Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 Diabetes

Approved Indication

Investigational

Study Number

CLAF237A2309E1

Title

A 52 week extension to a multicenter, randomized, double-blind, active controlled study to compare the effect of 52 weeks treatment with LAF237 50 mg bid to metformin up to 1000 mg bid in drug naïve patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

31 Jan 2005 to 02 Aug 2006

Study Design/Methodology

This was a 52-week, multicenter, double-blind extension study. Patients maintained their assigned treatment regimen assigned during the core trial throughout the extension. The last visit of the core study was the first visit of the extension study. Eligible patients were then to complete 4 additional visits over a period of 52 weeks of treatment with vildagliptin or metformin

Centres

123 centers in 7 countries: Argentina (4), Germany (12), Peru (5), Russia (11), Spain (6), UK (15), USA (70)

Publication

Objectives

Primary objective(s)

- Safety during 104 weeks of treatment
- Change from baseline in HbA1c at 104 weeks

Secondary objective(s)

- Change in HbA1c between 52 weeks and 104 weeks
- Change in fasting plasma glucose between 52 weeks and 104 weeks
- Change from baseline in fasting plasma glucose at 104 weeks
- Change from baseline in HOMA B at 104 weeks
- Change in HOMA B between 52 weeks and 104 weeks

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

Vildagliptin 50 mg tablets twice daily for oral administration

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

Metformin 500 mg tablets, up to 2,000 mg daily for oral administration

Criteria for Evaluation

Primary variables

Safety - Safety assessments included the monitoring of adverse events, vital signs, physical examinations, laboratory evaluations (hematology, biochemistry and urinalysis) and electrocardiograms.

HbA1c

Secondary variables

HbA1c
Fasting plasma glucose
Homeostatic model assessment – beta cell (HOMA-B)

Safety and tolerability

Safety - Safety assessments included the monitoring of adverse events, vital signs, physical examinations, laboratory evaluations (hematology, biochemistry and urinalysis) and electrocardiograms.

Pharmacology

Not applicable

Other

Quality of life questionnaire

Statistical Methods

The primary hypothesis tested was no difference between vildagliptin 50 mg bid and metformin 1000 mg bid for the effect of reducing HbA_{1c} after 104 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 estimated treatment difference (vildagliptin – metformin) and its 95% confidence interval were derived from the lease square mean change from baseline ('adjusted mean') of each treatment group. In addition, unadjusted changes from the end of core study (Week 52) to the end of the extension study were also summarized for primary and secondary endpoints.

Demographic and background data were summarized by treatment group. Safety data collected over the overall core and extension phases were summarized by treatment group. The incidence of gastrointestinal adverse events were compared between treatment groups using Fisher's exact test.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria for Extension: Participation in core study LAF237A2309. Written informed consent to participate in the extension study; ability to comply with all study requirements.

Exclusion criteria for Extension: Premature discontinuation from the core study (LAF237A2309); concomitant medical conditions that interfere with the interpretation of study results as defined in the core protocol; failure to comply with the core study protocol; potentially unreliable patients, and those judged by the investigator to be unsuitable for the study.

Number of Subjects

Patient disposition (Extension population)

Disposition Reason	Vilda 50 mg bid N=305 n (%)	Met 1000 mg bid N=158 n (%)	Total N=463 n (%)
Completed	260(85.2)	142(89.9)	402(86.8)
Discontinued	45(14.8)	16(10.1)	61(13.2)
Abnormal laboratory values	2(0.7)	0(0.0)	2(0.4)
Administrative problems	1(0.3)	1(0.6)	2(0.4)
Adverse Event(s)	6(2.0)	2(1.3)	8(1.7)
Death	1(0.3)	2(1.3)	3(0.6)
Lost to follow-up	9(3.0)	3(1.9)	12(2.6)
Protocol violation*	1(0.3)	1(0.6)	2(0.4)
Subject withdrew consent	15(4.9)	3(1.9)	18(3.9)
Unsatisfactory therapeutic effect	10(3.3)	4(2.5)	14(3.0)

* Refers to investigator's judgment during the study.

Demographic and Background Characteristics

Patient baseline demographic characteristics (Extension population)

	Vilda 50 mg bid N=305	Met 1000 mg bid N=158
N (Ext. Pop)	305	158
Mean age, years (SD)	53.84 (11.19)	54.08 (9.64)
Females:males	138:167	62:96
Race		
Caucasian	218(71.5%)	121(76.6%)
Black	21(6.9%)	7(4.4%)
Asian	6(2%)	2(1.2%)
Other	60(19.7%)	28(17.8)
Mean Wt, kg (SD)	92.27(19.95)	95.90(18.32)
Baseline HbA1c (%) Mean (SD)	8.53(1.00)	8.82(1.07)
Duration of Type 2 Diabetes (years) Mean (SD)	2.46(3.60)	2.20(2.89)

Primary Objective Result(s)

ANCOVA results for change in HbA1c (%) from baseline to Week 104 (Extension ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met 1000 mg bid (SE)	95% CI	p-value
Extension ITT population						
Vilda 50 mg bid	243	8.43 (0.06)	-0.98(0.09)	0.51 (0.13)	(0.25, 0.78)	<0.001*
Met 1000 mg bid	136	8.78 (0.09)	-1.49(0.12)			

*indicates statistical significance at the 5% level.

Secondary Objective Result(s)

Change in HbA1c (%) from Week 52 to extension study Week 104 (Extension ITT population)

Treatment	n	Week 52 mean (SE)	Unadjusted mean change from Week 52 (SE)	95% CI for change from Week 52[#]	p-value for change from Week 52[#]
Extension ITT population					
Vilda 50 mg bid	243	7.08 (0.07)	0.51 (0.06)	(0.40 , 0.63)	<0.001*
Met 1000 mg bid	136	6.92 (0.08)	0.24 (0.06)	(0.12 , 0.35)	<0.001*

[#]95% CI and p-value are based on one-sample t-distribution
*indicates statistical significance at the 5% level

Change in fasting plasma glucose (mmol/L) from Week 52 to extension study Week 104 (Extension ITT population)

Treatment	n	Week 52 mean (SE)	Unadjusted mean change from Week 52 (SE)	95% CI for change from Week 52[#]	p-value for change from Week 52[#]
Extension ITT population					
Vilda 50 mg bid	251	8.49 (0.14)	1.13 (0.14)	(0.85 , 1.41)	<0.001*
Met 1000 mg bid	140	7.85 (0.17)	0.83 (0.19)	(0.46 , 1.21)	<0.001*

[#]95% CI and p-value are based on one-sample t-distribution
*indicates statistical significance at the 5% level

ANCOVA results for change in fasting plasma glucose (mmol/L) from core baseline (week 1) to extension study endpoint (week 104) (Extension ITT population)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met 1000 mg bid (SE)	95% CI	p-value
Extension ITT population						
Vilda 50 mg bid	251	9.64 (0.15)	-0.28(0.20)	1.12 (0.28)	(0.57 , 1.67)	<0.001*
Met 1000 mg bid	140	10.16(0.22)	-1.40(0.25)			

* indicates statistical significance at the 5% level.

ANCOVA results for change in beta cell function / insulin resistance parameters from core baseline (week 1) to extension study endpoint (week 104) (Extension ITT population)

Parameter/ Treatment group	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met 1000 mg bid (SE)	95% CI	p-value
Homa-B						
Vilda 50 mg bid	169	65.56(4.68)	10.14(4.19)	-1.15(5.60)	(-12.2, 9.88)	0.838
Met 1000 mg bid	104	63.50(6.95)	11.29(5.11)			

Change in beta cell function / insulin resistance parameters from Week 52 to extension study endpoint (week 104) (Extension ITT population)

HOMA-B					
Vilda 50mg bid	173	84.31 (5.69)	-9.35 (3.72)	(-16.70,-2.01)	0.013*
Met 1000mg bid	104	85.89 (8.45)	-9.12 (5.00)	(-19.04, 0.80)	0.071

*indicated statistical significance at 5% level

Safety Results

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

Primary system organ class	Vilda 50 mg bid N=304 n (%)	Met 1000 mg bid N=158 n (%)
Any primary system organ class	245(80.6)	136(86.1)
Blood and lymphatic system disorders	4(1.3)	5(3.2)
Cardiac disorders	20(6.6)	13(8.2)
Congenital, familial and genetic disorders	1(0.3)	0(0.0)
Ear and labyrinth disorders	12(3.9)	6(3.8)
Endocrine disorders	3(1.0)	1(0.6)
Eye disorders	24(7.9)	9(5.7)
Gastrointestinal disorders	76(25.0)	72(45.6)
General disorders and administration site conditions	53(17.4)	28(17.7)
Hepatobiliary disorders	4(1.3)	2(1.3)
Immune system disorders	6(2.0)	7(4.4)
Infections and infestations	154(50.7)	70(44.3)
Injury, poisoning and procedural complications	55(18.1)	25(15.8)
Investigations	34(11.2)	14(8.9)
Metabolism and nutrition disorders	35(11.5)	21(13.3)
Musculoskeletal and connective tissue disorders	93(30.6)	51(32.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10(3.3)	4(2.5)
Nervous system disorders	88(28.9)	38(24.1)
Pregnancy, puerperium and perinatal conditions	0(0.0)	1(0.6)
Psychiatric disorders	34(11.2)	11(7.0)
Renal and urinary disorders	21(6.9)	18(11.4)
Reproductive system and breast disorders	21(6.9)	10(6.3)
Respiratory, thoracic and mediastinal disorders	44(14.5)	24(15.2)
Skin and subcutaneous tissue disorders	49(16.1)	22(13.9)
Social circumstances	1(0.3)	1(0.6)
Vascular disorders	33(10.9)	19(12.0)

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

Preferred term	Vilda 50 mg bid N=304 n (%)	Met 1000 mg bid N=158 n (%)
Nasopharyngitis	48(15.8)	19(12.0)
Headache	39(12.8)	14(8.9)
Upper respiratory tract infection	31(10.2)	16(10.1)
Back pain	28(9.2)	14(8.9)
Dizziness	25(8.2)	10(6.3)
Hypertension	23(7.6)	16(10.1)
Bronchitis	22(7.2)	10(6.3)
Arthralgia	19(6.3)	12(7.6)
Diarrhoea	19(6.3)	45(28.5)
Cough	16(5.3)	9(5.7)

Serious Adverse Events and Deaths

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

Preferred Term	Vilda 50 mg bid N=304 N(%)	Met 1000 mg bid N=158 N(%)
Deaths	1 (0.3)	1 (0.6)
SAEs	27 (8.9)	11 (7.0)
Discontinuation due to SAEs	5 (1.6)	3 (1.9)
AEs causing dose adjustment or study drug interruption	26 (8.6)	17 (10.8)
Clinically significant CCV AEs	13 (4.3)	5 (3.2)
Clinically significant IM AEs	3 (1.0)	3 (1.9)
Other clinically significant AEs	86 (28.3)	67 (42.4)

Number (%) patients with SAEs by preferred term (Extension safety population)

Preferred Term	Vilda 50 mg bid N=304 n (%)	Met 1000 mg bid N=158 n (%)
Any SAE	27(8.9)	11(7.0)
Angina unstable	3(1.0)	1(0.6)
Angina pectoris	2(0.7)	1(0.6)
Acute coronary syndrome	1(0.3)	0(0.0)
Atrial fibrillation	1(0.3)	0(0.0)
Basal cell carcinoma	1(0.3)	0(0.0)
Chest pain	1(0.3)	1(0.6)
Cholangitis acute	1(0.3)	0(0.0)
Cholelithiasis	1(0.3)	0(0.0)
Chondromatosis	1(0.3)	0(0.0)
Contusion	1(0.3)	0(0.0)
Conversion disorder	1(0.3)	0(0.0)
Coronary artery disease	1(0.3)	1(0.6)
Deep vein thrombosis	1(0.3)	0(0.0)
Diverticulum	1(0.3)	0(0.0)
Epistaxis	1(0.3)	0(0.0)
Gastritis erosive	1(0.3)	0(0.0)
Goitre	1(0.3)	0(0.0)
Haemarthrosis	1(0.3)	0(0.0)
Hepatic cancer stage IV	1(0.3)	0(0.0)
Hypertension	1(0.3)	0(0.0)
Hypertensive crisis	1(0.3)	0(0.0)
Intervertebral disc protrusion	1(0.3)	0(0.0)
Ischaemic stroke	1(0.3)	0(0.0)
Joint injury	1(0.3)	0(0.0)
Ligament injury	1(0.3)	0(0.0)
Limb injury	1(0.3)	0(0.0)
Myocardial infarction	1(0.3)	0(0.0)
Nephrolithiasis	1(0.3)	0(0.0)
Non-small cell lung cancer stage IV	1(0.3)	0(0.0)
Respiratory failure	1(0.3)	0(0.0)
Road traffic accident	1(0.3)	0(0.0)
Tachyarrhythmia	1(0.3)	0(0.0)

Anaemia	0(0.0)	1(0.6)
Cardiac failure	0(0.0)	1(0.6)
Duodenitis	0(0.0)	1(0.6)
Enterocolitis infectious	0(0.0)	1(0.6)
Erosive oesophagitis	0(0.0)	1(0.6)
Gastric ulcer haemorrhage	0(0.0)	1(0.6)
Gastritis	0(0.0)	1(0.6)
Gastrointestinal haemorrhage	0(0.0)	1(0.6)
Haematuria	0(0.0)	1(0.6)
Lung neoplasm malignant	0(0.0)	1(0.6)
Ovarian mass	0(0.0)	1(0.6)
Peritoneal adhesions	0(0.0)	1(0.6)
Pneumonia influenzal	0(0.0)	1(0.6)
Pregnancy	0(0.0)	1(0.6)
Syncope	0(0.0)	1(0.6)
Transitional cell carcinoma	0(0.0)	1(0.6)

Deaths: 1 traffic accident, 1 lung cancer

Other Relevant Findings

Number (%) of patients with gastrointestinal (GI) AEs (Extension safety population)

Preferred term	Vilda 50 mg bid N=304 n (%)	Met 1000 mg bid N=158 n (%)	p-value*
Any GI event	76 (25.0)	72 (45.6)	<0.001

* Fisher's exact test for Vilda 50mg bid vs. Metformin.

Date of Clinical Trial Report 15 Nov 2006
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