Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Investigational

Study Number

CLAF237A2310

Title

A multicenter, double-blind, randomized, active controlled study to compare the effect of long term treatment with LAF237 50 mg bid to gliclazide up to 320 mg daily in drug naïve patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

27-Jan-2005 to 11-Mar-2008

Study Design/Methodology

This was a multicenter, randomized, double-blind, active controlled study. Drug naïve patients with type 2 diabetes (HbA1c 7.5%-11%) were randomized to LAF237 50 mg bid or gliclazide up to 320 mg daily in a ratio of 1:1. Each patient attended one screening visit (Week -2) where the inclusion/exclusion criteria were assessed. Eligible patients were then randomized at visit 2 (Baseline; Day 1) and completed 13 additional visits over a period of 104 weeks of treatment with LAF237 or gliclazide. Telephone had been made at Week 46, to patient by site to ensure that patient was checked for any specific symptoms related to their liver function tests that may require additional blood test investigation. A final visit took place after a 1-week active-treatment free period at Week 105.

Centres

151 centers, Argentina (7), Brazil (3), Colombia (4), Germany (10), Denmark (7), Spain (20), UK/Ireland (18), Guatemala (3), Italy (23), Poland (5), Portugal (4), Romania (10), Russia (12), Turkey (8), Venezuela (3), South Africa (14)

Publication

Foley JE, Sreenan S. Efficacy and safety comparison between the DPP-4 inhibitor vildagliptin and the sulfonylurea gliclazide after two years of monotheraphy in drug-naïve patients with type 2 diabetes.

Horm Metab Res. 2009 Dec;41(12):905-9 Epub 2009 Aug 24.
PMID: 19705345

Objectives

Primary Objective

- To compare the efficacy of vildagliptin in patients with type 2 diabetes by testing the hypothesis that the HbA1c reduction with vildagliptin is not inferior to that with gliclazide after 104 weeks of treatment.

Secondary objectives

- To compare the safety of vildagliptin in patients with type 2 diabetes by showing that treatment with vildagliptin has a similar adverse event profile compared to gliclazide after 52 and 104 weeks of treatment.
- To compare the efficacy of vildagliptin in patients with type 2 diabetes by testing the hypothesis that the FPG reduction with vildagliptin is not inferior to that with gliclazide after 104 weeks of treatment.
- To compare the efficacy of vildagliptin in patients with type 2 diabetes by showing that the responder rates with vildagliptin are similar to those with gliclazide after 104 weeks of treatment.

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

Vildagliptin 50 mg bid

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

Gliclazide up to 320mg daily

Criteria for Evaluation

Primary Efficacy Parameter

The primary efficacy variable was HbA_{1c}, measured by Ion exchange High Performance Liquid Chromatography (HPLC).

Secondary Efficacy Parameters

- Fasting plasma glucose
- Fasting lipids: triglycerides, FFA, apo-A, apo-B, total cholesterol, calculated LDL, HDL, calculated VLDL, non-HDL cholesterol
- Body weight
- Beta-cell function: fasting proinsulin, fasting proinsulin/insulin ratio
- Insulin resistance: fasting insulin, HOMA IR
- Responder rates:
  - Endpoint $HbA_{1c} < 7\%$
  - $HbA_{1c} < 7\%$ in patients with baseline $HbA_{1c} <= 8\%$

- Endpoint HbA_{1c} <= 6.5%
- HbA_{1c} absolute reduction from baseline at endpoint >= 1%
- HbA_{1c} absolute reduction from baseline at endpoint >= 1% in patients with baseline HbA_{1c} > 9%
- HbA_{1c} absolute reduction from baseline at endpoint >= 0.7%
- HbA_{1c} absolute reduction from baseline at endpoint >= 0.5%

- Coefficient of failure for HbA_{1c} (24 weeks to 104 weeks).
- Post prandial parameters, e.g. area under the 0-4 hour prandial curve (AUC_{0-4hr}) for plasma glucose, insulin and C-peptide, 2-hr absolute glucose level, and area under the 0-2 hour prandial curve (AUC_{0-2hr}) for glucagon and active and total GLP-1, following a liquid meal challenge in a subset of patients.

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

Primary efficacy evaluation

The primary efficacy variable is change from baseline in HbA_{1c} (unit in %) at Week 104 or at the final visit with an HbA_{1c} measurement for those patients who do not have a Week 104 HbA_{1c} measurement, or the last visit with an HbA_{1c} measurement prior to start of rescue medication use. The primary population is the Per-Protocol population, censored at onset of rescue-medication use.

Method of statistical analysis

The test for the non-inferiority of vildagliptin to gliclazide, was based on the following null hypothesis and one-sided alternative hypothesis:

$$H_o: \delta_{\text{vilda 50 mg bid}} \geq \delta_{\text{glic up to 320mg daily}} + 0.3 \quad \text{vs.} \quad H_a: \delta_{\text{vilda 50 mg bid}} < \delta_{\text{glic up to 320 mg daily}} + 0.3$$

Where $\delta_{\text{vilda 50 mg bid}}$ and $\delta_{\text{glic up to 320mg daily}}$ are the mean change from baseline for vildagliptin 50

mg bid and gliclazide up to 320mg daily respectively.

The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment and pooled center as the classification variable and baseline HbA_{1c} as the covariate using the PROC GLM procedure in SAS®.

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 terms will not be included in the primary analysis model.

The least squares mean (adjusted mean) change from baseline for each treatment group and associated 95% confidence intervals, the difference between two treatment groups (vildagliptin 50mg bid) – (gliclazide up to 320 mg daily) and associated two-sided 95% 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 0.3.

Secondary efficacy variables associated with the primary endpoint – HbA_{1c}

Superiority of vildagliptin 50 mg bid vs. gliclazide up to 320 mg daily

Once non-inferiority is compared, superiority, based on null hypothesis H_o: $\delta_{\text{vilda 50 mg bid}} = \delta_{\text{glic up to 320 mg daily}}$ vs. the two-sided alternative hypothesis H_a: $\delta_{\text{vilda 50 mg bid}} =/ \delta_{\text{glic up to 320 mg daily}}$, could have been tested using the same confidence interval from which non-inferiority was concluded. If the confidence interval obtained from the above ANCOVA model for the treatment difference lies entirely below zero, the superiority of vildagliptin over gliclazide could have been established at the 5% level by a simple closed testing procedure. This analysis uses the Censored Per Protocol population.

Repeated measures analysis

As a sensitivity analysis to the LOCF approach, the change from baseline in HbA_{1c} at all available time points (up to the end of the double-blind treatment period) from all patients in the Censored PP population was analyzed using repeated measure approach with missing values imputed from the model. The treatment effects at the end of study visit will be estimated from the model and compared.

A general linear model with treatment, time, baseline HbA_{1c}, pooled center and treatment by time interaction as the fixed effects and patient as a random effect nested within treatment was used. The fixed effect terms treatment, time and pooled center were included as classification variables, and baseline HbA_{1c} was included as a continuous covariate.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population consisted of male and female adult patients of at least 18 years old, with a body mass index (BMI) ranging from 22 to 45 kg/m^2, whose hyperglycemia is not adequately controlled on diet and exercise, therapy with oral antidiabetic agents is typically started. Thus, in this study, patients diagnosed with type 2 diabetes according to the ADA or WHO definition, with a baseline HbA_{1c} in the range of 7.5%-11% and fasting plasma glucose less than 15 mmol/L (270 mg/dL) were recruited for participation.

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, e.g., Cushing's syndrome and acromegaly, acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma) within the past 6 months. Evidence of significant diabetic complications, e.g., symptomatic autonomic neuropathy or gastroparesis. Acute infections which may affect blood glucose control within 4 weeks prior to visit 1. A history of Torsades de pointes, sustained and clinically relevant ventricular tachycardia or ventricular fibrillation, percutaneous coronary intervention within the past 3 months, any of the following within the past 6 months: myocardial infarction (MI) (If the visit 1 ECG reveals patterns consistent with a MI and the date of the event cannot be determined, then the patient can enter the study at the discretion of the investigator and the sponsor); coronary artery bypass surgery; unstable angina; or stroke. Congestive heart failure NYHA class III or IV. Any of the following ECG abnormalities: second degree AV block (Mobitz 1 and 2) third degree AV block, prolonged QTc (> 500 ms). 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. Acromegaly or treatment with growth hormone or similar drugs. 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, significant blood loss equaling to at least one unit of blood within the past 2 weeks or a blood transfusion within the past 8 weeks. Contraindications and warnings according to the country specific label for gliclazide not listed in the other exclusion criteria. Known sensitivity to gliclazide or other sulfur containing drugs. Chronic insulin treatment (> 4 weeks of treatment in the absence of an intercurrent illness) within the past 6 months. Chronic oral or parenteral corticosteroid treatment (> 7 consecutive days of treatment) within 8 weeks prior to visit 1. Treatment with class Ia, Ib and Ic or III antiarrhythmics. Thyroid hormone replacement is allowed if the dosage has been stable for at least 3 months and the TSH is within normal limits at visit 1. Investigational drug treatment within 4 weeks prior to visit 1 unless local health authority guidelines mandate a longer period. Treatment with any drug with a known and frequent toxicity to a major organ system within the past 3 months (i.e., cytostatic drugs). Any of the following significant laboratory abnormalities, ALT, AST greater than 3 times the upper limit of the normal range at visit 1, Direct bilirubin greater than 1.3 times the upper limit of the normal range at visit 1, Serum creatinine levels ≥ 220 µmol/L (2.5 mg/dL) at visit 1, TSH outside of normal range at visit 1, Clinically significant laboratory abnormalities, confirmed by repeat measurement, other than hyperglycemia, hyperinsulinemia, and glycosuria at visit 1, Fasting triglycerides > 7.9 mmol/L (>700 mg/dL) at visit 1, History of substance abuse (including alcohol) within the past 2 years, Potentially unreliable patients, and those judged by the investigator to be unsuitable for the study.

Patient disposition (Randomized population)

Disposition Reason	Vilda 50 mg bid N=546 n (%)	Glic up to 320 mg daily N=546 n (%)	Total N=1092 n (%)
Completed	409 (74.9)	402 (73.6)	811 (74.3)
Discontinued	137 (25.1)	144 (26.4)	281 (25.7)
Abnormal laboratory value(s)	1 (0.2)	1 (0.2)	2 (0.2)
Administrative problems	4 (0.7)	7 (1.3)	11 (1.0)
Adverse event (s)	32 (5.9)	35 (6.4)	67 (6.1)
Death	6 (1.1)	9 (1.6)	15 (1.4)
Lost to follow-up	17 (3.1)	13 (2.4)	30 (2.7)
Protocol violation	8 (1.5)	9 (1.6)	17 (1.6)
Subject condition no longer requires study drug	0 (0.0)	1 (0.2)	1 (0.1)
Subject withdrew consent	41 (7.5)	42 (7.7)	83 (7.6)
Unsatisfactory therapeutic effect	28 (5.1)	27 (4.9)	55 (5.0)

Number (%) of patients in analysis populations

Population	Vilda 50 mg bid N=546	Glic up to 320 mg daily N=546	Total N=1092
Randomized	546 (100%)	546 (100%)	1092 (100%)
Intent-to-treat	543 (99.5%)	545 (99.8%)	1088 (99.6%)
Safety	545 (99.8%)	545 (99.8%)	1090 (99.8%)
Per protocol	409 (74.9%)	410 (75.1%)	819 (75.0%)

Patient baseline demographic characteristics (Randomized population)

Demographic variable	Vilda 50 mg bid N=546	Glic up to 320 mg daily N=546	Total N=1092
Age (years)			
n	546	546	1092
Mean ± SD	55.23 ± 10.62	54.27 ± 10.39	54.75 ± 10.51
Median	55	54	55
Min, Max	25 - 84	22 - 80	22 - 84
Age group (years)	n (%)	n (%)	n (%)
< 65	426(78.0%)	445(81.5%)	871(79.8%)
≥ 65	120(22.0%)	101(18.5%)	221(20.2%)
< 75	530(97.1%)	538(98.5%)	1068(97.8%)
≥ 75	16(2.9%)	8(1.5%)	24(2.2%)
Gender			
Male	321(58.8%)	288(52.7%)	609(55.8%)
Female	225(41.2%)	258(47.3%)	483(44.2%)
Race	n (%)		
Caucasian	405(74.2%)	401(73.4%)	806(73.8%)

Black	12(2.2%)	13(2.4%)	25(2.3%)
Asian (non Indian subcontinent)	2(0.4%)	4(0.7%)	6(0.5%)
Asian (Indian subcontinent)	17(3.1%)	13(2.4%)	30(2.7%)
Hispanic or Latino	82(15.0%)	82(15.0%)	164(15.0%)
Japanese	0(0.0%)	1(0.2%)	1(0.1%)
Other	28(5.1%)	32(5.9%)	60(5.5%)
Height (cm)			
n	546	546	1091
Mean ± SD	165.91 ± 9.69	165.30 ± 10.00	165.61 ± 9.85
Median	166	165	166
Min - Max	139 - 192	137 - 200	137 - 200
Body weight (kg)			
n	546	545	1091
Mean ± SD	84.24 ± 16.27	84.33 ± 17.62	84.29 ± 16.95
Median	82.60	81.20	82.00
Min - Max	47.7 – 147.0	45.8 - 157.3	45.8 - 157.3
Waist circumference (cm)			
n	541	545	1086
Mean ± SD	101.91 ± 11.51	101.30 ± 12.55	101.61 ± 12.04
Median	101.0	100	101.0
Min - Max	70.0 – 138.0	68.0 – 143.0	68 - 143.0
BMI (kg/m^2)			
n	546	545	1091
Mean ± SD	30.55 ± 5.02	30.80 ± 5.46	30.67 ± 5.25
Median	30.05	29.80	30.00
Min - Max	20.5 - 53.3	20.3 – 45.0	20.3 - 53.3
BMI group (kg/m^2)			
< 30	270(49.5%)	273(50.0%)	543(49.7%)
≥ 30	276(50.5%)	272(49.8%)	548(50.2%)
≥ 35	105(19.2%)	120(22.0%)	225(20.6%)
Not recorded	0(0.0%)	1(0.2%)	1(0.1%)

Patient baseline background characteristics (Randomized population)

Background Characteristic	Vilda 50 mg bid N=546	Glic up to 320 mg daily N=546	Total N=1092
HbA_{1c} (%)			
n	546	546	1092
Mean ± SD	8.60 ± 1.04	8.69 ± 1.07	8.64 ± 1.06
Median	8.4	8.5	8.4
Min - Max	5.9 -13.6	5.0 - 11.9	5.0 - 13.6
HbA_{1c} (%) group			
<= 8	194(35.5%)	181(33.2%)	375(34.3%)
> 8	352(64.5%)	365(66.8%)	717(65.7%)
<= 9	381(69.8%)	360(65.9%)	741(67.9%)
> 9	165(30.2%)	186(34.1%)	351(32.1%)
FPG (mmol/L)			
n	546	546	1092
Mean ± SD	10.78 ± 2.90	10.81 ± 2.93	10.80 ± 2.91

Median	10.5	10.2	10.3
Min - Max	4.9 – 24.8	3.9 - 25.8	3.9 - 25.8
Duration of Type 2 Diabetes (years)			
n	546	546	1092
Mean ± SD	2.43 ± 4.31	1.86 ± 3.12	2.14 ± 3.77
Median	0.57	0.50	0.52
Min - Max	0 - 40.02	0 - 28.32	0 - 40.02
GFR (MDRD) (mL/min) per 1.73 m^2			
Normal (>80)	394(72.2%)	389(71.2%)	783(71.7%)
Mild (>50 - <=80)	143(26.2%)	154(28.2%)	297(27.2%)
Moderate (>=30 - <=50)	9(1.6%)	3(0.5%)	12(1.1%)
GFR (CG) (mL/min) per 1.73 m^2			
Normal (>80)	450(82.4%)	457(83.7%)	907(83.1%)
Mild (>50 - <=80)	87(15.9%)	84(15.4%)	171(15.7%)
Moderate (>=30 - <=50)	9(1.6%)	5(0.9%)	14(1.3%)

Primary Efficacy Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to endpoint (censored at start of rescue medication use) (Per protocol and ITT populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glic up to 320 mg daily (SE)	95% CI
Per protocol population					
Vilda 50 mg bid	409	8.53 (0.05)	-0.47(0.08)	0.13 (0.10)	(-0.06, 0.33)
Glic up to 320 mg daily	409	8.70 (0.05)	-0.61(0.08)		
Intent to treat population					
Vilda 50 mg bid	530	8.60 (0.05)	-0.51(0.07)	0.19 (0.09)	(0.02 , 0.36)
Glic up to 320 mg daily	533	8.69 (0.05)	-0.71(0.07)		

Secondary Efficacy Result(s)

ANCOVA results for change in FPG (mmol/L) from baseline to endpoint (censored at start of rescue medication use) (Per protocol and ITT populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glic up to 320 mg daily (SE)	95% CI
Per protocol population					
Vilda 50 mg bid	409	10.60 (0.14)	-0.19 (0.17)	0.53 (0.20)	(0.13, 0.93)
Glic up to 320 mg daily	409	10.74 (0.13)	-0.72 (0.16)		
Intent to treat population					
Vilda 50 mg bid	535	10.80 (0.13)	-0.24 (0.15)	0.65 (0.18)	(0.29, 1.01)
Glic up to 320 mg daily	533	10.82 (0.13)	-0.88 (0.15)		

ANCOVA results for change in beta cell function / insulin resistance parameters from baseline to endpoint (censored at start of rescue medication use) (Per protocol population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glic up to 320mg daily (SE)	95% CI	p-value
Beta cell function parameters:						
Fasting pro-insulin (pmol/L)						
Vilda 50mg bid	291	34.54 (1.24)	-2.63 (1.29)	-8.65 (1.55)	(-11.7,-5.61)	<0.001*
Glic up to 320 mg	299	37.49 (1.58)	6.02 (1.25)			
Fasting pro-insulin/insulin ratio						
Vilda 50mg bid	268	0.62 (0.02)	-0.10 (0.02)	-0.06(0.02)	(-0.10,-0.02)	0.006 *
Gliclazide	275	0.60 (0.02)	-0.04 (0.02)			
Insulin resistance parameters:						
Fasting Insulin (pmol/L)						
Vilda 50mg bid	344	65.24 (2.26)	3.87 (3.33)	-11.9 (2.88)	(-17.6,-6.30)	<0.001*
Glic up to 320 mg	352	71.13 (2.61)	15.81(3.34)			
Homa-IR						
Vilda 50mg bid	340	4.36 (0.15)	0.01 (0.28)	-0.69 (0.24)	(-1.17,-0.22)	0.005 *
Glic up to 320 mg	351	4.84 (0.19)	0.71 (0.28)			

* indicates statistical significance at 5 % level.

Number (%) of patients who responded at endpoint (censored at start of rescue medication use) (Per protocol and ITT populations)

	Vilda 50mg bid n (%)	Glic up to 320mg daily n (%)	p-value*
Per protocol population	N=409	N=410	
N'[1]	409 (100.0)	409 (100.0)	
Responder Criterion			
At least one criterion met	210 (51.3)	244 (59.7)	0.017
HbA1c < 7% [2]	88/405 (21.7)	113/405 (27.9)	0.042
HbA1c < 7% in patients with baseline HbA1c <= 8% [3]	44/150 (29.3)	46/128 (35.9)	0.241
HbA1c <= 6.5% [2]	58/409 (14.2)	62/407 (15.2)	0.671
Reduction of HbA1c >= 1% [1]	148 (36.2)	170 (41.6)	0.115
Reduction of HbA1c >= 1% [1] in patients with baseline HbA1c > 9%	59/115 (51.3)	88/138 (63.8)	0.045
Reduction of HbA1c >= 0.7% [1]	181 (44.3)	204 (49.9)	0.107
Reduction of HbA1c >= 0.5% [1]	210 (51.3)	240 (58.7)	0.035
ITT population	N=543	N=545	
N'[1]	530 (100.0)	533 (100.0)	
Responder Criterion			
At least one criterion met	284 (53.6)	330 (61.9)	0.006
HbA1c < 7% [2]	120/523 (22.9)	153/522 (29.3)	0.019
HbA1c < 7% in patients with baseline HbA1c <= 8% [3]	58/183 (31.7)	62/166 (37.3)	0.267
HbA1c <= 6.5% [2]	76/529 (14.4)	91/530 (17.2)	0.211

Reduction of HbA1c >= 1% [1]	195 (36.8)	228 (42.8)	0.046
Reduction of HbA1c >= 1% [1] in patients with baseline HbA1c > 9% [4]	86/161 (53.4)	117/181 (64.6)	0.035
Reduction of HbA1c >= 0.7% [1]	241 (45.5)	279 (52.3)	0.025
Reduction of HbA1c >= 0.5% [1]	280 (52.8)	326 (61.2)	0.006

* Chi-square test for Vilda 50 mg bid vs Gliclazide up to 320 mg daily.
1 Number of patients with both baseline and endpoint HbA1c measurements in the specified population, which is used as denominator unless specified otherwise.
2 Denominator includes only patients with baseline HbA1c = 7% (> 6.5%) and endpoint HbA1c measurement.
3 Denominator includes only patients with 7% = baseline HbA1c = 8% and endpoint HbA1c measurement.
4 Denominator includes only patients with baseline HbA1c >9%.
Baseline is the measurement obtained on Day 1, or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 (Visit 2) measurement is missing.
Endpoint is the final available post-randomization assessment on or before the start of rescue medication and up to Week 104 visit (Visit 14) inclusive.

Change in prandial glucose, insulin, C-peptide, glucagon, active GLP-1, DPP-4 and Insulin Secretion Rate from baseline to endpoint (censored at start of rescue medication use) (Per protocol population, patients that participated in the meal challenge)

Parameter/ Treatment group	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glic (SE)	95% CI	p-value
Prandial plasma glucose AUC$_{(0\text{-}2hr)}$ (mmol x hr/L)						
Vilda 50 mg bid	24	27.73 (1.31)	-1.47 (2.02)	2.07 (1.73)	(-1.44, 5.58)	0.240
Glic up to 320mg	20	31.02 (1.64)	-3.54 (2.01)			
1-Hour prandial plasma glucose level (mmol/L)						
Vilda 50 mg bid	24	15.26 (0.67)	-1.29 (1.02)	0.80 (0.87)	(-0.97, 2.57)	0.364
Glic up to 320mg	20	16.99 (0.88)	-2.09 (1.01)			
Adjusted prandial plasma glucose AUC$_{(0\text{-}2hr)}$ (mmol x hr/L)						
Vilda 50 mg bid	24	8.31 (0.62)	-2.03 (0.94)	-1.06 (0.79)	(-2.67, 0.55)	0.191
Glic up to 320mg	20	8.86 (0.74)	-0.97 (0.95)			
Prandial insulin AUC$_{(0\text{-}2hr)}$ (pmol x hr/L)						
Vilda 50 mg bid	22	535.0 (97.93)	17.98 (92.63)	-62.7 (84.30)	(-234 ,109.0)	0.462
Glic up to 320mg	17	416.4 (54.93)	80.69 (96.48)			
Prandial C-peptide AUC (nmol x hr/L)						
Vilda 50 mg bid	24	4.85 (0.42)	-0.44 (0.42)	-0.43 (0.37)	(-1.19, 0.32)	0.251
Glic up to 320mg	18	4.52 (0.39)	-0.01 (0.43)			
Prandial Glucagon AUC$_{(0\text{-}2hr)}$ (pmol x hr/L)						
Vilda 50 mg bid	7	56.12 (8.66)	-4.17 (10.53)	-9.29 (13.81)	(-43.1,24.50)	0.526
Glic up to 320mg	6	50.12 (9.74)	5.12 (9.70)			
Prandial active GLP-1 AUC$_{(0\text{-}2hr)}$ (pmol x hr/L)						
Vilda 50 mg bid	2	57.50 (46.03)	3.93 (3.16)	3.31 (4.49)	(-16.0,22.64)	0.538
Glic up to 320mg	3	5.20 (0.38)	0.62 (2.44)			
Prandial DPP-4 AUC$_{(0\text{-}2hr)}$ (mU/ml x min)						
Vilda 50 mg bid	7	20.47 (3.09)	-13.7 (4.06)	-11.9 (4.54)	(-22.0,-1.74)	0.026 *
Glic up to 320mg	9	19.30 (1.70)	-1.88 (3.80)			
Insulin secretion rate (ISR) relative to glucose$_{(0\text{-}2hr)}$ (pmol/min/m^2/mmol/L)						
Vilda 50 mg bid	24	32.26 (3.93)	-2.05 (3.49)	-4.23 (3.13)	(-10.6, 2.13)	0.185
Glic up to 320mg	18	25.41 (2.99)	2.19 (3.56)			

* indicates statistical significance at 5 % level.

Change in fasting lipids from baseline to endpoint (censored at start of rescue medication use) (Per protocol population)

Parameter	Treatment	n	Baseline mean (SE)	Adjusted mean % change (SE)	Mean % difference to Glic (SE)	95% CI	p-value
Triglycerides	Vilda 50mg bid	408	2.18 (0.07)	7.58 (2.84)	3.12 (3.53)	(-3.81,10.05)	0.377
(mmol/L)	Glic up to 320 mg	405	2.25 (0.07)	4.47 (2.79)			
Total cholesterol	Vilda 50mg bid	408	5.42 (0.05)	-0.79 (0.89)	1.05 (1.10)	(-1.12, 3.22)	0.343
(mmol/L)	Glic up to 320 mg	405	5.49 (0.06)	-1.84 (0.88)			
LDL cholesterol	Vilda 50mg bid	374	3.28 (0.05)	-2.17 (1.37)	-0.63 (1.69)	(-3.95, 2.69)	0.710
(mmol/L)	Glic up to 320 mg	374	3.35 (0.05)	-1.53 (1.35)			
HDL cholesterol	Vilda 50mg bid	396	1.19 (0.02)	5.67 (0.99)	2.07 (1.23)	(-0.35, 4.50)	0.093
(mmol/L)	Glic up to 320 mg	390	1.15 (0.01)	3.59 (0.98)			
non-HDL cholesterol	Vilda 50mg bid	395	4.23 (0.05)	-2.22 (1.15)	0.27 (1.42)	(-2.52, 3.05)	0.851
(mmol/L)	Glic up to 320 mg	390	4.31 (0.06)	-2.49 (1.12)			
VLDL cholesterol	Vilda 50mg bid	386	0.88 (0.02)	4.76 (2.38)	-1.07 (2.96)	(-6.89, 4.75)	0.719
(mmol/L)	Glic up to 320 mg	385	0.92 (0.02)	5.83 (2.35)			
Free Fatty Acids	Vilda 50mg bid	300	528.7(11.63)	23.96 (5.33)	-1.99 (4.77)	(-11.4, 7.37)	0.676
(mmol/L)	Glic up to 320 mg	294	522.4(11.33)	25.96 (5.43)			
Apo-A	Vilda 50mg bid	381	1.47 (0.01)	3.74 (0.73)	4.27 (0.91)	(2.48 , 6.06)	<0.001*
(mg/dl)	Glic up to 320 mg	387	1.45 (0.01)	-0.52 (0.72)			
Apo-B	Vilda 50mg bid	381	1.13 (0.01)	-5.40 (1.10)	1.30 (1.37)	(-1.38, 3.99)	0.341
(mg/dl)	Glic up to 320 mg	387	1.16 (0.01)	-6.70 (1.08)			

* indicates statistical significance at 5 % level.

Change in body weight (kg) from baseline to endpoint (censored at start of rescue medication use) (Per protocol population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glic up to 320 mg daily (SE)	95% CI for change from baseline	p-value for change from baseline
Body weight (kg)						
Vilda 50mg bid	409	83.46 (0.77)	0.75 (0.24)	-0.85 (0.29)	(-1.42, -0.27)	0.004*
Gliclazide	409	84.98 (0.89)	1.60 (0.23)			

* 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 N=545 n (%)	Glic up to 320 mg daily N=545 n (%)
Any Primary system organ class	379 (69.5)	398 (73.0)
Blood and lymphatic system disorders	11 (2.0)	17 (3.1)
Cardiac disorders	48 (8.8)	55 (10.1)
Congenital, familial and genetic disorders	1 (0.2)	1 (0.2)
Ear and labyrinth disorders	14 (2.6)	24 (4.4)
Endocrine disorders	3 (0.6)	2 (0.4)
Eye disorders	32 (5.9)	34 (6.2)
Gastrointestinal disorders	129 (23.7)	113 (20.7)
General disorders and administration site conditions	61 (11.2)	81 (14.9)
Hepatobiliary disorders	11 (2.0)	16 (2.9)
Immune system disorders	7 (1.3)	5 (0.9)
Infections and infestations	202 (37.1)	207 (38.0)
Injury, poisoning and procedural complications	51 (9.4)	52 (9.5)
Investigations	28 (5.1)	39 (7.2)
Metabolism and nutrition disorders	66 (12.1)	59 (10.8)
Musculoskeletal and connective tissue disorders	138 (25.3)	135 (24.8)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	15 (2.8)	12 (2.2)
Nervous system disorders	113 (20.7)	130 (23.9)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	3 (0.6)
Psychiatric disorders	40 (7.3)	43 (7.9)
Renal and urinary disorders	38 (7.0)	29 (5.3)
Reproductive system and breast disorders	32 (5.9)	33 (6.1)
Respiratory, thoracic and mediastinal disorders	49 (9.0)	50 (9.2)
Skin and subcutaneous tissue disorders	59 (10.8)	78 (14.3)
Vascular disorders	52 (9.5)	61(11.2)

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

Preferred Term	Vilda 50mg bid N=545 n (%)	Glic up to 320 mg daily N=545 n (%)
Deaths	6 (1.1)	9 (1.7)
SAEs	80 (14.7)	66 (12.1)
Discontinuation of study drug due to AEs	38 (7.0)	45 (8.3)
AEs causing dose adjustment or study drug interruption	37 (6.8)	38 (7.0)

There were 15 deaths in the study:
Six (6) in the vildagliptin group: 2 patients died due to cardiac arrest, 3 patients due to myocardial infarction, 1 patient due to acute myocardial infarction

Nine (9) in the gliclazide group: 2 patients due to cardiac failure, 2 patients due to cerebral accident, 1 patient each due to myocardial ischemia, pneumonia, peritoneal sarcoma, ischaemia and angioedema.

Number (%) of patients with SAEs (greater than or equal to 0.5% in any group) by preferred term (Safety population)

	Vilda 50mg bid N=545 n (%)	Glic up to 320 mg daily N=545 n (%)
Any SAE	80 (14.7)	66 (12.1)
Angina pectoris	3 (0.6)	4 (0.7)
Angina unstable	2 (0.4)	4 (0.7)
Appendicitis	3 (0.6)	2 (0.4)
Cardiac failure	0 (0.0)	4 (0.7)
Coronary artery disease	3 (0.6)	3 (0.6)
Ischaemic stroke	3 (0.6)	0 (0.0)
Myocardial infarction	7 (1.3)	2 (0.4)

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

12-November-2008

Date Inclusion on Novartis Clinical Trial Results Database

10-March-2009

Date of Latest Update

15-March-2010