Sponsor

Novartis

Generic Drug Name

Vildagliptin

Trial Indication

Type 2 diabetes mellitus

Protocol Number

CLAF237A2304

Protocol 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 pioglitazone 45 mg qd in patients with type 2 diabetes inadequately controlled with thiazolidinedione monotherapy

Clinical Trial Phase

Phase III

Study Start/End Dates

05 May 2004 to 18 Jan 2006

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a multicenter, randomized, double-blind, placebo-controlled study. Patients with type 2 diabetes inadequately controlled on thiazolidinedione monotherapy (HbA1c 7.5-11%) were included in the trial. Eligible patients were randomized equally to vildagliptin 50 mg qd, 50 mg bid or placebo in addition to treatment with pioglitazone 45 mg qd. A 12-week pre-study period was offered to eligible patients who met the pre-study inclusion/exclusion criteria. Eligible patients received open-label pioglitazone at a minimum dose of 30 mg for the 12- week pre-study period. All study patients attended one screening visit (Week -4) where the inclusion/exclusion criteria were assessed. Eligible patients were placed on pioglitazone 45 mg qd and randomized 4 weeks later at visit 2 (Baseline, Day 1). Study patients then completed 4 further visits over a period of 24 weeks of treatment with vildagliptin or placebo added to pioglitazone.

Centers

123 centers in 2 countries: United States (99) and Romania (24)

Objectives:

Primary objective

To demonstrate the efficacy of add-on therapy with vildagliptin to pioglitazone in patients with type 2 diabetes inadequately controlled with prior thiazolidinedione monotherapy by testing the hypothesis that the reduction in glycosylated hemoglobin (HbA1c) seen with vildagliptin (50 mg qd or bid) treatment is superior to that with placebo after 24 weeks of treatment.

Secondary objectives

- To demonstrate the efficacy of add-on therapy with vildagliptin to pioglitazone in patients with type 2 diabetes by testing the hypothesis that the fasting plasma glucose (FPG) reduction with vildagliptin (50 mg qd or bid) is superior to that with placebo after 24 weeks of treatment.

- To demonstrate the safety of vildagliptin in patients with type 2 diabetes by showing that combination therapy with vildagliptin (50 mg qd or bid) and pioglitazone 45 mg qd has comparable adverse event (AE) profiles at these two dose levels and these are similar to placebo after 24 weeks of treatment.
- To demonstrate the efficacy of combination therapy with vildagliptin and pioglitazone in patients with type 2 diabetes by showing that the responder rates with Vildagliptin (50 mg qd or bid) are greater than those with placebo after 24 weeks of treatment.
- To demonstrate the efficacy of combined therapy with vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with prior thiazolidinedione monotherapy across baseline HbA1c subgroups to assess whether or not the therapeutic efficacy of vildagliptin (lowering of HbA1c with 50 mg qd or bid vs placebo) is greater in patients with high baseline HbA1c (>9%) than patients with lower baseline HbA1c (≤9%) after 24 weeks of treatment.

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

Vildagliptin 50 mg tablets administered orally, once or twice daily.

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 pioglitazone, in reducing HbA1c concentrations 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 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 have been summarized by treatment group.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients who had received a thiazolidinedione for at least three months and had been on a stable dosage of pioglitazone (at least 30 mg qd) or rosiglitazone (at least 4 mg qd) for at least 4 weeks prior to visit 1. Patients not already treated with pioglitazone 45 mg qd were to have been willing to switch to that drug and dose at visit 1.

- Patients who had demonstrated an initial therapeutic response to thiazolidinedione therapy manifested by either a clinically significant decrease in HbA1c or FPG or based on clinical history.
- Age in the range of 18 to 80 years inclusive.
- Body mass index (BMI) in the range of 22-45 kg/m2 inclusive at visit 1.
- HbA1c in the range of 7.5% to 11% inclusive at visit 1.
- FPG <270 mg/dL (15 mmol/L) at visit 1.
- Agreement to maintain prior diet and exercise habits during the full course of the study.
- Written informed consent to participate in the study.
- Ability to comply with all study requirements.

Exclusion criteria

- Type 1 diabetes
- Pregnancy or lactation
- Evidence of serious cardiovascular complications
- Evidence of serious diabetic complications
- Laboratory value abnormalities as defined by the protocol
- Known sensitivity to pioglitazone
- Treatment with any oral antidiabetic other than thiazolidinediones within 3 months prior to visit 1.
- 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 antiarrhythmic drugs

Participant Flow Table

Patient Disposition

Disposition Reason	Vilda 50mg qd + Pio 45mg n (%)	Vilda 50mg bid + Pio 45mg n (%)	Placebo + Pio 45mg n (%)	Total n (%)
Randomized population	N=147	N=158	N=158	N=463
Completed	124 (84.4)	124 (78.5)	128 (81.0)	376 (81.2)
Discontinued	23 (15.6)	34 (21.5)	30 (19.0)	87 (18.8)
Adverse events	7 (4.8)	5 (3.2)	4 (2.5)	16 (3.5)
Unsatisfactory therapeutic effect	3 (2.0)	5 (3.2)	13 (8.2)	21 (4.5)
Protocol violation	1 (0.7)	4 (2.5)	1 (0.6)	6 (1.3)
Patient withdrew consent	8 (5.4)	9 (5.7)	9 (5.7)	26 (5.6)
Loss to follow-up	4 (2.7)	9 (5.7)	3 (1.9)	16 (3.5)
Administrative problems	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.4)
Primary ITT population	N=124	N=136	N=138	N=398
Completed	110 (88.7)	110 (80.9)	115 (83.3)	335 (84.2)
Discontinued	14 (11.3)	26 (19.1)	23 (16.7)	63 (15.8)
Adverse events	4 (3.2)	4 (2.9)	3 (2.2)	11 (2.8)
Unsatisfactory therapeutic effect	3 (2.4)	4 (2.9)	11 (8.0)	18 (4.5)
Protocol violation	0 (0.0)	3 (2.2)	1 (0.7)	4 (1.0)
Patient withdrew consent	5 (4.0)	7 (5.1)	6 (4.3)	18 (4.5)
Loss to follow-up	2 (1.6)	6 (4.4)	2 (1.4)	10 (2.5)
Administrative problems	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.5)

Baseline Characteristics

Patient Baseline Demographic Characteristics (ITT Population)

Demographic variable	Vilda 50 mg qd + Pio 45 mg N=124 (%)	Vilda 50 mg bid + Pio 45 mg N=136 (%)	Placebo + Pio 45 mg N=138 (%)	Total N=398 (%)
Age (years) n	124	136	138	398
Mean ± SD	54.02 ± 8.16	54.03 ± 9.22	54.84 ± 10.63	54.31 ± 9.42
Median	54.00	54.00	55.00	54.00
Min – Max	28.00 - 74.00	32.00 - 81.00	25.00 - 81.00	25.00 - 81.00
Age group				
<65	112 (90.3)	118 (86.8)	110 (79.7)	340 (85.4)
>=65	12 (9.7)	18 (13.2	28 (20.3)	58 (14.6)
Sex				
Male	68 (54.8%)	61 (44.9%)	70 (50.7%)	199 (50.0%)
Female	56 (45.2%)	75 (55.1%)	68 (49.3%)	199 (50.0%)
Race				
Asian*	1 (0.8%)	1 (0.7%)	2 (1.4%)	4 (1.0%)
Asian **	1 (0.8%)	3 (2.2%)	2 (1.4%)	6 (1.5%)
Black	6 (4.8%)	11 (8.1%)	13 (9.4%)	30 (7.5%)
Caucasian	104 (83.9%)	108 (79.4%)	108 (78.3%)	320 (80.4%)
Hispanic	12 (9.7%)	12 (8.8%)	10 (7.2%)	34 (8.5%)
Japanese	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.3%)

Demographic variable	Vilda 50 mg qd + Pio 45 mg N=124 (%)	Vilda 50 mg bid + Pio 45 mg N=136 (%)	Placebo + Pio 45 mg N=138 (%)	Total N=398 (%)
Pacific islander	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.3%)
Other	0 (0.0%)	1 (0.7%)	1 (0.7%)	2 (0.5%)
Height (cm) n	124	136	138	398
Mean ± SD	168.65 ± 9.95	165.89 ± 9.49	168.81 ± 10.78	167.76 ± 10.16
Median	168.00	166.00	167.50	167.00
Min – Max	150.00 - 198.00	142.00 - 193.00	147.00 - 203.00	142.00 - 203.00
Body weight (kg) n	124	136	138	398
Mean ± SD	93.14 ± 18.11	88.84 ± 18.16	92.19 ± 19.95	91.34 ± 18.83
Median	90.65	85.00	89.55	89.00
Min – Max	56.00 - 151.50	55.30 - 149.60	55.00 - 153.50	55.00 - 153.50
BMI (kg/m2)** n	124	136	138	398
Mean ± SD	32.64 ± 4.99	32.24 ± 5.78	32.26 ± 5.77	32.37 ± 5.53
Median	32.60	31.20	31.20	31.50
Min – Max	22.10 - 44.80	22.90 - 48.50	22.00 - 47.40	22.00 - 48.50
BMI group				
<30 (kg/m**2)	39 (31.5%)	56 (41.2%)	52 (37.7%)	147 (36.9%)
>=30(kg/m**2)	85 (68.5%)	80 (58.8%)	86 (62.3%)	251 (63.1%)
<35 (kg/m**2)	84 (67.7%)	96 (70.6%)	101 (73.2%)	281 (70.6%)
>=35(kg/m**2)	40 (32.3%)	40 (29.4%)	37 (26.8%)	117 (29.4%)

* Indian subcontinent
** Non-Indian subcontinent

Summary of Efficacy

Primary Outcome Result

ANCOVA results for change in HbA1c (%) from baseline to endpoint (Primary ITT Population, per protocol Population, Sensitivity ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Placebo + Pio 45 mg (SE)	95% CI	p-value
Primary ITT population						
Vilda 50 mg qd + Pio 45 mg	124	8.62 (0.09)	-0.76 (0.10)	-0.46 (0.14)	(-0.73,-0.19)	0.001 *
Vilda 50 mg bid + Pio 45 mg	136	8.69 (0.11)	-0.97 (0.10)	-0.67 (0.14)	(-0.94,-0.40)	<0.001*
Placebo + Pio 45 mg	138	8.72 (0.10)	-0.30 (0.10)			
Per Protocol population						
Vilda 50 mg qd + Pio 45 mg	109	8.61 (0.10)	-0.79 (0.10)	-0.49 (0.14)	(-0.77,-0.21)	<0.001*
Vilda 50 mg bid + Pio 45 mg	112	8.60 (0.11)	-0.99 (0.10)	-0.68 (0.14)	(-0.96,-0.40)	<0.001*
Placebo + Pio 45 mg	116	8.67 (0.10)	-0.30 (0.10)			

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Placebo + Pio 45 mg (SE)	95% CI	p-value
Sensitivity ITT population^						
Vilda 50 mg qd + Pio 45 mg	141			-0.50 (0.13)	(-0.76,-0.24)	<0.001*
Vilda 50 mg bid + Pio 45 mg	153			-0.66 (0.13)	(-0.92,-0.41)	<0.001*
Placebo + Pio 45 mg	153					

* indicates statistical significance at 5% level according to the Hochberg step-up procedure.
^ Sensitivity ITT population includes patients with no valid baseline HbA1c values as well as patients incorrectly randomized due to BARC-US assay issues. The analysis is a weighted average of the treatment differences at the study endpoint in patients with and without baseline and therefore, no overall estimates of baseline or the change from baseline is available.

Number (%) of patients who responded at endpoint (Primary ITT population, Per protocol population, Sensitivity ITT population)

Responder criterion	Vilda 50 mg qd + Pio 45 mg n (%)	p-value*	Vilda 50 mg bid + Pio 45 mg n (%)	p-value**	Placebo + Pio 45 mg n (%)
Primary ITT population	N=124		N=136		N=138
N[1]	124 (100)		136 (100)		138 (100)
At least one criterion met	77 (62.1)	0.028	109 (80.1)	<0.001	67 (48.6)
HbA_{1c} <7%[2]	35/122 (28.7)	0.007	48/132 (36.4)	<0.001	20/135 (14.8)
HbA_{1c} <=6.5%[2]	24/124 (19.4)	0.090	32/136 (23.5)	0.011	16/136 (11.8)
Reduction of HbA_{1c} >=1%[1]	59 (47.6)	0.001	77 (56.6)	<0.001	39 (28.3)
Reduction of HbA_{1c} >=0.7%[1]	67 (54.0)	0.011	93 (68.4)	<0.001	53 (38.4)

Responder criterion	Vilda 50 mg qd + Pio 45 mg n (%)	p-value*	Vilda 50 mg bid + Pio 45 mg n (%)	p-value**	Placebo + Pio 45 mg n (%)
Reduction of HbA_{1c} >=0.5%[1]	75 (60.5)	0.030	109 (80.1)	<0.001	65 (47.1)
Per protocol population	N=109		N=112		N=116
N[1]	109 (100)		112 (100)		116 (100)
At least one criterion met	70 (64.2)	0.023	93 (83.0)	<0.001	57 (49.1)
HbA_{1c} <7%[2]	32/107 (29.9)	0.012	44/108 (40.7)	<0.001	18/114 (15.8)
HbA_{1c} <=6.5%[2]	22/109 (20.2)	0.103	30/112 (26.8)	0.005	14/115 (12.2)
Reduction of HbA_{1c} >=1%[1]	54 (49.5)	0.001	67 (59.8)	<0.001	33 (28.4)
Reduction of HbA_{1c} >=0.7%[1]	61 (56.0)	0.007	81 (72.3)	<0.001	44 (37.9)
Reduction of HbA_{1c} >=0.5%[1]	68 (62.4)	0.024	93 (83.0)	<0.001	55 (47.4)
Sensitivity ITT population	N=141		N=153		N=153
HbA_{1c} <7%[2]	44/134 (32.8)	0.001	56/144 (38.9)	<0.001	23/143 (16.1)
HbA_{1c} <=6.5%[2]	31/140 (22.1)	0.031	39/150 (26.0)	0.003	19/151 (12.6)

* Chi-square test for Vilda 50 mg qd + Pio 45 mg vs Placebo + Pio 45 mg.
** Chi-square test for Vilda 50 mg bid + Pio 45 mg vs Placebo + Pio 45 mg.
[1] Number of patients with both baseline and endpoint HbA1c measurements in the specified population, which is used as denominator unless otherwise specified.
[2] Denominator includes only patients without baseline or with baseline HbA1c >= 7% (>6.5%) and endpoint HbA1c measurement.

Mean changes from baseline in HbA1c (%) at endpoint: subgroup analyses (Primary ITT population)

		Vilda 50 mg qd + Pio 45 mg N=124			Vilda 50 mg bid + Pio 45 mg N=136			Placebo + Pio 45 mg N=138		
Subgroup	Category	n	BL mean	Change (SE)	n	BL mean	Change (SE)	n	BL mean	Change (SE)
HbA_{1c} at Baseline (%)	HbA_{1c} <=8%	43	7.58	-0.72 (0.131)	48	7.50	-0.78 (0.128)	50	7.51	-0.31 (0.112)
	HbA_{1c} >8%	81	9.17	-0.87 (0.139)	88	9.34	-1.14 (0.117)	88	9.41	-0.36 (0.158)
	HbA_{1c} <=9%	87	8.08	-0.70 (0.109)	96	8.03	-0.96 (0.093)	88	7.98	-0.24 (0.111)
	HbA_{1c} >9%	37	9.89	-1.09 (0.221)	40	10.27	-1.14 (0.206)	50	10.04	-0.52 (0.226)
BMI at Baseline (kg/m**2)	<30	39	8.37	-0.96 (0.173)	56	8.70	-1.00 (0.142)	52	8.80	-0.48 (0.178)
	>=30	85	8.73	-0.75 (0.125)	80	8.68	-1.02 (0.115)	86	8.68	-0.26 (0.137)
	>=35	40	8.68	-0.64 (0.178)	40	8.60	-1.08 (0.152)	37	8.61	-0.59 (0.145)
Age (years)	<65	112	8.64	-0.82 (0.109)	118	8.68	-0.98 (0.100)	110	8.73	-0.33 (0.112)
	>=65	12	8.43	-0.76 (0.258)	18	8.74	-1.23 (0.151)	28	8.72	-0.38 (0.311)
Gender	Male	68	8.66	-0.91 (0.137)	61	8.63	-1.09 (0.109)	70	8.82	-0.21 (0.156)
	Female	56	8.56	-0.71 (0.152)	75	8.73	-0.95 (0.136)	68	8.62	-0.47 (0.151)
Race	Caucasian	104	8.54	-0.80 (0.109)	108	8.67	-1.07 (0.090)	108	8.77	-0.38 (0.128)
	Black	6	8.92	-1.15 (0.694)	11	9.44	-1.00 (0.466)	13	8.17	-0.41 (0.243)
	Asian*	1	9.00	0.20	3	7.47	-1.47 (0.233)	2	7.95	0.45 (0.450)
	Asian**	1	9.80	-1.40	1	8.60	-2.20	2	10.90	-1.25 (0.550)
	Hispanic	12	9.03	-0.88 (0.309)	12	8.54	-0.35 (0.392)	10	8.87	0.00 (0.347)
	Japanese							1	7.50	-0.40
	Polynesian							1	7.90	2.50
	Other				1	7.80	-0.50	1	9.00	-1.40

* Indian subcontinent
** Non-Indian subcontinent

Secondary Outcome Results

ANCOVA results for change in fasting plasma glucose (mmol/L) from baseline to endpoint (Primary ITT population, Per protocol population, Sensitivity ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Placebo + Pio 45 mg (SE)	95% CI	p-value
Primary ITT population						
Vilda 50 mg qd + Pio 45 mg	124	10.32 (0.26)	-0.82 (0.22)	-0.35 (0.30)	(-0.93,0.24)	0.243
Vilda 50 mg bid + Pio 45 mg	136	9.97 (0.28)	-1.13 (0.21)	-0.66 (0.29)	(-1.23,-0.08)	0.025
Placebo + Pio 45 mg	138	10.05 (0.26)	-0.48 (0.21)			
Per Protocol population						
Vilda 50 mg qd + Pio 45 mg	109	10.24 (0.28)	-0.81 (0.22)	-0.55 (0.31)	(-1.16,0.06)	0.075
Vilda 50 mg bid + Pio 45 mg	112	9.78 (0.29)	-1.06 (0.22)	-0.80 (0.31)	(-1.40,-0.20)	0.009 *
Placebo + Pio 45 mg	116	9.78 (0.25)	-0.26 (0.22)			
Sensitivity ITT population						
Vilda 50 mg qd + Pio 45 mg	141	10.00 (0.25)	-0.88 (0.20)	-0.52 (0.28)	(-1.06,0.03)	0.065
Vilda 50 mg bid + Pio 45 mg	153	9.66 (0.26)	-1.03 (0.19)	-0.66 (0.27)	(-1.20,-0.13)	0.015 *
Placebo + Pio 45 mg	153	9.94 (0.25)	-0.36 (0.19)			

* indicates statistical significance at the 5% level according to the Hochberg step-up procedure.

Summary of Safety

Safety Results

Number (%) of patients with SAEs by preferred term (Safety population)

Preferred Term	Vilda 50mg qd + Pio 45mg N=146 n (%)	Vilda 50mg bid + Pio 45mg N=158 n (%)	Placebo + Pio 45mg N=158 n (%)
Any SAE	10 (6.8)	2 (1.3)	9 (5.7)
Contusion	0 (0.0)	1 (0.6)	0 (0.0)
Jaw fracture	0 (0.0)	1 (0.6)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.6)	0 (0.0)
Upper limb fracture	0 (0.0)	1 (0.6)	0 (0.0)
Anemia	1 (0.7)	0 (0.0)	0 (0.0)
Angina pectoris	1 (0.7)	0 (0.0)	1 (0.6)
Ankle fracture	0 (0.0)	0 (0.0)	1 (0.6)
Ascites	1 (0.7)	0 (0.0)	0 (0.0)
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (0.6)
Bipolar disorder	1 (0.7)	0 (0.0)	0 (0.0)
Cardiac failure	1 (0.7)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.6)
Chest discomfort	0 (0.0)	0 (0.0)	1 (0.6)
Chest pain	0 (0.0)	0 (0.0)	1 (0.6)
Cholecystitis acute	1 (0.7)	0 (0.0)	1 (0.6)
Coronary artery disease	0 (0.0)	0 (0.0)	1 (0.6)
Dehydration	0 (0.0)	0 (0.0)	1 (0.6)

Preferred Term	Vilda 50mg qd + Pio 45mg N=146 n (%)	Vilda 50mg bid + Pio 45mg N=158 n (%)	Placebo + Pio 45mg N=158 n (%)
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	1 (0.6)
Dizziness	0 (0.0)	0 (0.0)	1 (0.6)
Duodenal ulcer	1 (0.7)	0 (0.0)	0 (0.0)
Dyspnea	0 (0.0)	0 (0.0)	1 (0.6)
Endometrial cancer	1 (0.7)	0 (0.0)	0 (0.0)
Hepatic cirrhosis	1 (0.7)	0 (0.0)	0 (0.0)
Hepatitis chronic active	1 (0.7)	0 (0.0)	0 (0.0)
Hyperglycemia	1 (0.7)	0 (0.0)	1 (0.6)
Hypertension	1 (0.7)	0 (0.0)	0 (0.0)
Intervertebral disc degeneration	1 (0.7)	0 (0.0)	0 (0.0)
Metabolic disorder	0 (0.0)	0 (0.0)	1 (0.6)
Multiple myeloma	1 (0.7)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	1 (0.6)
Non-cardiac chest pain	1 (0.7)	0 (0.0)	0 (0.0)
Osteomyelitis	0 (0.0)	0 (0.0)	1 (0.6)
Pancreatitis acute	1 (0.7)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.7)	0 (0.0)	0 (0.0)
Polydipsia	0 (0.0)	0 (0.0)	1 (0.6)
Polyuria	0 (0.0)	0 (0.0)	1 (0.6)
Portal hypertension	1 (0.7)	0 (0.0)	0 (0.0)
Skin ulcer	0 (0.0)	0 (0.0)	1 (0.6)
Transient ischemic attack	0 (0.0)	0 (0.0)	1 (0.6)

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

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

Primary system organ class	Vilda 50 mg qd + Pio 45 mg N=146 n (%)	Vilda 50 mg bid + Pio 45 mg N=158 n (%)	Placebo + Pio 45 mg N=158 n (%)
Any primary system organ class	81 (55.5)	79 (50.0)	77 (48.7)
Infections and infestations	32 (21.9)	32 (20.3)	25 (15.8)
General disorders and administration site conditions	23 (15.8)	21 (13.3)	12 (7.6)
Musculoskeletal disorders	17 (11.6)	17 (10.8)	13 (8.2)
Nervous system disorders	20 (13.7)	16 (10.1)	18 (11.4)
Gastrointestinal disorders	22 (15.1)	12 (7.6)	11 (7.0)
Investigations	5 (3.4)	10 (6.3)	7 (4.4)
Skin and subcutaneous tissue disorders	12 (8.2)	9 (5.7)	8 (5.1)
Renal and urinary disorders	1 (0.7)	8 (5.1)	5 (3.2)
Respiratory disorders	9 (6.2)	7 (4.4)	6 (3.8)
Injury, poisoning and procedural complications	11 (7.5)	6 (3.8)	6 (3.8)
Metabolic and nutritional disorders	8 (5.5)	6 (3.8)	15 (9.5)
Cardiac disorders	4 (2.7)	3 (1.9)	12 (7.6)
Vascular disorders	4 (2.7)	3 (1.9)	5 (3.2)
Psychiatric disorders	5 (3.4)	2 (1.3)	6 (3.8)
Eye disorders	5 (3.4)	2 (1.3)	3 (1.9)
Reproductive system and breast disorders	1 (0.7)	1 (0.6)	0 (0.0)
Ear and labyrinth disorders	4 (2.7)	0 (0.0)	3 (1.9)
Hepatobiliary disorders	4 (2.7)	0 (0.0)	1 (0.6)
Blood and lymphatic system disorders	2 (1.4)	0 (0.0)	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.4)	0 (0.0)	2 (1.3)
Surgical and medical procedures	1 (0.7)	0 (0.0)	0 (0.0)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category
System organ classes are sorted by descending order of incidence in the Vildagliptin 50 mg bid + Pioglitazone 45 mg group.

Number (%) of patients reporting common AEs (greater or equal to 2% in any group) by preferred term (Safety population)

Preferred term	Vilda 50 mg qd + Pio 45 mg N=146 n (%)	Vilda 50 mg bid + Pio 45 mg N=158 n (%)	Placebo + Pio 45 mg N=158 n (%)
Any Preferred term	81 (55.5)	79 (50.0)	77 (48.7)
Edema peripheral	12 (8.2)	11 (7.0)	4 (2.5)
Arthralgia	4 (2.7)	8 (5.1)	2 (1.3)
Urinary tract infection	3 (2.1)	8 (5.1)	2 (1.3)
Weight increased	3 (2.1)	8 (5.1)	3 (1.9)
Nasopharyngitis	6 (4.1)	6 (3.8)	4 (2.5)
Asthenia	4 (2.7)	5 (3.2)	2 (1.3)
Back pain	6 (4.1)	5 (3.2)	3 (1.9)
Headache	9 (6.2)	5 (3.2)	4 (2.5)
Upper respiratory tract infection	3 (2.1)	5 (3.2)	7 (4.4)
Dizziness	8 (5.5)	4 (2.5)	5 (3.2)
Fatigue	1 (0.7)	4 (2.5)	2 (1.3)
Myalgia	1 (0.7)	4 (2.5)	3 (1.9)
Paraesthesia	0 (0.0)	4 (2.5)	1 (0.6)
Influenza	3 (2.1)	3 (1.9)	3 (1.9)
Diarrhoea	4 (2.7)	2 (1.3)	3 (1.9)
Dyspnea	3 (2.1)	2 (1.3)	2 (1.3)
Hyperhidrosis	3 (2.1)	2 (1.3)	0 (0.0)
Hypertension	3 (2.1)	2 (1.3)	1 (0.6)
Nausea	8 (5.5)	2 (1.3)	4 (2.5)
Bronchitis	3 (2.1)	1 (0.6)	1 (0.6)
Cough	5 (3.4)	1 (0.6)	1 (0.6)
Pain in extremity	5 (3.4)	1 (0.6)	2 (1.3)
Pyrexia	3 (2.1)	1 (0.6)	0 (0.0)
Rash	4 (2.7)	1 (0.6)	0 (0.0)
Vertigo	4 (2.7)	0 (0.0)	2 (1.3)
Sinusitis	3 (2.1)	0 (0.0)	3 (1.9)
Angina pectoris	1 (0.7)	0 (0.0)	4 (2.5)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category.
Preferred terms are sorted by descending order of incidence in the Vildagliptin 50 mg bid + Pioglitazone 45 mg group.

Serious Adverse Events\Deaths\Discontinuations

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

		Vilda 50mg qd + Pio 45mg N=146 n (%)	Vilda 50mg bid + Pio 45mg N=158 n (%)	Placebo + Pio 45mg N=158 n (%)
Deaths		0	0	0
SAEs		10 (6.8)	2 (1.3)	9 (5.7)
Discontinuation due to AEs		7 (4.8)	5 (3.2)	4 (2.5)
AEs causing dose adjustment or interruption		5 (3.4)	2 (1.3)	3 (1.9)
Clinically significant CCV AEs		1 (0.7)	1 (0.6)	2 (1.3)
Clinically significant IM AEs		0 (0.0)	1 (0.6)	1 (0.6)
Other clinically significant AEs	Severity			
	Mild	18 (12.3)	19 (12.0)	12 (7.6)
	Moderate	11 (7.5)	7 (4.4)	9 (5.7)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)

These categories are not mutually exclusive.
The study did not allow dose adjustment.

Other Relevant Findings

Number (%) of patients with hematological abnormalities based on notable criteria (Safety population)

Parameter	Criterion	Vilda 50 mg qd + Pio 45 mg (N=146) Total n (%)	Vilda 50 mg bid + Pio 45 mg (N=158) Total n (%)	Placebo + Pio 45 mg (N=158) Total n (%)
Any notable abnormality		142 6 (4.2)	154 2 (1.3)	154 4 (2.6)
Eosinophils	>=14 %	142 1 (0.7)	154 0 (0.0)	154 0 (0.0)
Hematocrit	<=0.37(m) <=0.32(f) V/V	142 2 (1.4)	154 1 (0.6)	154 3 (1.9)
Hb	<=115(m) <=95(f) g/L	142 1 (0.7)	154 1 (0.6)	154 0 (0.0)
Platelets	<=75 >=700 10E9/L	142 1 (0.7)	154 0 (0.0)	153 0 (0.0)
WBC	<=2.8 >=16 10E9/L	142 2 (1.4)	154 1 (0.6)	154 1 (0.6)

Total = number of patients with evaluable criterion.
n = Number of patients meeting the criterion (i.e. who were notably abnormal).
m=male f=female.

Number (%) of patients with relevant percent change from baseline in hematological variables (Safety population)

Parameter	Vilda 50 mg qd + Pio 45 mg (N=146) n (%)	Vilda 50 mg bid + Pio 45 mg (N=158) n (%)	Placebo + Pio 45 mg (N=158) n (%)
Any relevant % change Total No.	142 (100)	154 (100)	154 (100)
No. of patients meeting criterion	39 (27.5)	31 (20.1)	33 (21.4)
Hematocrit Total No	142 (100)	154 (100)	154 (100)
>25% decrease	0 (0.0)	0 (0.0)	0 (0.0)
Hb Total No	142 (100)	154 (100)	154 (100)
>25% decrease	1 (0.7)	0 (0.0)	0 (0.0)
Low (#)	1 (0.7)	0 (0.0)	0 (0.0)
Platelets Total No.	142 (100)	154 (100)	153 (100)
>50% increase	5 (3.5)	2 (1.3)	2 (1.3)
Normal (#)	5 (3.5)	2 (1.3)	2 (1.3)
>25% decrease	12 (8.5)	12 (7.8)	11 (7.2)
Normal (#)	7 (4.9)	10 (6.5)	9 (5.9)
Low (#)	5 (3.5)	2 (1.3)	2 (1.3)
WBC Total No.	142 (100)	154 (100)	154 (100)
>50% increase	8 (5.6)	8 (5.2)	9 (5.8)
High (#)	1 (0.7)	1 (0.6)	0 (0.0)
Normal (#)	7 (4.9)	7 (4.5)	9 (5.8)
>25% decrease	20 (14.1)	19 (12.3)	18 (11.7)
Normal (#)	11 (7.7)	8 (5.2)	10 (6.5)
Low (#)	9 (6.3)	11 (7.1)	8 (5.2)

Total No.: A patient must have both baseline and post-baseline values of the test to be included. This number may be smaller than the number of exposed patients in the group (N).
a further classification of patients who meet the specified criterion with respect to the laboratory normal ranges. Baseline is the measurement obtained on the day of randomization (Day 1, Visit 2), or the screening measurement (Week -4, Visit 1) if the Day 1 measurement was missing.

Number (%) of patients with biochemical abnormalities based on notable criteria (Safety population)

		Vilda 50 mg qd + Pio 45 mg (N=146)			Vilda 50 mg bid + Pio 45 mg (N=158)			Placebo + Pio 45 mg (N=158)		
Parameter	**Criterion**	**Total**	**n**	**(%)**	**Total**	**n**	**(%)**	**Total**	**n**	**(%)**
Any notable abnormality		142	4	(2.8)	154	7	(4.5)	154	8	(5.2)
ALT (xULN)	>=3*ULN	142	0	(0.0)	154	3	(1.9)	154	0	(0.0)
AST (xULN)	>=3*ULN	142	1	(0.7)	154	1	(0.6)	154	0	(0.0)
BUN (mmol/L)	>=9.99	142	2	(1.4)	154	3	(1.9)	154	6	(3.9)
Creatinine (umol/L)	>=176.8	142	0	(0.0)	154	0	(0.0)	154	0	(0.0)
CPK (xULN)	>=5*ULN	142	1	(0.7)	154	0	(0.0)	154	2	(1.3)
Sodium (mmol/L)	<=125 >=160	142	0	(0.0)	154	1	(0.6)	154	0	(0.0)

Total = number of patients with evaluable criterion.
n = Number of patients meeting the criterion (i.e. who are notably abnormal).

Number (%) of patients with relevant percent change from baseline in biochemistry variables (Safety population)

Parameter	Vilda 50 mg qd + Pio 45 mg (N=146) n (%)	Vilda 50 mg bid + Pio 45 mg (N=158) n (%)	Placebo + Pio 45 mg (N=158) n (%)
Any relevant % change Total No.	142 (100)	154 (100)	154 (100)
No. of patients meeting criterion	15 (10.6)	12 (7.8)	23 (14.9)
Creatinine Total No.	142 (100)	154 (100)	154 (100)
>40% increase	6 (4.2)	2 (1.3)	7 (4.5)
High (#)	3 (2.1)	1 (0.6)	2 (1.3)
Normal (#)	3 (2.1)	1 (0.6)	5 (3.2)
Potassium Total No.	140 (100)	151 (100)	153 (100)
>20% increase	8 (5.7)	7 (4.6)	11 (7.2)
High (#)	0 (0.0)	2 (1.3)	0 (0.0)
Normal (#)	8 (5.7)	5 (3.3)	11 (7.2)
>20% decrease	3 (2.1)	3 (2.0)	5 (3.3)
Normal (#)	3 (2.1)	3 (2.0)	4 (2.6)
Low (#)	0 (0.0)	0 (0.0)	1 (0.7)
Sodium Total No.	142 (100)	154 (100)	154 (100)
>10% increase	0 (0.0)	2 (1.3)	3 (1.9)
High (#)	0 (0.0)	0 (0.0)	2 (1.3)
Normal (#)	0 (0.0)	2 (1.3)	0 (0.0)
Low (#)	0 (0.0)	0 (0.0)	1 (0.6)

Total No.: A patient must have both baseline and post-baseline values of the test to be included. This number may be smaller than the number of exposed patients in the group (N).
a further classification of patients who meet the specified criterion with respect to the laboratory normal ranges. Baseline is the measurement obtained on the day of randomization (Day 1, Visit 2), or the screening measurement (Week -4, Visit 1) if the Day 1 measurement was missing.

Categorical analysis of conduction intervals measured at routine ECG evaluations (Safety population)

	Week 12		Week 24		Any time during DB treatment	
	N'	n (%)	N'	n (%)	N'	n (%)
QT >= 500 msec						
Vilda 50mg qd + Pio 45mg	122	0 (0.0)	105	0 (0.0)	137	0 (0.0)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	131	1 (0.8)	105	0 (0.0)	146	1 (0.7)
QTcB >= 500 msec						
Vilda 50mg qd + Pio 45mg	122	0 (0.0)	105	0 (0.0)	137	0 (0.0)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	131	1 (0.8)	105	0 (0.0)	146	1 (0.7)
QTcF >= 500 msec						
Vilda 50mg qd + Pio 45mg	122	0 (0.0)	105	0 (0.0)	137	0 (0.0)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	131	1 (0.8)	105	0 (0.0)	146	1 (0.7)
Change from Baseline in QT >= 30 msec						
Vilda 50mg qd + Pio 45mg	122	7 (5.7)	105	8 (7.6)	137	15 (10.9)
Vilda 50mg bid + Pio 45mg	129	4 (3.1)	103	5 (4.9)	144	9 (6.3)
Placebo + Pio 45mg	131	9 (6.9)	105	7 (6.7)	146	15 (10.3)
Change from Baseline in QTcB >= 30 msec						
Vilda 50mg qd + Pio 45mg	122	2 (1.6)	105	3 (2.9)	137	3 (2.2)
Vilda 50mg bid + Pio 45mg	129	5 (3.9)	103	2 (1.9)	144	6 (4.2)
Placebo + Pio 45mg	131	8 (6.1)	105	9 (8.6)	146	15 (10.3)

Change from Baseline in QTcF >= 30 msec						
Vilda 50mg qd + Pio 45mg	122	3 (2.5)	105	2 (1.9)	137	3 (2.2)
Vilda 50mg bid + Pio 45mg	129	2 (1.6)	103	2 (1.9)	144	4 (2.8)
Placebo + Pio 45mg	131	7 (5.3)	105	4 (3.8)	146	10 (6.8)
Change from Baseline in QT >= 60 msec						
Vilda 50mg qd + Pio 45mg	122	1 (0.8)	105	0 (0.0)	137	1 (0.7)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	131	2 (1.5)	105	1 (1.0)	146	2 (1.4)
Change from Baseline in QTcB >= 60 msec						
Vilda 50mg qd + Pio 45mg	122	0 (0.0)	105	0 (0.0)	137	0 (0.0)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	131	1 (0.8)	105	0 (0.0)	146	1 (0.7)
Change from Baseline in QTcF >= 60 msec						
Vilda 50mg qd + Pio 45mg	122	0 (0.0)	105	0 (0.0)	137	0 (0.0)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	131	1 (0.8)	105	0 (0.0)	146	1 (0.7)

Change from Baseline in PR >= 25% and resultant PR > 200 msec						
Vilda 50mg qd + Pio 45mg	120	0 (0.0)	105	0 (0.0)	135	0 (0.0)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	130	0 (0.0)	104	0 (0.0)	145	1 (0.7)
Change from Baseline in QRS >= 25% and resultant QRS > 110 msec						
Vilda 50mg qd + Pio 45mg	122	1 (0.8)	105	0 (0.0)	137	1 (0.7)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	0 (0.0)	144	0 (0.0)
Placebo + Pio 45mg	131	0 (0.0)	105	0 (0.0)	146	0 (0.0)
Decrease from baseline in RR >=25%* or increase from baseline in RR >= 25%**						
Vilda 50mg qd + Pio 45mg	122	0 (0.0)	105	0 (0.0)	137	0 (0.0)
Vilda 50mg bid + Pio 45mg	129	0 (0.0)	103	1 (1.0)	144	1 (0.7)
Placebo + Pio 45mg	131	1 (0.8)	105	0 (0.0)	146	1 (0.7)

Baseline is the average of all pre-treatment visits regardless of whether scheduled or unscheduled.
ECG measurement meeting the criterion at any scheduled or unscheduled visit post-baseline during double-blind (DB) treatment period
* Corresponding to HR > 100 bpm.
** Corresponding to HR < 50 bpm.
N' is the number of patients with a measurement at both baseline and relevant time point (Week 12 Week 24 and at any time during double-blind (DB) treatment period respectively)
n is the number of patients meeting the criterion

Treatment emergent ECG abnormalities by treatment group (Safety population)

Abnormality Type	Vilda 50mg qd + Pio 45mg N=146 n (%)	Vilda 50mg bid + Pio 45mg N=158 n (%)	Placebo + Pio 45mg N=158 n (%)
Any ECG abnormality	14 (9.6)	8 (5.1)	16 (10.1)
Rhythm	0 (0.0)	1 (0.6)	0 (0.0)
Other abnormal rhythm	0 (0.0)	1 (0.6)	0 (0.0)
Conduction	5 (3.4)	3 (1.9)	5 (3.2)
First degree AV block	2 (1.4)	2 (1.3)	2 (1.3)
RBBB	1 (0.7)	0 (0.0)	1 (0.6)
IVCD	1 (0.7)	0 (0.0)	0 (0.0)
LBBB	0 (0.0)	0 (0.0)	1 (0.6)
LAH	1 (0.7)	1 (0.6)	1 (0.6)
Morphology	2 (1.4)	0 (0.0)	1 (0.6)
LAA	0 (0.0)	0 (0.0)	1 (0.6)
Low voltage	2 (1.4)	0 (0.0)	0 (0.0)
ST segment	0 (0.0)	0 (0.0)	2 (1.3)
Depressed ST segment	0 (0.0)	0 (0.0)	1 (0.6)
Elevated ST segment	0 (0.0)	0 (0.0)	1 (0.6)
T waves	7 (4.8)	4 (2.5)	9 (5.7)
Flat T waves	6 (4.1)	3 (1.9)	6 (3.8)
Inverted T waves	0 (0.0)	1 (0.6)	2 (1.3)
Biphasic T waves	1 (0.7)	0 (0.0)	1 (0.6)

ECG findings presented exclude findings in sinus bradycardia, sinus tachycardia, artificial pacemaker ectopic supraventricular rhythm, VPC(s), APC(s), sinus pause(s)
A treatment-emergent ECG abnormality is defined as an abnormal ECG finding at any time during the randomized double blind treatment period which is not present at any of the pre-treatment visits.

Hypoglycemic events (Safety population)

Event category	Vilda 50 mg qd + Pio 45mg N=146	Vilda 50 mg bid + Pio 45mg N=158	Placebo + Pio 45mg N=158
Number(%) of patients with at least one hypoglycemic event	0 (0.0)	1 (0.6)	3 (1.9)
Number(%) of patients with			
one hypoglycemic event	0 (0.0)	0 (0.0)	3 (1.9)
two hypoglycemic events	0 (0.0)	1 (0.6)	0 (0.0)
Number(%) of patients who discontinued due to hypoglycemic events	0 (0.0)	0 (0.0)	0 (0.0)
Total number of events	0	2	3
Plasma glucose value(mmol/L)			
<=2.2	0 (0.0)	0 (0.0)	1 (33.3)
>2.2-2.8	0 (0.0)	2 (100.0)	1 (33.3)
>2.8-<3.1	0 (0.0)	0 (0.0)	1 (33.3)
Grade			
Grade 1	0 (0.0)	2 (100.0)	3 (100.0)

Hypoglycemic events are defined as a) symptoms suggestive of hypoglycemia, where the patient is able to initiate self-treatment and plasma glucose measurement is <3.1 mmol/L (grade 1), b) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and plasma glucose measurement is <3.1 mmol/L (grade 2) and c) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and no plasma glucose measurement is available (suspected grade 2).
A patient may have had more than one type of event

Publication

Garber AJ, Schweizer A, Baron MA, Rochotte E, Dejager S (2007) Vildagliptin in combination with pioglitazone improves glycemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. Diabetes obesity and metabolism; 9(2): 166-174

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