Sponsor

Novartis

Generic Drug Name

Vildagliptin (LAF237)

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Investigational

Study Number

CLAF237A2323

Title

A multicenter, randomized, double-blind, active controlled study to compare the effects of 24 weeks treatment with LAF237 50 mg bid to acarbose up to 100 mg tid in drug naïve patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

4 Apr 2005 to 24 Dec 2006

Study Design/Methodology

This was a 24-week multicenter, randomized, double-blind, active controlled study. Drug naïve patients with type 2 diabetes (HbA_{1c} 7.5 – 11%) were randomized to vildagliptin 50 mg bid or to acarbose up to 100 mg tid in a ratio of 2:1.

Each patient attended one screening visit (Week -2) where the inclusion/exclusion criteria were assessed. Thereafter, eligible patients were randomized at visit 2 (Baseline, day1 = first day of medication) and completed 4 further visits over a period of 24 weeks of treatment with vildagliptin or acarbose

Centers

31 centers in 3 countries: China (15), Romania (9) and Spain (7)

Objectives

Primary objective(s)

The efficacy (reduction of HbA1c) of vildagliptin in patients with type 2 diabetes mellitus (T2DM) is non-inferior to acarbose after 24 weeks of treatment.

Secondary objective(s)

The efficacy of vildagliptin in patients with T2DM is non-inferior to acarbose in the subset of Chinese patients after 24 weeks of treatment
The responder rates observed in vildagliptin were not less than those in acarbose after 24 weeks of treatment
The reduction of fasting plasma glucose in vildagliptin group is non-inferior to acarbose after 24 weeks of treatment
Overall adverse event profile after 24 weeks of treatment between two treatment groups was similar with vildagliptin demonstrating a better gastrointestinal side effect profile than acarbose

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

Vildagliptin 50 mg oral tablets for twice daily administration
Acarbose 50 mg capsules up to 100 mg tid in a ratio of 2:1 using double dummy technique

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

Vildagliptin placebo; acarbose placebo

Criteria for Evaluation

Primary efficacy variables

The primary efficacy variable was HbA1c

Secondary efficacy variable

Fasting plasma glucose

Safety and tolerability

Safety assessments included adverse events, hypoglycemic events and serious adverse events, physical examination, vital signs, laboratory evaluations, and electrocardiograms (ECGs)

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The primary efficacy variable was change from baseline in HbA_{1c} (unit in %) at the end of the study (i.e. the measurement at the end of study – baseline measurement). For patients who did not have a Week 24 HbA_{1c}, the last observation was carried forward (LOCF). The analysis of the primary efficacy variable used the ITT population as the primary basis of conclusion.

The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment and pre-defined pooled center as the classification variables and baseline HbA_{1c} as the covariate. The possibility of a treatment by pooled-center interaction, or a treatment by baseline HbA_{1c} interaction was examined to assess the consistency of treatment effect across pooled centers and across baseline HbA_{1c} level, although the interaction term was not included in the primary analysis model. The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least square mean changes between the vildagliptin group and acarbose group (vildagliptin-acarbose) were obtained from the primary analysis model as well as the p values for the treatment differences and the two-sided 95% confidence intervals. The null hypothesis was rejected and non-inferiority established if the upper limit of the confidence interval did not exceed 0.4. Upon establishing the non-inferiority at a margin of 0.4%, a further assessment at 0.3% was then performed.

The safety evaluations during the study period were summarized by treatment group for the safety population. Endpoint was defined as the last on-treatment value regardless of whether it was obtained at a scheduled or unscheduled visit up to the last scheduled visit.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients were male or female (non-fertile or using a medically approved birth control method); age >= 18 years; drug naïve patients with type 2 diabetes; body mass index (BMI) of 20 – 40 kg/m2 inclusive; HbA1c 7.5 - 11% inclusive; fasting plasma glucose (FPG) < 15 mmol/L (270 mg/dL); and agreement to maintain prior diet and exercise.

Exclusion criteria included pregnant or lactating female; a history of type 1 diabetes; any secondary forms of diabetes, acute metabolic diabetic complications within the past 6 months; acute infections which may affect blood glucose control within 4 weeks prior to visit 1; a series of cardiac-related conditions (Torsades de pointes, ventricular tachycardia or fibrillation; percutaneous coronary intervention within the past 3 months; myocardial infarction, coronary artery bypass surgery, unstable angina, or stroke within the past 6 months; congestive heart failure NYHA class III or IV; second degree atrioventricular (AV) block (Mobitz 1 and 2), third degree AV block, prolonged QTc), chronic insulin treatment within the past 6 months; chronic corticosteroid treatment within 8 weeks prior to visit 1; treatment with class Ia, Ib and Ic or III anti-arrhythmics.

Number of Subjects

Patient disposition (randomized population)

Disposition Reason	Vilda 50 mg bid N = 441 n (%)	Acarb up to 100 mg tid N = 220 n (%)	Total N = 661 n (%)
Completed	399 (90.5)	192 (87.3)	591 (89.4)
Discontinued	42 (9.5)	28 (12.7)	70 (10.6)
Administrative problems	1 (0.2)	1 (0.5)	2 (0.3)
Adverse event(s)	11 (2.5)	7 (3.2)	18 (2.7)
Lost to follow-up	7 (1.6)	3 (1.4)	10 (1.5)
Protocol violation	3 (0.7)	2 (0.9)	5 (0.8)
Subject withdrew consent	14 (3.2)	7 (3.2)	21 (3.2)
Unsatisfactory therapeutic effect	6 (1.4)	8 (3.6)	14 (2.1)

Demographic and Background Characteristics

Patient baseline demographic characteristics

Demographic variable	Vilda 50 mg bid N=441	Acarb up to 100 mg tid N=220	Total N=661
Mean Age, years (SD)	51.79 (10.13)	51.93 (10.34)	51.84 (10.19)
Females:Males	40:60	37:63	12:88
Race			
Asian (non-Indian subcontinent)	399 (90.5%)	202 (91.8%)	601 (90.9)
Caucasian	42 (9.5%)	18 (8.2%)	60 (9.1%)
Mean Body Weight, kg (SD)	72.63 (11.76)	71.96 (12.52)	72.40 (12.02)
HbA1c % Mean (SD)	8.64 (0.92)	8.62 (1.01)	8.63 (0.95)
Duration of Type 2 Diabetes (years): Mean (SD)	1.21 (2.41)	1.25 (2.38)	1.22 (2.40)

Primary Objective Result(s)

ANCOVA results for change in HbA1c (%) from baseline to study endpoint (ITT population)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Difference in adjusted means ^ (SE)	95% CI	p-value
ITT population (LOCF)						
Vilda 50 mg bid	431	8.65 (0.04)	-1.40 (0.07)	-0.11 (0.11)	(-0.32, 0.10)#	0.307
Acarb up to 100 mg tid	216	8.64 (0.07)	-1.29 (0.09)			

# Indicates statistical significance for non-inferiority of vildagliptin to acarbose at margin 0.4% and at 2.5% level.

Secondary Objective Results

ANCOVA results for change in HbA1c (%) from baseline to study endpoint among Chinese patients (ITT population)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Difference in adjusted means ^ (SE)	95% CI	p-value
ITT population (LOCF)						
Vilda 50 mg bid	394	8.65 (0.05)	-1.44 (0.07)	-0.09 (0.12)	(-0.32,0.14)#	0.445
Acarb up to 100 mg tid	199	8.67 (0.07)	-1.36 (0.10)			

# Indicates statistical significance for non-inferiority of vildagliptin to acarbose at margin 0.4% and at 2.5% level.

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

	Vilda 50 mg bid N=431	Acarb up to 100 mg tid N=216	p-value
HbA1c < 7%[1]	198/427 (46.4)	101/215 (47.0)	0.884
Reduction of HbA1c >= 0.7%	314 (72.9)	157 (72.7)	0.964

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

ANCOVA results for change in fasting plasma glucose (mmol/L) from baseline to study endpoint (ITT population)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Difference in adjusted means^ (SE)	95% CI for change from baseline	p-value for change from baseline
ITT population						
Vilda 50 mg bid	431	10.05 (0.12)	-1.19 (0.11)	0.29 (0.18)	(-0.07,0.65)	0.112
Acarb up to 100 mg tid	216	10.15 (0.17)	-1.48 (0.15)			

Safety Results

Adverse Events by System Organ Class

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

Primary system organ class	Vilda 50 mg bid N = 440 n (%)	Acarb up to 100 mg tid N = 220 n (%)
Patients with at least one AE	154 (35.0)	113 (51.4)
Blood and lymphatic system disorders	6 (1.4)	2 (0.9)
Cardiac disorders	21 (4.8)	6 (2.7)
Ear and labyrinth disorders	2 (0.5)	2 (0.9)
Eye disorders	6 (1.4)	2 (0.9)
Gastrointestinal disorders	54 (12.3)	56 (25.5)
General disorders and administration site conditions	23 (5.2)	13 (5.9)
Hepatobiliary disorders	6 (1.4)	2 (0.9)
Immune system disorders	1 (0.2)	0
Infections and infestations	47 (10.7)	31 (14.1)
Injury, poisoning and procedural complications	5 (1.1)	3 (1.4)
Investigations	5 (1.1)	1 (0.5)
Metabolism and nutrition disorders	7 (1.6)	7 (3.2)
Musculoskeletal and connective tissue disorders	12 (2.7)	11 (5.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	0
Nervous system disorders	28 (6.4)	14 (6.4)
Pregnancy, puerperium and perinatal conditions	0	1 (0.5)
Psychiatric disorders	6 (1.4)	4 (1.8)
Renal and urinary disorders	2 (0.5)	3 (1.4)
Reproductive system and breast disorders	2 (0.5)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	10 (2.3)	3 (1.4)
Skin and subcutaneous tissue disorders	15 (3.4)	6 (2.7)
Vascular disorders	7 (1.6)	2 (0.9)

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

Number (%) of patients reporting common AEs (at least 1% in any group) by preferred term (Safety population)

Preferred term	Vilda 50 mg bid N = 440 n (%)	Acarb up to 100 mg tid N = 220 n (%)
Patients with at least one AE	154 (35.0)	113 (51.4)
Nasopharyngitis	18 (4.1)	14 (6.4)
Dizziness	17 (3.9)	9 (4.1)
Palpitations	16 (3.6)	3 (1.4)
Upper respiratory tract infection	15 (3.4)	11 (5.0)
Abdominal distension	12 (2.7)	20 (9.1)
Diarrhoea	11 (2.5)	6 (2.7)
Flatulence	11 (2.5)	26 (11.8)
Constipation	5 (1.1)	3 (1.4)
Frequent Bowel movements	5 (1.1)	2 (0.9)
Hunger	5 (1.1)	2 (0.9)

Serious Adverse Events and Deaths

	Vilda 50mg bid	Acarb up to 100mg tid
No. (%) of patients studied	440	220
Patients with at least one AE	154 (35.0)	113 (51.4)
Death	0	0 (0.0)
SAEs	7 (1.6)	2 (0.9)
Discontinued due to AEs	11 (2.5)	7 (3.2)
Discontinued due to SAEs	3 (0.7)	0

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

Preferred term	Vilda 50 mg bid N = 440 n (%)	Acarb up to 100 mg tid N = 220 n (%)
Any SAE	7 (1.6)	2 (0.9)
Angina unstable	1 (0.2)	0
Bile duct obstruction	1 (0.2)	0
Cholangitis	1 (0.2)	0
Cholecystitis	1 (0.2)	0
Coronary artery disease	1 (0.2)	0
Gastric polyps	1 (0.2)	0
Iron deficiency anaemia	1 (0.2)	0
Lung neoplasm malignant	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Pancreatitis acute	1 (0.2)	0
Pneumonia	1 (0.2)	0
Acute myocardial infarction	0	1 (0.5)
Intercostal neuralgia	0	1 (0.5)

Other Relevant Findings

No hypoglycemic events were observed during this study.

Date of Clinical Trial Report

March 30, 2007

Date Inclusion on Novartis Clinical Trial Results Database

January 14, 2008

Date of Latest Update

January 27, 2009