Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Type 2 diabetes

Study Number

CLAF237A2308

Title

A multicenter, randomized, double-blind, active controlled study to compare the long-term effect of treatment with LAF237 50 mg bid to glimepiride up to 6 mg daily as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy

Phase of Development

Phase III

Study Start/End Dates

15-Mar-2005 to 20-May-2008

Study Design/Methodology

The original primary endpoint of the study was to compare the long term 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 risk of failure of glycemic control over time (defined as HbA_{1c} > 8.0%) is lower with vildagliptin compared to that with glimepiride. This study was designed to provide data for submission to regulatory authorities to expand the initial labeling of vildagliptin. Glimepiride is a second generation sulfonylurea and is frequently used in combination with metformin to attain optimal glycemic control in type 2 diabetics. Glimepiride is therefore, a suitable choice against which to compare a new treatment such as vildagliptin.

By amendment no. 6 the primary objective of the study was amended to 'change in HbA_{1c} from baseline to Week 104 endpoint' whilst the previous primary objective became an exploratory objective considering the risk of failure of glycemic control over time. Due to a higher observed discontinuation rate (~20% after two years compared with expected 20% after 5 years) and lower observed failure of glycemic control event rate (approximately 10% after 2 years based on

blinded data, compared with an expected rate of 15% after the first 6 months and of 50% after 5 years in the glimepiride arm), the power to detect superiority with respect to the original primary variable, time to failure of therapy (HbA_{1c}>8%), with the number of patients randomized (3120) was low (approximately 60%). In addition, regardless of any potential patient retention activities aimed at maintaining the current discontinuation rate and regardless of extending the duration of the study to attain the maximum number of events, the power of this study would have been expected to remain below 80%, therefore the study was amended for reasons of futility. The revised study design was a safety and efficacy study with a primary endpoint of change from baseline in HbA_{1c} to Week 104 endpoint.

Patients with type 2 diabetes who were inadequately controlled on metformin are candidates for treatment with a second oral anti-diabetic agent. Patients with type 2 diabetes treated with metformin for at least three months and at a stable maximum tolerated dose of at least 1500 mg daily for a minimum of 4 weeks prior to Visit 1 were eligible to participate in the trial. The dose of metformin was maintained unchanged throughout the trial.

Centres
402 centers in 25 countries screened at least one patient (number of centers in brackets): Argentina, (11), Belgium (12), Canada (41), Columbia (4), Denmark (13), Egypt (3), Estonia (10), Finland (11), France (11), Germany (94), Greece (2), Guatemala (4), Hong-Kong (1), Israel (2), Italy (43), Latvia (11), Lithuania (9), Netherlands (14),Peru (4), South Africa (6), Spain (50) Turkey (3), Ukraine (5), United Kingdom (14) and United States (25).

Objectives

Primary Objective

- To compare the long term efficacy of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that HbA_{1c} reduction with vildagliptin is non-inferior to that with glimepiride at Week 104 endpoint.

Secondary objectives

- To compare the 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, including the frequency and severity of hypoglycemia, compared to glimepiride over the duration of the study.
- To compare 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 fasting plasma glucose (FPG) reduction with vildagliptin is non-inferior to that with glimepiride at Week 104 endpoint.
- To compare 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 glimepiride at the Week 104 endpoint.

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

Vildagliptin 50 mg bid (added to metformin $\geq$ 1500 mg bid), taken orally

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

Glimepiride up to 6 mg qd (added to metformin $\geq$ 1500 mg bid)

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:

- fasting plasma glucose (FPG)
- body weight

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 efficacy variable is change from baseline to Week 104 endpoint in HbA_{1c} (unit in %). Week 104 endpoint is the measurement obtained at the Week 104 visit or at the final visit prior to Week 104 with an HbA_{1c} measurement for those patients who did not have a Week 104 HbA_{1c} measurement. For patients who took rescue medication, the week 104 endpoint is defined as the measurement obtained at the last visit prior to the initiation of rescue medication. The baseline value is the Day 1 measurement, or the measurement obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing. The primary population is the PP population.

The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment and 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 were examined, to assess the consistency of treatment effect across pooled centers and across baseline HbA_{1c} level although the interaction terms were not included in the primary analysis model.

The least squares mean (adjusted mean) change from baseline for each treatment group and associated 97.5% confidence intervals, the difference between two treatment groups ((LAF237 plus metformin) – (glimepiride plus metformin) and associated two-sided 97.5% confidence interval were obtained from the primary analysis model and presented. The null hypothesis was to be rejected and non-inferiority established if the upper limit of the confidence interval for the treatment difference obtained from the above ANCOVA model does not exceed 0.4. Furthermore, if the upper limit of the 97.5% confidence interval did not exceed 0.3%, the non-inferiority of LAF237 plus metformin vs. glimepiride plus metformin would also be established at the 0.3% margin. If non-inferiority was compared using the 0.3% margin, the superiority of LAF237 plus metformin vs. glimepiride plus metformin was to be tested using the same 97.5% confidence interval and established if the upper limit of the confidence interval was below zero. The ANCOVA analysis was performed on the Per protocol population and on the ITT population.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population consisted of male and female adult patients, age 18 to 73 years, with body mass index (BMI) ranging from 22 to 45 kg/m^2, whose type 2 diabetes was inadequately controlled (HbA_{1c}, 6.5-8.5% 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 glimepiride; known sensitivity to glimepiride or other sulfur containing 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 50mg bid+Met N=1562	Glim up to 6mg daily+Met N=1556	Total N=3118	
Randomized	1562 (100%)	1556 (100%)	3118 (100%)	
Safety	1553 (99.4%)	1546 (99.4%)	3099 (99.4%)	
Intent to treat	1539 (98.5%)	1520 (97.7%)	3059 (98.1%)	
Per protocol	1051 (67.3%)	1009 (64.8%)	2060 (66.1%)	
Completed	994 (63.6)	953 (61.2)	1947 (62.4)	
Discontinued	568 (36.4)	603 (38.8)	1171 (37.6)	
Abnormal laboratory value(s)	14 (0.9)	10 (0.6)	24 (0.8)	
Abnormal test procedure result(s)	0 (0.0)	1 (0.1)	1 (0.0)	
Administrative problems	131 (8.4)	122 (7.8)	253 (8.1)	

Demographic and Background Characteristics

	Vilda 50mg bid+Met	Glim up to 6mg daily+Met	Total	
N (randomized)	1562	1556	3118	
Females : males	733:829	718:838	1451:1667	
Mean age, years (SD)	57.5 (9.07)	57.5 (9.19)	57.5 (9.13)	
Mean body weight, kg (SD)	89.5 (18.08)	88.9 (17.84)	89.2 (17.96)	
Mean BMI, kg/m^2 (SD)	31.9 (5.33)	31.7 (5.26)	31.8 (5.29)	
Race Caucasian n (%)	1364 (87.3%)	1343 (86.3%)	2707 (86.8%)	
Black	18 (1.2%)	19 (1.2%)	37 (1.2%)	
Asian (non indian subcontinent)	30 (1.9%)	30 (1.9%)	60 (1.9%)	
Asian (indian subcontinent)	14 (0.9%)	16 (1.0%)	30 (1.0%)	

Hispanic or latino	129 (8.3%)	133 (8.5%)	262 (8.4%)	
Japanese	0 (0.0%)	1 (0.1%)	1 (0.0%)	
Native american	3 (0.2%)	3 (0.2%)	6 (0.2%)	
Pacific islander	1 (0.1%)	2 (0.1%)	3 (0.1%)	
Other	3 (0.2%)	9 (0.6%)	12 (0.4%)	
Mean HbA_{1c} % (SD)	7.3 (0.65)	7.3 (0.66)	7.3 (0.65)	
Mean FPG, mmol/L (SD)	9.2 (2.25)	9.2 (2.22)	9.2 (2.23)	
Mean duration of diabetes, years (SD)	5.7 (5.20)	5.7 (5.04)	5.7 (5.12)	
Mean metformin usage, months (SD)	35.6 (34.58)	35.4 (34.85)	35.5 (34.71)	

Primary Efficacy Result(s)

Change in HbA_{1c} from baseline to Week 104 Endpoint (ITT and PP populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change at end-point (SE)	Mean difference to comparator (SE)	95% CI
ITT population					
Vilda 50mg bid + Met	1518	7.31 (0.02)	-0.03(0.02)	0.10 (0.03)	(0.03 , 0.17)
Glim up to 6mg daily + Met	1476	7.31 (0.02)	-0.13(0.02)		
Per protocol (PP) population					
Vilda 50mg bid + Met	1050	7.32 (0.02)	-0.06(0.03)	0.08 (0.04)	(-0.00, 0.17)
Glim up to 6mg daily + Met	1008	7.32 (0.02)	-0.14(0.03)		

Secondary Efficacy Results

Change in FPG (mmol/L) from baseline to Week 104 endpoint (ITT and PP populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to comparator (SE)	97.5% CI
ITT population					
Vilda 50mg bid + Met	1524	9.15 (0.06)	-0.47(0.05)	0.17 (0.07)	(0.02 , 0.31)
Glim up to 6mg daily + Met	1491	9.18 (0.06)	-0.64(0.05)		
Per protocol population					
Vilda 50mg bid + Met	1048	9.12 (0.06)	-0.54(0.06)	0.16 (0.09)	(-0.01, 0.33)
Glim up to 6mg daily + Met	1009	9.16 (0.07)	-0.70(0.06)		

Change in body weight (kg) from baseline to Week 104 endpoint (ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to comparator (SE)	95% CI	p-value
Vilda 50mg bid + Met	1539	89.42(0.46)	-0.26(0.11)	-1.45(0.15)	(-1.74,-1.16)	<0.001*
Glim up to 6mg daily + Met	1520	88.76(0.46)	1.19 (0.11)			

* indicates statistical significance at 5 % level.

Safety Results

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

Primary system organ class	Vilda 50mg bid+Met N=1553 n (%)	Glim up to 6mg daily+Met N=1546 n (%)
Any primary system organ class	1291(83.1)	1335(86.4)
Blood and lymphatic system disorders	44(2.8)	47(3.0)
Cardiac disorders	151(9.7)	156(10.1)
Congenital, familial and genetic disorders	6(0.4)	4(0.3)
Ear and labyrinth disorders	89(5.7)	124(8.0)
Endocrine disorders	21(1.4)	21(1.4)
Eye disorders	167(10.8)	185(12.0)
Gastrointestinal disorders	506(32.6)	474(30.7)
General disorders and administration site conditions	315(20.3)	491(31.8)
Hepatobiliary disorders	50(3.2)	51(3.3)
Immune system disorders	24(1.5)	19(1.2)
Infections and infestations	762(49.1)	683(44.2)
Injury, poisoning and procedural complications	232(14.9)	215(13.9)
Investigations	150(9.7)	216(14.0)
Metabolism and nutrition disorders	161(10.4)	381(24.6)
Musculoskeletal and connective tissue disorders	544(35.0)	543(35.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	69(4.4)	73(4.7)
Nervous system disorders	479(30.8)	701(45.3)
Psychiatric disorders	190(12.2)	224(14.5)
Renal and urinary disorders	97(6.2)	89(5.8)
Reproductive system and breast disorders	96(6.2)	96(6.2)
Respiratory, thoracic and mediastinal disorders	245(15.8)	243(15.7)
Skin and subcutaneous tissue disorders	308(19.8)	462(29.9)
Social circumstances	7(0.5)	2(0.1)
Surgical and medical procedures	10(0.6)	4(0.3)
Vascular disorders	187(12.0)	220(14.2)

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

Preferred term	Vilda 50mg bid+Met N=1553 n (%)	Glim up to 6mg daily+Met N=1546 n (%)
Nasopharyngitis	229(14.7)	210(13.6)
Headache	149(9.6)	142(9.2)
Back pain	146(9.4)	147(9.5)
Bronchitis	141(9.1)	113(7.3)
Dizziness	128(8.2)	247(16.0)
Arthralgia	121(7.8)	97(6.3)
Influenza	118(7.6)	99(6.4)
Diarrhea	115(7.4)	113(7.3)
Hypertension	104(6.7)	125(8.1)
Upper respiratory tract infection	102(6.6)	80(5.2)

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

	Vilda 50mg bid + Met N=1553 n (%)	Glim up to 6mg qd + Met N=1546 n (%)
Deaths	7 (0.5)	6 (0.4)
SAEs	236 (15.2)	253 (16.4)
Discontinuation due to AEs	130(8.4)	166(10.7)
Adverse events requiring dose adjustment or study-drug interruption	153(9.9)	181(11.7)
Clinically significant CCV AEs	59(3.8)	60(3.9)
Clinically significant IM AEs	31(2.0)	21(1.4)
Other clinically significant AEs	388 (25.0)	443 (28.7)

There were 13 deaths in this study out of which 7 occurred in the vildagliptin treamtent group (1 patient: infarction, cardiac arrest, syncope, sudden death, 2 patients: myocardial infarction, 1 patient: meso-thelioma, 1 patient: road traffic accident, 1 patient: respiratory tract infection, dyspnea, respiratory failure, interstitial lung disease, 1 patient: metastatic neoplasm) and 6 occurred in the glimepriride treamtent group.

Number (%) of patients with SAEs by preferred term

Preferred Term	Vilda 50mg bid+Met N=1553 n (%)	Glim up to 6mg daily+Met N=1546 n (%)
Any SAE	236(15.2)	253(16.4)
Abdominal pain	4(0.3)	1(0.1)
Acute myocardial infarction	4(0.3)	3(0.2)
Angina pectoris	6(0.4)	12(0.8)
Angina unstable	4(0.3)	2(0.1)
Ankle fracture	4(0.3)	1(0.1)
Asthma	0(0.0)	3(0.2)
Atrial fibrillation	2(0.1)	6(0.4)
Breast cancer	5(0.3)	3(0.2)

Cardiac failure	3(0.2)	3(0.2)
Carotid artery stenosis	3(0.2)	1(0.1)
Cellulitis	0(0.0)	5(0.3)
Cerebrovascular accident	8(0.5)	6(0.4)
Chest pain	4(0.3)	1(0.1)
Cholecystitis	6(0.4)	2(0.1)
Cholelithiasis	10(0.6)	3(0.2)
Concussion	0(0.0)	4(0.3)
Coronary artery disease	6(0.4)	8(0.5)
Coronary artery stenosis	4(0.3)	2(0.1)
Dermatitis allergic	0(0.0)	3(0.2)
Diarrhea	3(0.2)	1(0.1)
Dizziness	1(0.1)	3(0.2)
Dyspnea	3(0.2)	3(0.2)
Erysipelas	3(0.2)	3(0.2)
Hypertensive crisis	4(0.3)	1(0.1)
Hypoglycaemia	1(0.1)	13(0.8)
Inguinal hernia	2(0.1)	3(0.2)
Intervertebral disc protrusion	1(0.1)	4(0.3)
Myocardial infarction	12(0.8)	6(0.4)
Nephrolithiasis	2(0.1)	5(0.3)
Non-cardiac chest pain	1(0.1)	4(0.3)
Osteoarthritis	4(0.3)	4(0.3)
Pancreatitis acute	3(0.2)	2(0.1)
Pneumonia	8(0.5)	3(0.2)
Prostate cancer	4(0.3)	4(0.3)
Respiratory tract infection	3(0.2)	0(0.0)
Rib fracture	1(0.1)	3(0.2)
Sepsis	3(0.2)	0(0.0)
Sleep apnea syndrome	1(0.1)	3(0.2)
Syncope	5(0.3)	5(0.3)
Urinary tract infection	1(0.1)	3(0.2)

Other Relevant Findings

Not applicable

Date of Clinical Trial Report 11 November 2008
Date Inclusion on Novartis Clinical Trial Results Database 12 May 2009
Date of Latest Update