NOVARTIS

**Sponsor**
Novartis

**Generic Drug Name**
Vildagliptin

**Therapeutic Area of Trial**
Type 2 diabetes

**Approved Indication**
Investigational

**Study Number**
CLAF237A2305

**Title**
A multicenter, double-blind, randomized, parallel-group study to compare the effect of 24 weeks treatment with LAF237 (50 mg qd or bid) to placebo as add-on therapy to glimepiride in patients with type 2 diabetes inadequately controlled with sulfonylurea monotherapy

**Phase of Development**
Phase III

**Study Start/End Dates**
04-May-2004 to 14-Oct-2005

**Study Design/Methodology**
This was a multicenter, randomized, double-blind, placebo-controlled study. Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy (hemoglobin $A_{1c}$ [HbA1c] 7.5- 11%) were included in the trial. Eligible patients were randomly assigned in a 1:1:1 ratio to either vildagliptin 50 mg daily (qd), 50 mg twice daily (bid), or placebo, each treatment as add-on combination to glimepiride. Patients were treated for 24 weeks.

**Centres**
114 centers in 5 countries: US (88), Sweden (9), Finland (7), Argentina (6), and Lithuania (4).

**Objectives**

**Primary outcome/efficacy objective(s)**

To measure HbA1c for add-on therapy with vildagliptin to glimepiride in patients with type 2 diabetes inadequately controlled with prior sulfonylurea monotherapy

**Secondary outcome/efficacy objective(s)**

- Change from baseline in fasting plasma glucose (FPG) at 24 weeks
- Percent of patients with endpoint HbA1c <7% after 24 weeks
- Percent of patients with reduction in HbA1c greater than or equal to 0.7% after 24 weeks
- Adverse event profile after 24 weeks of treatment
- Change from baseline in HbA1c at 24 weeks for patients with high baseline HbA1c vs. low baseline HbA1c

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

Vildagliptin 50 mg tablets for oral administration, dosed once- or twice-daily

**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 HbA1c measured by ion exchange or boronate affinity 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 HbA1c < 7%, 2. Endpoint HbA1c <= 6.5%, 3. HbA1c absolute reduction from baseline at endpoint >= 1%, 4. HbA1c absolute reduction from baseline at endpoint >= 0.7%, 5. HbA1c absolute reduction from baseline at endpoint >= 0.5%; and prandial efficacy parameters including area under the 0-4 hour prandial curve (AUC0-4hr) for plasma glucose, insulin and C-peptide, adjusted AUC0-4hr 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 a Week 24 meal test.

Other:

Quality of life was measured via questionnaire.

**Statistical Methods**

The primary hypotheses tested were the superiority of vildagliptin (50 mg qd and 50 mg bid) over placebo, both vildagliptin and placebo combined with glimepiride, for the effect of reducing HbA1c 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 HbA1c assessment at baseline.

Critical secondary endpoint FPG was also analyzed on all four populations. Other secondary endpoints were analyzed for the Primary and Sensitivity ITT populations. The estimated treatment differences (vildagliptin - placebo) and 95% confidence intervals 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 HbA1c 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 child-bearing potential using a medically approved birth control method) patients with type 2 diabetes, aged 18- 80 years of age, with HbA1c 7.5- 11%, body mass index (BMI) 22- 45 kg/m2, and FPG < 270 mg/dL (15 mmol/L). Patients must have been receiving a sulfonylurea for at least three months at a stable dose (at least 7.5 mg glyburide qd, 7.5 mg glipizide qd, or 2 mg glimepiride qd) for a minimum of four weeks prior to Visit 1.

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; 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: alanine aminotransferase (ALT), aspartate aminotransferase (AST) greater than 3 times the upper limit of the normal range (ULN), direct bilirubin greater than 1.3 times ULN, 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 50 mg qd +glimepiride | Vildagliptin 50 mg bid +glimepiride | Placebo +glimepiride |
|---|---|---|---|
| Planned N | 115 | 115 | 115 |
| Randomised n | 170 | 169 | 176 |
| Completed n (%) | 144 (84.7) | 137 (81.1) | 132 (80.2) |
| Withdrawn n (%) | 26 (15.3) | 32 (18.9) | 44 (25.0) |
| Included in the primary analysis n (%) | 132 (77.6) | 132 (78.1) | 144 (81.8) |
| Withdrawn due to adverse events n (%) | 4 (2.4) | 5 (3.0) | 3 (1.7) |
| Withdrawn due to lack of efficacy n (%) | 7 (4.1) | 7 (4.1) | 17 (9.7) |
| Withdrawn for other reasons n (%) | 15 (8.8) | 20 (11.8) | 24 (13.6) |

**Demographic and Background Characteristics**

| | Vildagliptin 50 mg qd +glimepiride | Vildagliptin 50 mg bid +glimepiride | Placebo +glimepiride |
|---|---|---|---|
| N (Primary ITT) | 132 | 132 | 144 |
| Females:males (%) | 41% : 59% | 40% : 60% | 42% : 58% |
| Mean age, years (SD) | 58.6 (10.6) | 58.2 (11.07) | 57.9(10.46) |
| Mean weight, kg (SD) | 91.59 (18.46) | 87.31 (17.79) | 89.28(19.38) |
| Race<br>White n (%)<br>Black n (%)<br>Asian (Indian | <br>91 (68.9)<br>14 (10.6)<br>1 (0.8) | <br>93 (70.5)<br>11 (8.3)<br>2 (1.5) | <br>97 (67.4)<br>15 (10.4)<br>1 (0.7) |

| | | | |
|---|---|---|---|
| subcontinent) n (%)<br>Asian (non-Indian subcontinent) n (%)<br>Hispanic or Latino<br>Other n (%) | <br>1 (0.8)<br><br>24 (18.2)<br>1 (0.8) | <br>1 (0.8)<br><br>24 (18.2)<br>1 (0.8) | <br>0 (0)<br><br>27 (18.8)<br>4 (2.8) |
| Mean HbA1c % (SD) | 8.53 (0.89) | 8.55 (0.99) | 8.53 (1.01) |
| Mean duration of diabetes –yrs (SD) | 6.85 (5.16) | 6.66 (5.27) | 7.78 (5.8) |

**Primary Efficacy Result(s)**

| Treatment | n | Baseline mean (SE) | Adjusted mean change from baseline (SE) | Mean difference to Placebo + Glim (SE) | 95% CI | p-value |
|---|---|---|---|---|---|---|
| **Primary ITT population** | | | | | | |
| Vilda 50mg qd + Glim | 132 | 8.53 ( 0.08) | -0.58 ( 0.10) | -0.64 ( 0.13) | (-0.90,-0.39) | <0.001* |
| Vilda 50mg bid + Glim | 132 | 8.55 ( 0.09) | -0.63 ( 0.09) | -0.70 ( 0.13) | (-0.95,-0.44) | <0.001* |
| Placebo + Glim | 144 | 8.53 ( 0.08) | 0.07 ( 0.09) | | | |

**Secondary efficacy result(s)**

| | Vildagliptin 50 mg qd + glimepiride | Vildagliptin 50 mg bid + glimepiride | Placebo + glimepiride |
|---|---|---|---|
| Number (%) of patients who responded at endpoint, Primary ITT population | | | |
| HbA1c < 7%<br>P Value | 28 (21.2)<br>0.039 | 32 (24.8)<br>0.006 | 17 (12.0) |
| Reduction in HbA1c >= 0.7%<br>P value | 62 (47.)<br><0.001 | 67 (50.8)<br><0.001 | 28 (19.4) |
| Mean changes from baseline in HbA1c (%) at endpoint, Primary ITT pop. | | | |
| HbA1c <= 9% | -0.38; mean baseline=8.13 | -0.49; mean baseline=8.02 | 0.15; mean baseline=7.97 |
| HbA1c > 9% | -1.01; mean baseline=9.78 | -0.90; mean baseline=9.80 | 0.03; mean baseline=9.75 |

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

| Population/ Treatment group | n | Baseline mean (SE) | Adjusted mean change (SE) | Mean difference to comparator (SE) | 95% CI | p-value |
|---|---|---|---|---|---|---|
| **Primary ITT population** | | | | | | |
| Vilda 50mg qd + Glim | 132 | 10.50 ( 0.26) | -0.32 ( 0.24) | -0.50 ( 0.32) | (-1.13,0.13) | 0.118 |
| Vilda 50mg bid + Glim | 132 | 10.47 ( 0.24) | -0.44 ( 0.23) | -0.61 ( 0.32) | (-1.24,0.01) | 0.056 |
| Placebo + Glim | 144 | 10.33 ( 0.24) | 0.18 ( 0.22) | | | |

## Safety Results

## Adverse Events by System Organ Class

| Primary system organ class | Vilda 50mg qd + Glim N=170 n (%) | Vilda 50mg bid + Glim N=169 n (%) | Placebo + Glim N=176 n (%) |
|---|---|---|---|
| Any Primary system organ class | 114 (67.1) | 112 (66.3) | 113 (64.2) |
| Blood and lymphatic system disorders | 1 ( 0.6) | 3 ( 1.8) | 2 ( 1.1) |
| Cardiac disorders | 5 ( 2.9) | 4 ( 2.4) | 6( 3.4) |
| Congenital, familial and genetic disorders | 1 ( 0.6) | 0 ( 0.0) | 2 ( 1.1) |
| Ear and labyrinth disorders | 1 ( 0.6) | 6 ( 3.6) | 2 ( 1.1) |
| Endocrine disorders | 1 ( 0.6) | 0 ( 0.0) | 1 ( 0.6) |
| Eye disorders | 7 ( 4.1) | 5 ( 3.0) | 2 ( 1.1) |
| Gastrointestinal disorders | 23 (13.5) | 27 (16.0) | 23 (13.1) |
| General disorders and administration site conditions | 26 (15.3) | 21 (12.4) | 17 ( 9.7) |
| Hepatobiliary disorders | 0 ( 0.0) | 1 ( 0.6) | 2 ( 1.1) |
| Immune system disorders | 3 ( 1.8) | 1 ( 0.6) | 1 ( 0.6) |
| Infections and infestations | 47 (27.6) | 45 (26.6) | 44 (25.0) |
| Injury, poisoning and procedural complications | 13 ( 7.6) | 13 ( 7.7) | 11 ( 6.3) |
| Investigations | 8 ( 4.7) | 6 ( 3.6) | 10 ( 5.7) |
| Metabolism and nutrition disorders | 10 ( 5.9) | 8 ( 4.7) | 4 ( 2.3) |
| Musculoskeletal and connective tissue disorders | 25 (14.7) | 20 (11.8) | 28 (15.9) |
| Neoplasms benign, malignant, unspecified (incl cysts / polyps) | 3 ( 1.8) | 1 ( 0.6) | 3 ( 1.7) |
| Nervous system disorders | 32 (18.8) | 26 (15.4) | 28 (15.9) |
| Psychiatric disorders | 6 ( 3.5) | 8 ( 4.7) | 11 ( 6.3) |
| Renal and urinary disorders | 5 ( 2.9) | 3 ( 1.8) | 4 ( 2.3) |
| Reproductive system and breast disorders | 3 ( 1.8) | 2 ( 1.2) | 3 ( 1.7) |
| Respiratory, thoracic & mediastinal disorders | 9 ( 5.3) | 6 ( 3.6) | 13 ( 7.4) |
| Skin and subcutaneous tissue disorders | 18 (10.6) | 14 ( 8.3) | 10 ( 5.7) |
| Surgical and medical procedures | 0 ( 0.0) | 1 ( 0.6) | 1 ( 0.6) |
| Vascular disorders | 7 ( 4.1) | 5 ( 3.0) | 2 ( 1.1) |

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

| Preferred Term | Vilda 50mg qd + Glim N=170 n (%) | Vilda 50mg bid + Glim N=169 n (%) | Placebo + Glim N=176 n (%) |
|---|---|---|---|
| Any Preferred term | 114 (67.1) | 112 (66.3) | 113 (64.2) |
| Asthenia | 14 ( 8.2) | 10 ( 5.9) | 4 ( 2.3) |
| Nasopharyngitis | 8 ( 4.7) | 10 ( 5.9) | 4 ( 2.3) |
| Upper respiratory tract infection | 11 ( 6.5) | 9 ( 5.3) | 3 ( 1.7) |
| Dizziness | 15 ( 8.8) | 8 ( 4.7) | 7 ( 4.0) |
| Influenza | 7 ( 4.1) | 8 ( 4.7) | 13 ( 7.4) |
| Headache | 7 ( 4.1) | 6 ( 3.6) | 4 ( 2.3) |
| Hypoglycemia | 2 ( 1.2) | 6 ( 3.6) | 1 ( 0.6) |
| Nausea | 3 ( 1.8) | 6 ( 3.6) | 6 ( 3.4) |
| Tremor | 12 ( 7.1) | 6 ( 3.6) | 5 ( 2.8) |
| Arthralgia | 3 ( 1.8) | 5 ( 3.0) | 5 ( 2.8) |

**Serious Adverse Events and Deaths**

| | Vilda 50mg qd + Glim N=170 n (%) | Vilda 50mg bid + Glim N=169 n (%) | Placebo + Glim N=176 n (%) |
|---|---|---|---|
| Deaths | 0 ( 0.0) | ( 0.0) | 0 ( 0.0) |
| SAEs | 5 ( 2.9) | 4 ( 2.4) | 9 ( 5.1) |
| Discontinuation due to AEs | 4 ( 2.4) | 5 ( 3.0) | 3 ( 1.7) |
| AEs causing dose adjustment or study drug interruption | 4 ( 2.4) | 6 ( 3.6) | 6 ( 3.4) |
| Clinically significant CCV AEs | 3 ( 1.8) | 0 ( 0.0) | 1 ( 0.6) |
| Clinically significant IM AEs | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.6) |
| Other clinically significant AEs - Total | 21 (12.4) | 28 (16.6) | 28 (15.9) |
| Mild | 13 ( 7.6) | 19 (11.2) | 19 (10.8) |
| Moderate | 7 ( 4.1) | 9 ( 5.3) | 9( 5.1) |
| Severe | 1 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |

**Other Relevant Findings**

Not applicable

**Date of Clinical Trial Report**

14 December 2005

**Date Inclusion on Novartis Clinical Trial Results Database**

21 March 2007

**Date of Latest Update**

21 January 2009