clinically significant AEs	24(14.8)	22(14.6)	19(12.3)	26 (16.6)

* One patient died 23 days after discontinuation from the study.

** One patient had a serious adverse event of transient ischemic attack 5 days after completing the study; the data are not included in the table of SAEs below.

Number (%) of patients with SAEs by preferred term (Safety population)

Preferred Term	Vilda 50mg qd N=162 n (%)	Vilda 50mg bid N=151 n (%)	Vilda 100mg qd N=155 n (%)	Placebo N=157 n (%)
Total no. of patients with any SAE	8 (4.9)	6 (4.0)	3 (1.9)	5 (3.2)
Cardiac failure	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Mental status changes	0 (0.0)	1 (0.7)[3]	0 (0.0)	0 (0.0)
Multiple drug overdose intentional	0 (0.0)	1 (0.7)[3]	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Radius fracture	0 (0.0)	1 (0.7)[2]	0 (0.0)	0 (0.0)
Ulna fracture	0 (0.0)	1 (0.7)[2]	0 (0.0)	0 (0.0)
Angina pectoris	1 (0.6)[1]	0 (0.0)	0 (0.0)	0 (0.0)
Angioneurotic edema	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Contrast media reaction	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Diverticulitis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Grand mal convulsion	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Heat stroke	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	1 (0.6)[1]	0 (0.0)	0 (0.0)	0 (0.0)
Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Pneumonia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Road traffic accident	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Tooth abscess	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)

Other Relevant Findings Not applicable.
Date of Clinical Trial Report 14 December 2005
Date Inclusion on Novartis Clinical Trial Results Database 23 March 2007
Date of Latest Update 7 April 2008