Sponsor Novartis
Generic Drug Name Vildagliptin
Therapeutic Area of Trial Type 2 diabetes
Approved Indication Investigational
Study Number CLAF237A2329
Title A Multicenter, Double-Blind, Randomized, Active Controlled, Parallel Group Study to Compare the Effect of 12 Weeks Treatment with LAF237 50 mg BID to 50 mg QD in Patients with Type 2 Diabetes with HbA1c 9-11%
Phase of Development Phase III
Study Start/End Dates 31-Mar-2004 to 30-Jun-2005
Study Design/Methodology This was a multicenter, double-blind, randomized, parallel group, active controlled study of the safety and efficacy of two dosing regimens of vildagliptin compared to pioglitazone in patients with type 2 diabetes. Patients were randomized to receive either vildagliptin 50 mg qd, 50 mg bid, or pioglitazone 30 mg qd in a ratio for 12 weeks.
Centres 46 centers in 8 countries: Brazil (8), Canada (8), Czech Republic (4), India (3), Italy (8), Slovakia (9), Taiwan (4) and Turkey (2).
Publication Ongoing

Objectives

Primary outcome/efficacy objective(s)

To compare the efficacy of vildagliptin 50 mg qd and vildagliptin 50 mg bid in reducing HbA1c after 12 weeks treatment in patients with type 2 diabetes.

Secondary outcome/efficacy objective(s)

1. To compare the responder rates with vildagliptin 50 mg bid and vildagliptin 50 mg qd after 12 weeks of treatment in patients with type 2.

2. To compare the responder rates with vildagliptin 50 mg bid and pioglitazone 30 mg qd after 12 weeks of treatment in patients with type 2 diabetes .

3. To explore the efficacy of vildagliptin 50 mg bid compared to vildagliptin 50 mg qd in reducing FPG after 12 weeks of treatment in patients with type 2 diabetes.

4. To explore the mechanism of action of vildagliptin by comparing the effect of vildagliptin 50 mg bid compared to vildagliptin 50 mg qd in improving beta cell function and reducing insulin resistance after 12 weeks of treatment in patients with type 2 diabetes.

5. To compare the effect of vildagliptin 50 mg bid and pioglitazone 30 mg qd on body weight after 12 weeks of treatment in patients with type 2 diabetes .

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

vildagliptin 50 mg tablets, dosed daily (qd) and vildagliptin twice daily (bid), for oral administration

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

pioglitazone 15 mg capsules, dosed qd, for oral administration

placebo for both vildagliptin 50 mg tablets administered in the same manner as vildagliptin

placebo for pioglitazone 15 mg capsules, administered in the same manner as pioglitazone

Criteria for Evaluation

Primary efficacy:

The primary efficacy variable was HbA1c measured by High Performance Liquid Chromatography (HPLC)

Secondary efficacy:

The secondary efficacy variables included: fasting plasma glucose, fasting lipids (triglycerides, total cholesterol, calculated LDL, HDL, calculated VLDL, calculated non-HDL); body weight; beta-cell function (fasting proinsulin, fasting proinsulin/insulin ratio, HOMA B); insulin resistance (fasting insulin, HOMA IR); responder rates: HbA1c absolute reduction from baseline at endpoint = 0.7%.

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:

Pharmacokinetic assessments were not performed in this study.

Other: N/A

Statistical Methods

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 50 mg bid - vildagliptin 50 mg qd) and its 95% confidence interval were derived from the least square mean change from baseline ('adjusted mean') of each treatment group. The primary hypothesis was based on the Primary intent-to-treat (ITT) population. This population consists of all randomized patients who had a qualifying HbA1c assay result, prior to randomization, from an NGSP level 1 certified laboratory = 7.4%; received at least one dose of study drug and; had a baseline and at least one post-baseline HbA1c value from an NGSP level 1 certified laboratory.

To provide a context for interpreting any observed difference between the two dose groups, an

exploratory comparison between the vildagliptin 50 mg bid and the pioglitazone 30 mg qd group was made in a similar way as between both vildagliptin groups. Secondary efficacy endpoints were also analyzed for the Primary ITT population in a similar way as for the primary efficacy analysis. Demographic and background data as well as safety data were summarized by treatment group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria included male and female (non-fertile or of childbearing potential using a medically approved birth control method) drug-naïve patients aged = 18 years, with an HbA1c of 9-11% at visit 1. Fasting C-peptide must have been > 0.6 ng/mL (0.2 nmol/L) and body mass index (BMI) in the range of 22-45 kg/m2 inclusive, at 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 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 2.5 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

	Vilda 50 mg bid	**Vilda 50 mg qd**	**Pio 30 mg qd**	**Total**
	n (%)	n (%)	n (%)	n (%)
Planned	100	100	50	250
Randomized population	N=109	N=109	N=55	N=273
Completed	101 (92.7)	97 (89.0)	46 (83.6)	244 (89.4)
Withdrawn	8 (7.3)	12 (11.0)	9 (16.4)	29 (10.6)
Included in the primary analysis	101	102	46	249
Withdrawn due to adverse events	2 (1.8)	1 (0.9)	2 (3.6)	5 (1.8)
Withdrawn due to lack of efficacy	1 (0.9)	3 (2.8)	1 (1.8)	5 (1.8)
Withdrawn for other reasons	5 (5.0)	8 (8.2)	6 (13.0)	19 (7.6)

Demographic and Background Characteristics

	Vilda 50 mg bid	Vilda 50 mg qd	Pio 30 mg qd	Total
N (Primary ITT)	101	102	46	249
Females:males (%)	41/59	38/62	44/56	40/60
Mean age, years	52.07	52.29	53.70	52.46
Mean weight, kg	82.21	79.29	79.16	80.45
Race (%)				
Asian (Indian Subcontinent)	17 (16.8)	17 (16.7)	6 (13.0)	40 (16.1)
Asian (non Indian Subcontinent)	9 (8.9)	11 (10.8)	5 (10.9)	25 (10.0)
Black	0 (0.0)	1 (1.0)	2 (4.3)	3 (1.2)
Caucasian	66 (65.3)	67 (65.7)	32 (69.6)	165 (66.3)
Hispanic or Latino	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)
Other	8 (7.9)	6 (5.9)	1 (2.2)	15 (6.0)
Mean HbA1c (%)	9.96	9.97	9.98	9.96
Mean duration of diabetes (yr)	1.80	2.16	1.84	1.95

Primary Efficacy Result(s)

	Vildagliptin 50 mg bid	Vildagliptin 50 mg qd
Change in HbA1c (%) from baseline to endpoint (Primary ITT population)	-1.56	-1.13
P value	0.035	

Secondary efficacy result(s)

	Vildagliptin 50 mg bid	Vildagliptin 50 mg qd
Number (%) of patients with reduction in HbA1c = 0.7%	81 (80.2)	66 (64.7)
P value	0.014	
Change from baseline in fasting plasma glucose (mmol/L)	-1.61	-1.02
P value	0.089	
Change from baseline in HOMA B	19.34	5.93
P Value	0.320	
Change from baseline in HOMA IR	-1.75	-0.08
P value	0.403	

	Vildagliptin 50 mg bid	Pioglitazone 30 mg qd
Number (%) of patients with reduction in HbA1c = 0.7% P value	81 (80.2) 0.506	39 (84.8)
Change from baseline in body weight (kg) P value	-0.08 0.472	-0.43

Safety Results

Adverse Events by System Organ Class

Primary system organ class	Vilda 50 mg bid N=107 n (%)	Vilda 50 mg qd N=108 n (%)	Pio 30 mg qd N=55 n (%)
Any Primary system organ class	46 (43.0)	43 (39.8)	25 (45.5)
Blood and lymphatic system disorders	0 (0.0)	1 (0.9)	1 (1.8)
Cardiac disorders	1 (0.9)	2 (1.9)	2 (3.6)
Ear and labyrinth disorders	1 (0.9)	0 (0.0)	0 (0.0)
Eye disorders	1 (0.9)	3 (2.8)	0 (0.0)
Gastrointestinal disorders	9 (8.4)	5 (4.6)	6 (10.9)
General disorders & administration site conditions	7 (6.5)	6 (5.6)	6 (10.9)
Hepatobiliary disorders	0 (0.0)	1 (0.9)	0 (0.0)
Infections and infestations	14 (13.1)	14 (13.0)	7 (12.7)
Injury, poisoning and procedural complications	2 (1.9)	1 (0.9)	1 (1.8)
Investigations	1 (0.9)	1 (0.9)	1 (1.8)
Metabolism and nutrition disorders	4 (3.7)	3 (2.8)	1 (1.8)
Musculoskeletal and connective tissue disorders	13 (12.1)	11 (10.2)	8 (14.5)
Neoplasms benign, malignant and unspecified	0 (0.0)	2 (1.9)	0 (0.0)
Nervous system disorders	9 (8.4)	10 (9.3)	6 (10.9)
Psychiatric disorders	3 (2.8)	0 (0.0)	0 (0.0)
Renal and urinary disorders	2 (1.9)	0 (0.0)	2 (3.6)
Reproductive system and breast disorders	1 (0.9)	0 (0.0)	1 (1.8)
Respiratory, thoracic and mediastinal disorders	1 (0.9)	2 (1.9)	1 (1.8)
Skin and subcutaneous tissue disorders	7 (6.5)	3 (2.8)	3 (5.5)
Vascular disorders	6 (5.6)	2 (1.9)	2 (3.6)

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

Preferred term	Vilda 50 mg bid N=107 n (%)	Vilda 50 mg qd N=108 n (%)	Pio 30 mg qd N=55 n (%)
Any Preferred term	46 (43.0)	43 (39.8)	25 (45.5)
Dizziness	5 (4.7)	6 (5.6)	2 (3.6)
Headache	5 (4.7)	4 (3.7)	3 (5.5)
Back pain	4 (3.7)	3 (2.8)	1 (1.8)
Hypertension	4 (3.7)	2 (1.9)	2 (3.6)
Alopecia	3 (2.8)	1 (0.9)	0 (0.0)
Arthralgia	3 (2.8)	3 (2.8)	2 (3.6)
Pain in extremity	3 (2.8)	2 (1.9)	1 (1.8)
Viral infection	3 (2.8)	0 (0.0)	0 (0.0)
Influenza	2 (1.9)	3 (2.8)	2 (3.6)
Edema peripheral	2 (1.9)	1 (0.9)	2 (3.6)

Serious Adverse Events and Deaths
Number (%) of patients with serious or clinically significant AEs (Safety population)

Preferred Term	Vilda 50 mg bid N=107 n (%)	Vilda 50 mg qd N=108 n (%)	Pio 30 mg qd N=55 n (%)
Deaths	0	1 (0.9)	0
SAEs	0	3 (2.8)	0
Discontinuation due to AEs	2 (1.9)	2 (1.9)	2 (3.6)
AEs causing dose adjustment or study drug interruption	1 (0.9)	1 (0.9)	0 (0.0)
Clinically significant CCV AEs	0 (0.0)	0 (0.0)	0 (0.0)
Clinically significant IM AEs	0 (0.0)	1 (0.9)	0 (0.0)
Other clinically significant AEs	11 (10.3)	10 (9.3)	10 (18.2)

One patient randomized to vildagliptin 50 mg qd died on day 67 of the study, 29 days after discontinuation of the study drug. The cause of death was reported as pyopneumothorax secondary to underlying pulmonary tuberculosis. This event was not suspected as being related to the study medication by the investigator. Three patients experienced at least one SAE. One of these was the patient who died as a result of pyopneumothorax secondary to underlying pulmonary tuberculosis; one patient had fever, pancytopenia and an increase in liver enzymes, and one patient had newly diagnosed rectal carcinoma and intestinal hemorrhage. None of these SAEs were suspected to be related to study drug.

Other Relevant Findings
There were no hypoglycemic events reported in any of the treatment groups.
Date of Clinical Trial Report
9 November 2005
Date Inclusion on Novartis Clinical Trial Results Database
10 April 2007
Date of Latest Update
16 March 2007

Sponsor

Novartis

Generic Drug Name

Vildagliptin (LAF237)

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Investigational

Study Number

CLAF237A2329E1

Title

A 52 week extension to a multicenter, double-blind, randomized, active controlled, parallel group study to compare the effect of 12 weeks treatment with LAF237 50 mg BID to 50 mg OD in patients with type 2 diabetes with HbA_{1c} 9-11%

Phase of Development

Phase III

Study Start/End Dates

30 June 2004 to 21 June 2006

Study Design/Methodology

This was a 52-week, multicenter, open-label extension study with one treatment arm. Patients who completed the 12-week core protocol with an HbA_{1c} reduction of at least 0.3 absolute unit compared to baseline were enrolled in this extension study. All patients received a combination of vildagliptin 50 mg qd and pioglitazone 30 mg qd independent of their treatment in the core study. From week 24 onwards, vildagliptin was to be titrated to 50 mg bid if (FPG) was >180 mg/dL (10 mmol/L). The last visit of the core study was also the first visit of the extension study. Eligible patients then completed 5 additional visits over a period of 52 weeks of treatment with vildagliptin and pioglitazone.

Centres

A total of 38 centers in 8 countries screened at least one patient: Brazil (8), Canada (6), Czech Republic (4), India (2), Italy (6), Slovakia (8), Taiwan (2) and Turkey (2).

Publication

None

Objectives

Primary objective(s)

Safety in combination with pioglitazone after 52 weeks
Change from extension baseline HbA1c at 52 weeks

Secondary objective(s)

Change from extension baseline in fasting plasma glucose at 52 weeks
Change from extension baseline in fasting lipids at 52 weeks
Change from extension baseline in bodyweight at 52 weeks
Change from extension baseline in (HOMA B) at 52 weeks
Change form extension baseline in (HOMA IR) at 52 weeks

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

Vildagliptin 50 mg oral tablets for once daily administration (twice daily if FPG>180mg/dL after Week 24 visit); pioglitazone 15 mg oral capsules (two tablets before the breakfast meal)

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

None

Criteria for Evaluation

Primary variables

The primary efficacy variable was HbA1c from extension baseline (end of core study value) to the end of the study

Secondary variables

Fasting plasma glucose
Fasting plasma lipids
Body weight
Beta-cell function: HOMA B
Insulin resistance: HOMA IR

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events including serious adverse events (during the extension phase, i.e. post-Week 12 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 electrocardiograms. Full details are provided in the core study protocol.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

Descriptive statistics were provided to summarize both safety and efficacy data. Safety was assessed over the 52 weeks of extension treatment period in the extension safety population by evaluating the frequency of treatment emergent adverse events, determining the number of patients with laboratory values that fall outside of pre-determined ranges, and the frequency and severity of hypoglycemic events. For efficacy variables, the mean change from Week 12 of the core study at endpoint along with 95% confidence interval was presented for the Extension intent-to-treat (ITT) and Per Protocol Populations.

Study Population: Inclusion/Exclusion Criteria and Demographics

In addition to the inclusion and exclusion criteria in the core study, eligible patients for the extension study were defined by the following inclusion/exclusion criteria

Inclusion criteria:

1. Patients who completed the 12-week core protocol LAF237A2329, with an HbA1c reduction of at least 0.3 absolute unit compared to baseline were enrolled in this extension study
2. Written informed consent to participate in the extension study.
3. Ability to comply with all study requirements.

Exclusion criteria

1. Premature discontinuation from the core study.
2. Concomitant medical conditions that interfere with the interpretation of study results as defined in the core protocol.
3. Failure to comply with the core study protocol.
4. Any patients that the primary investigator decided to not participate in the extension study.

Number of Subjects

Patient disposition (Extension population)

Disposition Reason	Vilda 50mg qd (core) + combination (ext) N = 78 n (%)	Vilda 50mg bid (core) + combination (ext) N = 87 n (%)	Pio 30mg qd (core) +combination (ext) N = 35 n (%)	Vilda 50mg qd/bid + Pio 30mg qd (total) N = 200 n (%)
Completed	62 (79.5)	65 (74.7)	28 (80.0)	155 (77.5)
Discontinued	16 (20.5)	22 (25.3)	7 (20.0)	45 (22.5)
Administrative problems	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.5)
Adverse event(s)	3 (3.8)	4 (4.6)	2 (5.7)	9 (4.5)
Lost to follow-up	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Protocol violation	0 (0.0)	2 (2.3)	0 (0.0)	2 (1.0)
Subject withdrew consent	3 (3.8)	4 (4.6)	2 (5.7)	9 (4.5)
Unsatisfactory therapeutic effect	10 (12.8)	11 (12.6)	2 (5.7)	23 (11.5)

Demographic and Background Characteristics

Patient baseline demographic characteristics at core baseline (Extension population)

Demographic Variable	Vilda 50mg qd (core) + combination (ext) N=78	Vilda 50mg bid (core) + combination (ext) N=87	Pio 30 mg qd (core) + combination (ext) N=35	Vilda 50 mg qd/bid + Pio 30 mg qd (total) N=200
Mean age, years (SD)	52.41 (9.81)	51.68 (11.76)	51.31 (10.48)	51.90 (10.77)
Females:males	31:47	37:50	12:23	80:120
Race				
White	53 (67.9)	59 (67.8)	26 (74.3)	138 (69.0)
Black	1 (1.3)	0 (0.0)	1 (2.9)	2 (1.0)
Asian (non indian subcontinent	5 (6.4)	3 (3.4)	1 (2.9)	9 (4.5)
Asian (indian subcontinent)	12 (15.4)	16 (18.4)	6 (17.1)	34 (17.0)
Hispanic or latino	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Other	7 (9.0)	8 (9.2)	1 (2.9)	16 (8.0)
Mean weight, kg (SD)	81.06 (17.04)	84.77 (18.10)	83.46 (12.82)	83.09 (16.88)

Patient baseline background characteristics at core baseline (Extension population)

	Vilda 50mg qd (core) + combination (ext) N=78	Vilda 50mg bid (core) + combination (ext) N=87	Pio 30mg qd (core) + combination (ext) N=35	Vilda 50 mg qd/bid +Pio 30mg qd (total) N=200
HbA1c Mean (SD)	9.76(0.92)	9.82(0.86)	9.90(1.06)	9.81(0.91)
FPG (mmol/L) mean (SD)	11.12 (2.92)	11.15 (3.09)	11.16 (2.76)	11.14 (2.95)
Duration of type 2 diabetes-years Mean:SD	2.02(2.79	1.75(3.19)	1.81(3.46)	1.87(3.08)

Primary Objective Result(s)

Mean change in HbA1c (%) from extension baseline to endpoint (Extension ITT population)

Treatment group	n	Corresponding baseline mean (SE)	Mean change (CI)
Extension ITT population			
Vilda 50mg qd	78	8.40 (0.16)	-0.99 (-1.18, -0.81)
Vilda 50mg bid	83	8.11 (0.16)	-0.60 (-0.82, -0.38)
Pio 30mg qd	33	8.17 (0.29)	-1.03 (-1.34, -0.72)
Total	194	8.24 (0.11)	-0.83 (-0.96, -0.70)

Secondary Objective Result(s)

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

Treatment group	n	Corresponding baseline mean (SE)	Mean change (CI)
Extension ITT population			
Vilda 50mg qd	78	9.88 (0.31)	-1.45 (-1.90, -0.99)
Vilda 50mg bid	84	9.40 (0.32)	-0.84 (-1.42, -0.27)
Pio 30mg qd	34	8.89 (0.44)	-0.78 (-1.33, -0.23)
Total	196	9.50 (0.20)	-1.07 (-1.39, -0.75)

Mean percent change in fasting lipid parameters from extension baseline to endpoint (Extension ITT population)

Parameter/Treatment group	n	Corresponding baseline mean (SE)	Mean percent change (CI)
Triglycerides (mmol/L)			
Vilda 50mg qd	77	1.79 (0.10)	9.51 (-3.08, 22.10)
Vilda 50mg bid	84	2.37 (0.27)	-2.74 (-12.36, 6.87)
Pio 30mg qd	34	1.74 (0.17)	0.68 (-11.82, 13.17)
Total	195	2.03 (0.13)	2.69 (-4.08, 9.46)
Total Cholesterol (mmol/L)			
Vilda 50mg qd	77	5.00 (0.12)	6.75 (0.85, 12.65)
Vilda 50mg bid	84	5.16 (0.13)	3.95 (0.87, 7.04)
Pio 30mg qd	34	5.06 (0.23)	1.19 (-3.54, 5.93)
Total	195	5.08 (0.08)	4.58 (1.80, 7.35)
LDL cholesterol (mmol/L)			
Vilda 50mg qd	75	3.01 (0.11)	6.19 (-0.68, 13.05)
Vilda 50mg bid	77	3.10 (0.12)	5.28 (0.63, 9.93)
Pio 30mg qd	32	2.86 (0.17)	4.48 (-3.19, 12.15)
Total	184	3.02 (0.07)	5.51 (1.92, 9.11)
HDL cholesterol (mmol/L)			
Vilda 50mg qd	77	1.20 (0.04)	10.50 (6.35, 14.64)
Vilda 50mg bid	84	1.18 (0.03)	11.10 (7.79, 14.40)
Pio 30mg qd	34	1.31 (0.05)	3.65 (-1.02, 8.32)
Total	195	1.21 (0.02)	9.56 (7.25, 11.87)

Mean change in body weight (kg) from extension baseline to endpoint (Extension ITT population)

Treatment group	n	Corresponding baseline mean (SE)	Mean change (CI)
Vilda 50mg qd	77	79.52 (1.89)	3.94 (3.05, 4.82)
Vilda 50mg bid	84	84.93 (2.00)	4.72 (3.59, 5.84)
Pio 30mg qd	33	81.42 (2.11)	4.34 (2.66, 6.01)
Total	194	82.18 (1.21)	4.34 (3.69, 5.00)

Baseline = extension baseline, and refers to the measurement obtained at the end of the core study (i.e. Week 12). If Week 12 value is missing carry forward the last on-treatment observation (scheduled or unscheduled) from Week 8 onwards.
Endpoint is the final available post-Week 12 (Visit 5) assessment up to the last regular scheduled visit.

Mean change in beta cell function/insulin resistance parameters from extension baseline to endpoint (Extension ITT population)

Parameter/Treatment group	n	Corresponding baseline mean (SE)	Mean change (CI)
Homa B			
Vilda 50mg qd	78	57.00 (7.05)	7.94 (-4.06, 19.94)
Vilda 50mg bid	83	83.14 (21.65)	6.22 (-18.89, 31.33)
Pio 30mg qd	34	48.45 (5.70)	1.78 (-6.71, 10.28)
Total	195	66.64 (9.71)	6.14 (-5.53, 17.80)
Homa IR			
Vilda 50mg qd	78	5.67 (0.36)	-0.87 (-2.70, 0.95)
Vilda 50mg bid	83	12.06 (5.87)	-6.87 (-17.18, 3.44)
Pio 30mg qd	34	4.72 (0.99)	-0.49 (-1.22, 0.24)
Total	195	8.22 (2.51)	-3.36 (-7.78, 1.06)

Safety Results

Adverse Events by System Organ Class

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

Primary system organ class	Vilda 50mg qd (core) + combination (ext) N = 78 n (%)	Vilda 50mg bid (core) + combination (ext) N = 87 n (%)	Pio 30mg qd (core) +combination (ext) N = 35 n (%)	Vilda 50mg qd/bid + Pio 30mg qd (total) N = 200 n (%)
Any primary system organ class	34 (43.6)	45 (51.7)	20 (57.1)	99 (49.5)
Blood and lymphatic system disorders	3 (3.8)	0 (0.0)	1 (2.9)	4 (2.0)
Cardiac disorders	1 (1.3)	5 (5.7)	2 (5.7)	8 (4.0)
Ear and labyrinth disorders	1 (1.3)	1 (1.1)	1 (2.9)	3 (1.5)
Eye disorders	2 (2.6)	4 (4.6)	3 (8.6)	9 (4.5)
Gastrointestinal disorders	5 (6.4)	9 (10.3)	2 (5.7)	16 (8.0)
General disorders and administration site conditions	5 (6.4)	8 (9.2)	4 (11.4)	17 (8.5)
Hepatobiliary disorders	2 (2.6)	2 (2.3)	0 (0.0)	4 (2.0)
Infections & infestations	10 (12.8)	15 (17.2)	6 (17.1)	31 (15.5)
Injury, poisoning and procedural complications	2 (2.6)	5 (5.7)	1 (2.9)	8 (4.0)
Investigations	3 (3.8)	5 (5.7)	2 (5.7)	10 (5.0)
Metabolism & nutrition disorders	3 (3.8)	5 (5.7)	3 (8.6)	11 (5.5)
Musculoskeletal and connective tissue disorders	9 (11.5)	18 (20.7)	7 (20.0)	34 (17.0)
Nervous system disorders	9 (11.5)	12 (13.8)	6 (17.1)	27 (13.5)
Psychiatric disorders	1 (1.3)	2 (2.3)	2 (5.7)	5 (2.5)
Renal and urinary disorders	2 (2.6)	1 (1.1)	1 (2.9)	4 (2.0)
Reproductive system and breast disorders	2 (2.6)	1 (1.1)	1 (2.9)	4 (2.0)
Respiratory, thoracic and mediastinal disorders	2 (2.6)	5 (5.7)	2 (5.7)	9 (4.5)
Skin and subcutaneous tissue disorders	3 (3.8)	3 (3.4)	1 (2.9)	7 (3.5)
Vascular disorders	2 (2.6)	4 (4.6)	2 (5.7)	8 (4.0)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category.

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

Number (%) of patients reporting common AEs by preferred term (Extension Safety population)

Preferred term	Vilda 50mg qd (core) + combination (ext) N = 78 n (%)	Vilda 50mg bid (core) + combination (ext) N = 87 n (%)	Pio 30mg qd (core) +combination (ext) N = 35 n (%)	Vilda 50mg qd/bid + Pio 30mg qd (total) N = 200 n (%)
Any AE	34 (43.6)	45 (51.7)	20 (57.1)	99 (49.5)
Back pain	2 (2.6)	7 (8.0)	2 (5.7)	11 (5.5)
Dizziness	4 (5.1)	5 (5.7)	2 (5.7)	11 (5.5)
Nasopharyngitis	3 (3.8)	5 (5.7)	2 (5.7)	10 (5.0)
Edema peripheral	4 (5.1)	6 (6.9)	0 (0.0)	10 (5.0)
Weight increased	3 (3.8)	4 (4.6)	2 (5.7)	9 (4.5)
Headache	3 (3.8)	2 (2.3)	3 (8.6)	8 (4.0)
Arthralgia	1 (1.3)	4 (4.6)	1 (2.9)	6 (3.0)
Hypertension	1 (1.3)	3 (3.4)	2 (5.7)	6 (3.0)
Pain in extremity	2 (2.6)	3 (3.4)	1 (2.9)	6 (3.0)
Urinary tract infection	1 (1.3)	4 (4.6)	1 (2.9)	6 (3.0)

Serious Adverse Events and Deaths

Number of patients with SAEs during the extension phase by preferred term (Extension Safety population)

Preferred term	Vilda 50mg qd (core) + combination (ext) N = 78 n (%)	Vilda 50mg bid (core) + combination (ext) N = 87 n (%)	Pio 30mg qd (core) +combination (ext) N = 35 n (%)	Vilda 50mg qd/bid + Pio 30mg qd (total) N = 200 n (%)
Any SAE	3 (3.8)	6 (6.9)	3 (8.6)	12 (6.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.5)
Angina unstable	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.5)
Back pain	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Cardiac failure congestive	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Cerebrovascular accident	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Diarrhea	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.5)
Hepatic cirrhosis	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Hyperglycemia	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Lower limb fracture	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Pulmonary edema	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Retinopathy proliferative	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Rib fracture	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Road traffic accident	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Vomiting	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Whiplash injury	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)

No deaths were reported during the study extension.

Other Relevant Findings

There were no hypoglycemic events reported in the study extension.

Date of Clinical Trial Report

4 December 2006

Date Inclusion on Novartis Clinical Trial Results Database

30 October 2007

Date of Latest Update

29 October 2007