Sponsor

Novartis

Generic Drug Name

Vildagliptin

Trial Indication(s)

Type 2 diabetes

Protocol Number

CLAF237A2338

Protocol Title

A Multicenter, Double-Blind, Randomized, Active Controlled Study to Compare the Effect of 52 Weeks Treatment with LAF237 50 mg bid to Gliclazide up to 320 mg Daily as Add-On Therapy in Patients with Type 2 Diabetes Inadequately Controlled with Metformin Monotherapy.

Clinical Trial Phase

Phase III

Study Start/End Dates

24-Jan-2005 to 19-Jan-2009

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a multicenter, randomized, double-blind, active controlled study. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (HbA 1c 7.5%-11%) were included in the trial. Eligible patients were randomized to vildagliptin 50 mg bid or gliclazide up to 320 mg daily in a ratio of 1:1 in addition to their continued metformin treatment. Each patient attended one screening visit (Week -4) where the inclusion/exclusion criteria were assessed. Eligible patients were then randomized at visit 2 (Baseline; Day 1) and complete 9 additional visits and one phone call over a period of 52 weeks of treatment with vildagliptin or gliclazide added to metformin.

Centers

220 centers in 22 countries: Argentina (10), Australia (4), Brazil 3), Canada (6), Chile (2), Colombia (7), Czech Republic (6), Denmark (4), France (9), Germany (46), Guatemala (8), Hungary (4), India (7), Italy (25), Peru (2), Romania (10), Russia (4), Slovakia (10), Spain (31), Switzerland (9), Turkey (5) and United Kingdom (8).

Objectives:

Primary objective:

To confirm the efficacy of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the HbA 1c reduction with vildagliptin is not inferior to that with gliclazide after 52 weeks of treatment.

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

In addition to their continued metformin treatment, patients were treated with either Vildagliptin 50 mg bid or gliclazide up to 320 mg daily in a ratio of 1:1. Gliclazide was titrated from initially 80 mg to a maximum daily dose of 320 mg based on fasting fingerstick capillary glucose measurements.

Statistical Methods

The primary efficacy variable was change from baseline in HbA 1c at Week 52 or at the final visit. The primary hypothesis tested was the non-inferiority of vildagliptin 50 mg bid to gliclazide up to 320 mg, both combined with metformin, for the effect of reducing HbA 1c, based on a 0.4% non-inferiority margin. 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 null hypothesis was to be rejected and non-inferiority established if the upper limit of the 95% CI for the treatment difference did not exceed 0.4%. Once non-inferiority was demonstrated, superiority was to be tested using the same confidence interval from which non-inferiority was concluded. The primary population was the per protocol population, robustness of the results was assessed in the ITT population. The percentage of patients meeting each of the pre-defined responder criteria (categorical changes in HbA) was summarized in both the ITT and Per Protocol populations. For the critical secondary endpoint mean change from baseline in FPG, superiority of vildagliptin 50 mg bid to gliclazide up to 320 mg, both combined with metformin, was tested for the ITT population using the same ANCOVA model as specified for the primary efficacy variable. 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 0.6 mmol/l. Demographic and background data as well as safety data were summarized by treatment group.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion criteria:

1. On a stable dose of metformin as defined by the protocol.
2. Blood glucose criteria must be met.
3. Body mass index (BMI) in the range 22-45 kg/m^2.

Key Exclusion Criteria:

1. Pregnancy or lactation.
2. Type 1 diabetes.
3. Evidence of significant diabetic complications.
4. Evidence of serious cardiovascular complications.

5. Laboratory value abnormalities as defined by the protocol.

Participant Flow Table

Patient disposition (Randomized population)

Disposition Reason	Vilda 50mg bid + Met N=513 n (%)	Glic up to 320 mg daily + Met N=494 n (%)	Total N=1007 n (%)
Completed	407 (79.3)	412 (83.4)	819 (81.3)
Discontinued	106 (20.7)	82 (16.6)	188 (18.7)
Abnormal laboratory value(s)	4 (0.8)	5 (1.0)	9 (0.9)
Abnormal test procedure result(s)	1 (0.2)	0 (0.0)	1 (0.1)
Administrative problems	5 (1.0)	5 (1.0)	10 (1.0)
Adverse event(s)	33 (6.4)	22 (4.5)	55 (5.5)
Death	1 (0.2)	1 (0.2)	2 (0.2)
Lost to follow-up	6 (1.2)	7 (1.4)	13 (1.3)
Patient's condition no longer requires study drug	1 (0.2)	0 (0.0)	1 (0.1)
Patient withdrew consent	27 (5.3)	26 (5.3)	53 (5.3)
Protocol violation	6 (1.2)	3 (0.6)	9 (0.9)
Unsatisfactory therapeutic effect	22 (4.3)	13 (2.6)	35 (3.5)

*Due to GCP issues found at center 144, patients from that center were removed from all analysis populations.

Baseline Characteristics

Patient baseline demographic characteristics (Randomized population)

Demographic variable	Vilda 50mg bid + Met N=513	Glic up to 320 mg daily + Met N=494	Total N=1007
Age (years)			
Mean ± SD	59.2 ± 9.91	59.7 ± 10.17	59.5 ± 10.04
Median	60.0	61.0	61.0
Min, Max	27.0, 78.0	22.0, 78.0	22.0, 78.0
Age group (years)			
< 65	329 (64.1%)	288 (58.3%)	617 (61.3%)
≥ 65	184 (35.9%)	206 (41.7%)	390 (38.7%)
< 75	493 (96.1%)	477 (96.6%)	970 (96.3%)
≥ 75	20 (3.9%)	17 (3.4%)	37 (3.7%)
Sex			
Male	268 (52.2%)	256 (51.8%)	524 (52.0%)
Female	245 (47.8%)	238 (48.2%)	483 (48.0%)
Race			
Asian (Indian subcontinent)	40 (7.8%)	41 (8.3%)	81 (8.0%)
Asian (non Indian subcontinent)	3 (0.6%)	0 (0.0%)	3 (0.3%)
Black	3 (0.6%)	6 (1.2%)	9 (0.9%)
Caucasian	405 (78.9%)	383 (77.5%)	788 (78.3%)
Hispanic or latino	58 (11.3%)	59 (11.9%)	117 (11.6%)
Japanese	0 (0.0%)	1 (0.2%)	1 (0.1%)
Native american	2 (0.4%)	1 (0.2%)	3 (0.3%)
Other	2 (0.4%)	3 (0.6%)	5 (0.5%)
Height (cm)	n = 511	n = 494	n = 1005
Mean ± SD	165.5 ± 9.95	165.0 ± 10.41	165.2 ± 10.18
Median	165.0	165.0	165.0
Min, Max	140.0, 190.0	139.0, 202.0	139.0, 202.0

Demographic variable	Vilda 50mg bid + Met N=513	Glic up to 320 mg daily + Met N=494	Total N=1007
Body weight (kg)	n = 511	n = 494	n = 1005
Mean ± SD	85.7 ± 16.55	84.2 ± 17.86	85.0 ± 17.21
Median	84.8	82.0	84.0
Min, Max	45.6, 145.0	45.5, 156.0	45.5, 156.0
BMI (kg/m^2)	n = 511	n = 494	n = 1005
Mean ± SD	31.2 ± 5.03	30.8 ± 4.99	31.0 ± 5.02
Median	30.3	30.4	30.3
Min, Max	22.1, 44.9	22.0, 44.8	22.0, 44.9
BMI group (kg/m^2)			
< 30	235 (45.8%)	236 (47.8%)	471 (46.8%)
≥ 30	276 (53.8%)	258 (52.2%)	534 (53.0%)
≥ 35	113 (22.0%)	90 (18.2%)	203 (20.2%)
Not recorded	2 (0.4%)	0 (0.0%)	2 (0.2%)

*Demography information is collected on the day of the screening measurement (Week -4, Visit 1).

Patient baseline background characteristics (Randomized population)

Background Characteristic	Vilda 50mg bid + Met N=513	Glic up to 320 mg daily + Met N=494	Total N=1007
HbA_{1c} (%)	n = 512	n = 494	n = 1006
Mean ± SD	8.5 ± 1.02	8.5 ± 0.93	8.5 ± 0.98
Median	8.3	8.3	8.3
Min, Max	5.2, 13.1	5.8, 11.3	5.2, 13.1
HbA_{1c} (%)			
≤ 8	207 (40.4%)	176 (35.6%)	383 (38.0%)
> 8	305 (59.5%)	318 (64.4%)	623 (61.9%)
≤ 9	387 (75.4%)	370 (74.9%)	757 (75.2%)
> 9	125 (24.4%)	124 (25.1%)	249 (24.7%)
Not recorded	1 (0.2%)	0 (0.0%)	1 (0.1%)
FPG (mmol/L)	n = 513	n = 494	n = 1006
Mean ± SD	10.8 ± 2.78	10.6 ± 2.78	10.7 ± 2.78
Median	10.4	10.4	10.4
Min, Max	5.1, 24.8	3.1, 31.2	3.1, 31.2
Duration of Type 2 diabetes (years)	n = 512	n = 494	n = 1006
Mean ± SD	6.4 ± 5.11	6.8 ± 5.28	6.6 ± 5.19
Median	5.3	5.7	5.4
Min, Max	0.2, 35.1	0.3, 34.3	0.2, 35.1
GFR (MDRD) (mL/min) per 1.73 m^2			
Normal (>80)	348 (67.8%)	335 (67.8%)	683 (67.8%)
Mild (≥50 - ≤80)	156 (30.4%)	152 (30.8%)	308 (30.6%)
Moderate (≥30 - <50)	9 (1.8%)	7 (1.4%)	16 (1.6%)

Background Characteristic	Vilda 50mg bid + Met N=513	Glic up to 320 mg daily + Met N=494	Total N=1007
GFR (CG) (mL/min)			
Normal (>80)	409 (79.7%)	383 (77.5%)	792 (78.6%)
Mild (≥50 - ≤80)	96 (18.7%)	99 (20.0%)	195 (19.4%)
Moderate (≥30 - <50)	7 (1.4%)	12 (2.4%)	19 (1.9%)
Missing	1 (0.2%)	0 (0.0%)	1 (0.1%)
GAD categories			
Negative	416 (81.1%)	396 (80.2%)	812 (80.6%)
Positive	20 (3.9%)	14 (2.8%)	34 (3.4%)
Not recorded	77 (15.0%)	84 (17.0%)	161 (16.0%)

*Duration of type 2 diabetes is collected on the day of the screening measurement (Week -4, Visit 1).
GAD Antibodies: Negative (< 1000 U/L), Positive (≥ 1000 U/L)
For baseline HbA 1c measurements, only patients with at least one measurement on or prior to Day 1 are included.
Baseline HbA 1c and baseline FPG are the sample obtained on day 1 or the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing.
GFR (MDRD)= GFR estimated using the MDRD formula. GFR (CG)= GFR estimated using the CG formula. GFR is calculated using the serum creatinine and body weight value at the Day 1 measurement, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing.

Summary of Efficacy

Primary Outcome Result(s)

ANCOVA results for change in HbA 1c (%) from baseline to endpoint (Per protocol population and ITT population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to to comparator (SE)	95% CI	p-value
Per protocol population						
Vilda 50mg bid+Met	386	8.43 (0.05)	-0.81 (0.06)	0.04 (0.08)	(-0.11, 0.20)*	0.590
Glic up to 320 mg daily+Met	393	8.45 (0.05)	-0.85 (0.06)			
Intent to treat population						
Vilda 50mg bid+Met	499	8.46 (0.05)	-0.80 (0.05)	0.01 (0.07)	(-0.13, 0.15)*	0.867
Glic up to 320 mg daily+Met	487	8.48 (0.04)	-0.81 (0.05)			

Baseline is 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 measurement is missing. Endpoint is the final available post-randomization assessment up to the last regular scheduled visit. In the case of a missing scheduled visit sample, the closest unscheduled visit within 7 days of scheduled visit is used. n is the number of patients with observations at both baseline and endpoint. Adjusted means and the associated standard errors (SE), confidence intervals (CI), and p values were from an ANCOVA model containing terms for treatment, baseline and pooled centers.* Indicates non-inferiority to comparator at the one-sided 2.5% alpha level. Non-inferiority margin is 0.4%.

Number (%) of patients who responded at endpoint (Per protocol population and ITT Population)

	Vilda 50mg bid+Met n (%)	Glic up to 320 mg daily+Met n (%)	p-value*
Per protocol population	N=386	N=393	
N'[1]	386 (100.0)	393 (100.0)	
Responder Criterion			
At least one criterion met	267 (69.2)	269 (68.4)	0.828
HbA_{1c} < 7% [2]	112/379 (29.6)	123/385 (31.9)	0.473
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	63/143 (44.1)	67/139 (48.2)	0.485
HbA_{1c} ≤ 6.5% [2]	59/383 (15.4)	82/389 (21.1)	0.041
Reduction of HbA_{1c} ≥ 1% [1]	181 (46.9)	202 (51.4)	0.208
Reduction of HbA_{1c} ≥ 1% [1] in patients with baseline HbA_{1c} > 9% $	61/91 (67.0)	78/100 (78.0)	0.089
Reduction of HbA_{1c} ≥ 0.7% [1]	231 (59.8)	241 (61.3)	0.673
Reduction of HbA_{1c} ≥ 0.5% [1]	262 (67.9)	266 (67.7)	0.954
ITT population	N=503	N=490	
N'[1]	499 (100.0)	487 (100.0)	
Responder Criterion			
At least one criterion met	338 (67.7)	322 (66.1)	0.590
HbA_{1c} < 7% [2]	133/487 (27.3)	144/478 (30.1)	0.334
HbA_{1c} < 7% in patients with baseline HbA_{1c} ≤ 8% [3]	77/180 (42.8)	77/164 (47.0)	0.437
HbA_{1c} ≤ 6.5% [2]	76/496 (15.3)	96/483 (19.9)	0.061

	Vilda 50mg bid+Met n (%)	Glic up to 320 mg daily+Met n (%)	p-value*
Reduction of HbA_{1c} ≥ 1% [1]	220 (44.1)	234 (48.0)	0.212
Reduction of HbA_{1c} ≥ 1% [1] in patients with baseline HbA_{1c} > 9% $	78/122 (63.9)	85/123 (69.1)	0.391
Reduction of HbA_{1c} ≥ 0.7% [1]	281 (56.3)	284 (58.3)	0.525
Reduction of HbA_{1c} ≥ 0.5% [1]	331 (66.3)	319 (65.5)	0.783

Baseline is 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 measurement is missing. Endpoint is the final available post-randomization assessment up to the last regular scheduled visit. In the case of a missing scheduled visitsample, the closest unscheduled visit within 7 days of scheduled visit is used.* Chi-square test for vildagliptin vs. comparator treatment group.
[1]Number of patients with both baseline and endpoint HbA 1c measurements, which is used as denominatorunless specified otherwise.
[2]Denominator includes only patients with baseline HbA 1c ≥ 7% (> 6.5%) and endpoint HbA 1c measurement.
[3]Denominator includes only patients with 7% < baseline HbA 1c ≤ 8% and endpoint HbA 1c measurement.
[$] Denominator includes only patients with baseline HbA 1c >9% and endpoint HbA 1c measurement.

Coefficient of failure in HbA 1c from Week 24 to Week 52 (Per protocol population)

Treatment	n	Week 24 mean HbA1c (SE)	Week 52 mean HbA1c (SE)	Estimated CF % Per year (SE)	p-value
Vilda 50mg bid+Met	379	7.39 (0.05)	7.59 (0.06)	0.42 (0.09)	0.183
Glic up to 320 mg daily+Met	389	7.24 (0.05)	7.54 (0.06)	0.58 (0.08)	

CF = Coefficient of Failure. SE = Standard error.
n is the number of patients who have at least 3 HbA 1c measurements obtained at scheduled visits between Week 24 and Week 52, inclusive.
* Indicates statistical significance at 5% level.

Mean changes from baseline in HbA 1c (%) at endpoint: subgroup analyses (ITT population)

		Vilda 50mg bid+Met N = 386			Glic up to 320 mg daily+Met N = 393		
Subgroup	**Category**	**n**	**BL mean**	**Change (SE)**	**n**	**BL mean**	**Change (SE)**
HbA_{1c} at baseline (%)	≤ 8	157	7.56	-0.47 (0.06)	148	7.56	-0.54 (0.08)
	> 8	229	9.03	-1.05 (0.08)	245	8.98	-1.07 (0.09)
	≤ 9	295	8.00	-0.64 (0.06)	293	8.02	-0.62 (0.07)
	> 9	91	9.85	-1.38 (0.14)	100	9.69	-1.59 (0.11)
BMI at baseline	< 30	186	8.49	-0.85 (0.08)	193	8.46	-0.88 (0.10)
(kg/m^2)	≥ 30	200	8.38	-0.77 (0.08)	200	8.44	-0.86 (0.08)
	≥ 35	81	8.57	-0.85 (0.13)	67	8.36	-0.65 (0.15)
Age(years)	≤ 65	243	8.43	-0.71 (0.07)	234	8.46	-0.84 (0.08)
	>65	143	8.44	-0.98 (0.09)	159	8.43	-0.91 (0.11)
Gender	Male	197	8.39	-0.80 (0.08)	200	8.42	-0.94 (0.09)
	Female	189	8.48	-0.82 (0.09)	193	8.48	-0.80 (0.09)

*Baseline is 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 measurement is missing. Endpoint is the final available post-randomization assessment up to the last regular scheduled visit. In the case of a missing scheduled visit sample, the closest unscheduled visit within 7 days of scheduled visit is used.

Summary of Safety

Safety Results

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

Primary system organ class	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Any primary system organ class	315 (61.8)	302 (61.3)
Blood and lymphatic system disorders	8 (1.6)	9 (1.8)
Cardiac disorders	25 (4.9)	27 (5.5)
Ear and labyrinth disorders	10 (2.0)	15 (3.0)
Endocrine disorders	2 (0.4)	1 (0.2)
Eye disorders	17 (3.3)	23 (4.7)
Gastrointestinal disorders	98 (19.2)	102 (20.7)
General disorders and administration site conditions	48 (9.4)	79 (16.0)
General disorders and administration site conditions	48 (9.4)	79 (16.0)
Hepatobiliary disorders	11 (2.2)	5 (1.0)
Immune system disorders	1 (0.2)	4 (0.8)
Infections and infestations	130 (25.5)	132 (26.8)
Injury, poisoning and procedural complications	28 (5.5)	33 (6.7)
Investigations	7 (1.4)	12 (2.4)
Metabolism and nutrition disorders	25 (4.9)	22 (4.5)
Musculoskeletal and connective tissue disorders	87 (17.1)	90 (18.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (1.6)	5 (1.0)
Nervous system disorders	79 (15.5)	97 (19.7)

Primary system organ class	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Psychiatric disorders	27 (5.3)	34 (6.9)
Renal and urinary disorders	17 (3.3)	18 (3.7)
Reproductive system and breast disorders	15 (2.9)	9 (1.8)
Respiratory, thoracic and mediastinal disorders	32 (6.3)	35 (7.1)
Skin and subcutaneous tissue disorders	35 (6.9)	55 (11.2)
Social circumstances	1 (0.2)	0 (0.0)
Vascular disorders	37 (7.3)	40 (8.1)

*Primary system organ classes are presented alphabetically.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category. A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Number (%) of patients reporting common AEs (greater than or equal to 1% in any group) by preferred term (Safety population)

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Any Preferred term	315 (61.8)	302 (61.3)
Nasopharyngitis	32 (6.3)	28 (5.7)
Hypertension	29 (5.7)	31 (6.3)
Diarrhea	26 (5.1)	27 (5.5)
Dizziness	18 (3.5)	17 (3.4)
Back pain	17 (3.3)	19 (3.9)
Nausea	17 (3.3)	19 (3.9)
Headache	16 (3.1)	28 (5.7)
Abdominal pain upper	14 (2.7)	14 (2.8)
Arthralgia	14 (2.7)	18 (3.7)
Dyspepsia	14 (2.7)	15 (3.0)
Influenza	14 (2.7)	15 (3.0)
Pain in extremity	14 (2.7)	22 (4.5)
Constipation	13 (2.5)	8 (1.6)
Osteoarthritis	12 (2.4)	5 (1.0)
Urinary tract infection	12 (2.4)	14 (2.8)
Vomiting	12 (2.4)	7 (1.4)
Asthenia	11 (2.2)	24 (4.9)
Cough	11 (2.2)	10 (2.0)
Paresthesia	11 (2.2)	15 (3.0)
Bronchitis	10 (2.0)	20 (4.1)
Fatigue	10 (2.0)	20 (4.1)
Toothache	10 (2.0)	6 (1.2)
Upper respiratory tract infection	10 (2.0)	7 (1.4)
Tremor	9 (1.8)	24 (4.9)

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Gastroenteritis	8 (1.6)	8 (1.6)
Muscle spasms	8 (1.6)	5 (1.0)
Edema peripheral	8 (1.6)	6 (1.2)
Oropharyngeal pain	8 (1.6)	2 (0.4)
Palpitations	8 (1.6)	10 (2.0)
Contusion	7 (1.4)	0 (0.0)
Depression	7 (1.4)	4 (0.8)
Hyperhidrosis	7 (1.4)	26 (5.3)
Hypoesthesia	7 (1.4)	4 (0.8)
Musculoskeletal pain	7 (1.4)	3 (0.6)
Pyrexia	7 (1.4)	6 (1.2)
Sciatica	7 (1.4)	1 (0.2)
Anxiety	6 (1.2)	8 (1.6)
Pharyngitis	6 (1.2)	2 (0.4)
Pruritus	6 (1.2)	4 (0.8)
Somnolence	6 (1.2)	4 (0.8)
Vision blurred	6 (1.2)	7 (1.4)
Hepatic steatosis	5 (1.0)	2 (0.4)
Hyperglycemia	5 (1.0)	2 (0.4)
Hypoglycemia	5 (1.0)	5 (1.0)
Insomnia	5 (1.0)	5 (1.0)

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Iron deficiency anemia	5 (1.0)	2 (0.4)
Myalgia	5 (1.0)	3 (0.6)
Non-cardiac chest pain	5 (1.0)	7 (1.4)
Respiratory tract infection	5 (1.0)	4 (0.8)
Vertigo	5 (1.0)	6 (1.2)
Cystitis	4 (0.8)	7 (1.4)
Dry mouth	4 (0.8)	5 (1.0)
Disposal exertional	4 (0.8)	5 (1.0)
Hunger	4 (0.8)	5 (1.0)
Limb injury	4 (0.8)	5 (1.0)
Sinusitis	4 (0.8)	5 (1.0)
Gastritis	3 (0.6)	7 (1.4)
Lower respiratory tract infection	3 (0.6)	5 (1.0)
Malaise	3 (0.6)	9 (1.8)
Abdominal distension	2 (0.4)	5 (1.0)
Eczema	2 (0.4)	5 (1.0)
Spinal osteoarthritis	2 (0.4)	6 (1.2)
Abdominal pain	1 (0.2)	14 (2.8)
Anemia	1 (0.2)	7 (1.4)
Conjunctivitis	1 (0.2)	5 (1.0)
Thirst	1 (0.2)	6 (1.2)
Weight increased	1 (0.2)	5 (1.0)

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

Serious Adverse Events by System Organ Class

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

Preferred Term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Deaths	1 (0.2)	1 (0.2)
SAEs	34 (6.7)	43 (8.7)
Discontinuation due to AEs	34 (6.7)	23 (4.7)
Other clinically significant AEs	33 (6.5)	32 (6.5)
Mild	18 (3.5)	20 (4.1)
Moderate	14 (2.7)	6 (1.2)
Severe	1 (0.2)	2 (0.4)

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

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

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Any SAE	34 (6.7)	43 (8.7)
Abscess	1 (0.2)	0 (0.0)
Acute myocardial infarction	1 (0.2)	0 (0.0)
Amnesia	1 (0.2)	0 (0.0)
Angina unstable	1 (0.2)	0 (0.0)
Arrhythmia	1 (0.2)	0 (0.0)
Ascites	1 (0.2)	0 (0.0)
Ataxia	1 (0.2)	0 (0.0)
Atrial fibrillation	1 (0.2)	1 (0.2)
Back pain	1 (0.2)	0 (0.0)
Benign prostatic hyperplasia	1 (0.2)	0 (0.0)
Bladder disorder	1 (0.2)	0 (0.0)
Breast cancer	1 (0.2)	0 (0.0)
Carotid arteriosclerosis	1 (0.2)	0 (0.0)
Cellulitis	1 (0.2)	1 (0.2)
Cerebral hemorrhage	1 (0.2)	0 (0.0)
Cholecystitis	1 (0.2)	0 (0.0)
Cholelithiasis	1 (0.2)	1 (0.2)
Cognitive disorder	1 (0.2)	0 (0.0)
Coronary artery disease	1 (0.2)	0 (0.0)

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Depression	1 (0.2)	0 (0.0)
Disorientation	1 (0.2)	0 (0.0)
Head injury	1 (0.2)	0 (0.0)
Hepatic neoplasm	1 (0.2)	0 (0.0)
Hip fracture	1 (0.2)	1 (0.2)
Hyperglycemia	1 (0.2)	1 (0.2)
Hypertensive crisis	1 (0.2)	1 (0.2)
Hypoesthesia	1 (0.2)	0 (0.0)
Inguinal hernia	1 (0.2)	0 (0.0)
Injection site cellulitis	1 (0.2)	0 (0.0)
Ischemic stroke	1 (0.2)	0 (0.0)
Lip and/or oral cavity cancer	1 (0.2)	0 (0.0)
Localised infection	1 (0.2)	0 (0.0)
Lordosis	1 (0.2)	0 (0.0)
Metrorrhagia	1 (0.2)	0 (0.0)
Multiple injuries	1 (0.2)	0 (0.0)
Muscular weakness	1 (0.2)	0 (0.0)
Myelitis	1 (0.2)	0 (0.0)
Non-Hodgkin's lymphoma	1 (0.2)	0 (0.0)
Osteomyelitis	1 (0.2)	0 (0.0)
Par aesthesia	1 (0.2)	0 (0.0)
Peritonitis bacterial	1 (0.2)	0 (0.0)
Renal failure acute	1 (0.2)	0 (0.0)
Road traffic accident	1 (0.2)	0 (0.0)
Sepsis	1 (0.2)	0 (0.0)
Skin burning sensation	1 (0.2)	0 (0.0)

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Synovial cyst	1 (0.2)	0 (0.0)
Transient ischemic attack	1 (0.2)	0 (0.0)
Urinary retention	1 (0.2)	0 (0.0)
Venous insufficiency	1 (0.2)	0 (0.0)
Ventricular pre-excitation	1 (0.2)	0 (0.0)
Anemia	0 (0.0)	1 (0.2)
Angina pectoris	0 (0.0)	1 (0.2)
Anxiety	0 (0.0)	1 (0.2)
Atrioventricular block first degree	0 (0.0)	1 (0.2)
Atrioventricular block second degree	0 (0.0)	1 (0.2)
Blister infected	0 (0.0)	1 (0.2)
Cardiac failure	0 (0.0)	3 (0.6)
Cerebral infarction	0 (0.0)	1 (0.2)
Cerebrovascular accident	0 (0.0)	2 (0.4)
Chemical poisoning	0 (0.0)	1 (0.2)
Confusional state	0 (0.0)	1 (0.2)
Cystitis	0 (0.0)	1 (0.2)
Erysipelas	0 (0.0)	1 (0.2)

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Femoral artery occlusion	0 (0.0)	1 (0.2)
Foot fracture	0 (0.0)	1 (0.2)
Fungal skin infection	0 (0.0)	1 (0.2)
Gastrointestinal hemorrhage	0 (0.0)	1 (0.2)
Hypoacusis	0 (0.0)	2 (0.4)
Hypocalcaemia	0 (0.0)	1 (0.2)
Incisional hernia	0 (0.0)	1 (0.2)
Intervertebral disc protrusion	0 (0.0)	1 (0.2)
Loss of consciousness	0 (0.0)	1 (0.2)
Lower respiratory tract infection	0 (0.0)	1 (0.2)
Meniscus lesion	0 (0.0)	1 (0.2)
Mesenteric panniculitis	0 (0.0)	1 (0.2)
Myocardial infarction	0 (0.0)	1 (0.2)
Nephrolithiasis	0 (0.0)	1 (0.2)
Non-cardiac chest pain	0 (0.0)	1 (0.2)
Osteoarthritis	0 (0.0)	2 (0.4)
Pancreatitis acute	0 (0.0)	1 (0.2)
Paralysis flaccid	0 (0.0)	1 (0.2)
Postoperative abscess	0 (0.0)	1 (0.2)
Prostatomegaly	0 (0.0)	1 (0.2)
Radius fracture	0 (0.0)	1 (0.2)
Renal colic	0 (0.0)	2 (0.4)

Preferred term	Vilda 50mg bid + Met N=510 n (%)	Glic up to 320 mg daily + Met N=493 n (%)
Respiratory distress	0 (0.0)	1 (0.2)
Rotator cuff syndrome	0 (0.0)	1 (0.2)
Salpingitis	0 (0.0)	1 (0.2)
Sudden cardiac death	0 (0.0)	1 (0.2)
Thyroid neoplasm	0 (0.0)	1 (0.2)
Urinary tract infection	0 (0.0)	1 (0.2)
Vertigo	0 (0.0)	1 (0.2)
Vomiting	0 (0.0)	1 (0.2)

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

Other Relevant Findings

None

Date of Clinical Trial Report

31-Aug-2009