Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 Diabetes

Approved Indication

Type 2 Diabetes
As monotherapy and SU combination therapy

Protocol Number

CLAF237A1308

Title

A multicenter, open label, long term safety study of 52-week treatment with LAF237 in patients with type 2 diabetes

Phase of Development

Phase III

Study Start/End Dates

29 June 2010 to 14 January 2012

Study Design/Methodology

The study was designed as a multicenter, open label, long-term study of vildagliptin 50 mg given twice daily (morning and evening) as add on therapy in patients inadequately controlled with metformin, thiazolidinedione, α-GI, or glinides for 52 weeks. If it was considered difficult to continue vildagliptin 50 mg twice daily (bid) by the investigator or subinvestigator because of any adverse event, the dosing regimen could be changed to vildagliptin 50 mg once daily (qd) (morning) for efficacy and safety evaluation, when appropriate, after examination of the type and severity of symptom and others.

Centres

24 centers in Japan

Publication

M. Suzuki, I Hamada, M. Odawara., Vildagliptin as add-on therapy to other oral antidiabetics in Japanese patients with type 2 diabetes. Diabetologia. 2012; 55 (Suppl1):S354

Outcome measures

Primary outcome measures(s)

Incidence of adverse events during the treatment period [Time Frame: 52 weeks]

Secondary outcome measures(s)

- Change from baseline in HBA1c [Time Frame: 52 weeks]
- Change from baseline in Fasting Plasma Glucose [Time Frame: 52 weeks]
- Change from baseline in Fasting Insulin [Time Frame: 52 weeks]
- Change from baseline in Fasting C-peptide [Time Frame: 52 weeks]
- Change from baseline in HOMA-B [Time Frame: 52 weeks]

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

Oral tablets of vildagliptin 50 mg given twice daily (morning and evening)

Statistical Methods

Efficacy:

No primary efficacy variable (endpoint) was established in the study.
The main secondary variable was changes in HbA1c (%) from baseline (Day 0, Visit 2) at the time of last evaluation. Baseline was defined as the day (Visit 2, Day 0) of enrollment in the treatment phase. If the value at Visit 2 was missing, a value at a time immediately prior to Visit 2 (at a scheduled or unscheduled visit) was handled as a baseline value. All values available after the start of treatment with the study drug were handled as values obtained during the course of treatment with the study drug. The last observation carried forward (LOCF) method was employed for subjects without Week 52 HbA1c value. Data after discontinuation for any reason were imputed by carrying forward the last on-treatment value (at a scheduled or unscheduled visit) through to the end of the study (Week 52, Visit 16). HbA1c values obtained in the study were expressed in JDS values.
Actual values of HbA1c and changes in HbA1c from baseline, which were determined in the FAS population, were summarized by concomitant medication and by visit. For changes in HbA1c (%) from baseline at the time of last evaluation, two-sided 95% confidence intervals based on t distribution were also presented. Furthermore, changes in mean HbA1c plotted versus time during the treatment period, which were determined in the FAS population, were presented by treatment group. The same analyses as applied to the main secondary endpoints were applied to other secondary endpoints in the FAS population. For analysis of fasting lipids, changes from baseline were also handled as an analytical variable.

Safety:
The primary objective of the study was to evaluate the long-term safety of vildagliptin given in combination with metformin, thiazolidinedione, α-GI, or glinides in patients with type 2 diabetes. The frequency (incidence) of adverse events during the treatment period was established as a primary safety endpoint.
During the study period, safety was evaluated in the safety analysis set (SAF). For that purpose, adverse events, hypoglycemic events, laboratory test values, vital signs, and ECG results were summarized by treatment group and presented in listings.
The incidence of adverse events (events that newly occurred after the start of treatment with the study drug or those which were present before drug administration and whose severity was increased after drug administration) in each treatment group was summarized by system organ

class (SOC) and preferred term (PT). The adverse events were further summarized by severity and by causal relationship to the study drug. All adverse events entered after the end of treatment with the study drug and before database lock were included in tabulation and listings of events.

The number of deaths/subjects with other serious adverse events, adverse events leading to treatment discontinuation, or adverse events requiring interruption or dose reduction of the study drug and the incidence of them were tabulated separately. And other predefined significant adverse events (skin, vascular, muscular, hepatic disorder, acute pancreatitis-related, infections, lactic acidosis-related, and neuropsychiatric adverse events) were also tabulated. Furthermore, the number of subjects with the following events assessed by the adjudication committee in each treatment group and the incidence of them were tabulated: significant cardiovascular/cerebrovascular adverse events, significant hepatic adverse events, significant skin, vascular, edema, and muscular (SVEM) adverse events, significant breast cancer-related adverse events.

Study Population: Key Inclusion/Exclusion Criteria and Demographics

Key Inclusion criteria

- patients with type 2 diabetes inadequately controlled with diet, exercise and metformin, thiazolidinedione, or α-GI, or glinides monotherapy
- Age in the 20 years or over inclusive
- HbA1c in the range of ≥ 6.5 to ≤ 10%

Key Exclusion Criteria:

- Type 1 diabetes mellitus, diabetes that is a result of pancreatic injury, or secondary forms of diabetes
- Significant heart diseases
- Significant diabetic complications

Other protocol defined inclusion/exclusion criteria applied.

Participant Flow

Disposition of subjects (Enrolled Set)

Treatment group	Vilda + Met* N = 58 n (%)	Vilda + TZD N = 62 n (%)	Vilda + α-GI N = 62 n (%)	Vilda + glinides N = 63 n (%)	Total Vilda N = 245 n (%)
Completed	53(91.4)	52(83.9)	58(93.5)	48(76.2)	211(86.1)
Discontinued	5(8.6)	10(16.1)	4(6.5)	15(23.8)	34(13.9)
Reasons for discontinuation					
Adverse events	3(5.2)	4(6.5)	4(6.5)	6(9.5)	17(6.9)
Inadequate therapeutic effects	0(0.0)	3(4.8)	0(0.0)	4(6.3)	7(2.9)
Withdrawal of consent	0(0.0)	1(1.6)	0(0.0)	5(7.9)	6(2.4)
Management-related problem	0(0.0)	2(3.2)	0(0.0)	0(0.0)	2(0.8)
Protocol deviations	2(3.4)	0(0.0)	0(0.0)	0(0.0)	2(0.8)

*Vilda = Vildagliptin, Met = Metformin, TZD = Thiazolidinedione, α-GI = α- glucosidase inhibitor, glinides = Rapid-acting insulin secretagogues

Baseline Characteristics (Enrolled Set)

Background factors		Vilda + Met N = 58	Vilda + TZD N = 62	Vilda + α-GI N = 62	Vilda + glinides N = 63	Total Vilda N = 245
Age (yrs old)	n	58	62	62	63	245
	Mean	58.0	59.0	60.9	59.9	59.5
	SD	11.06	11.24	10.41	12.10	11.21
Gender n (%)	Male	35(60.3%)	50(80.6%)	42(67.7%)	45(71.4%)	172(70.2%)
	Female	23(39.7%)	12(19.4%)	20(32.3%)	18(28.6%)	73(29.8%)
Body weight (kg)	n	58	62	62	63	245
	Mean	68.6	72.1	65.8	66.8	68.3
	SD	9.79	13.61	13.06	13.63	12.82
BMI (kg/m^2)	n	58	62	62	63	245
	Mean	26.0	26.5	24.8	25.0	25.6
	SD	3.47	3.77	3.73	3.55	3.68
HbA1c (%)	n	58	62	62	63	245
	Mean	7.4	7.4	7.3	7.6	7.4
	SD	0.87	0.91	0.76	0.89	0.86
FPG (mg/dL)	n	58	62	62	63	245
	Mean	156.1	155.5	155.2	177.7	161.3
	SD	32.97	32.16	28.18	51.10	38.32
Duration of type 2 diabetes (yrs)						
	n	58	62	62	63	245
	Mean	6.8	6.6	6.9	5.7	6.5
	SD	5.91	4.90	5.25	4.76	5.20
GFR category (MDRD) n (%)						
	Normal (>80)	52(89.7%)	58(93.5%)	52(83.9%)	53(84.1%)	215(87.8%)
	Mild (≥50 - ≤80)	6(10.3%)	4(6.5%)	9(14.5%)	10(15.9%)	29(11.8%)
	Moderate (≥30 - <50)	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	1(0.4%)

Outcome measures

Primary Outcome Result(s)

Please refer to Safety Result section for the primary results. There were no primary efficacy outcomes defined for this study.

Secondary Outcome Result(s)

Changes in HbA1c from baseline at the time of last evaluation (FAS)

	Vilda + Met* N = 58	Vilda + TZD N = 62	Vilda + α-GI N = 62	Vilda + glinides N = 63	Total Vilda N = 245
n [a)]	58	62	62	63	245
Baseline mean (SE) [b)]	7.40 (0.115)	7.40 (0.116)	7.26 (0.097)	7.57 (0.112)	7.41 (0.055)
Mean change (SE) [b)]	−0.75 (0.112)	−0.92 (0.083)	−0.94 (0.102)	−0.64 (0.107)	−0.81 (0.051)
95%CI [c)]	(−0.97, −0.52)	(−1.08, −0.75)	(−1.15, −0.74)	(−0.85, −0.43)	(−0.91, −0.71)

HbA1c unit: %
Baseline was defined as the first day (Day 0, Visit 2) of the treatment period. If the value at Visit 2 was missing, a value at a time immediately prior to Visit 2 (at a scheduled or unscheduled visit) was handled as a baseline value.
The last evaluation was performed with last values obtained during a period between the first day of the treatment period and the day of scheduled visit at Week 52.
HbA1c values are expressed in JDS unit (%). HbA1c (NGSP, %) = HbA1c (JDS, %) + 0.4

*Vilda = Vildagliptin, Met = Metformin, TZD = Thiazolidinedione, α-GI = α- glucosidase inhibitor, glinides = Rapid-acting insulin secretagogues

a) n represents the number of subjects from whom values both at baseline and at the time of last evaluation could be obtained.

b) SE: standard error

c) CI: confidence interval based on 1-sample t-distribution

Changes in FPG from baseline at the time of last evaluation (FAS)

	Vilda + Met N = 58	Vilda + TZD N = 62	Vilda + α-GI N = 62	Vilda + glinides N = 63	Total Vilda N = 245
n [a)]	58	62	62	63	245
Baseline mean (SE) [b)]	156.1 (4.33)	155.5 (4.08)	155.2 (3.58)	177.7 (6.44)	161.3 (2.45)
Mean change (SE) [b)]	−14.0 (3.78)	−19.6 (2.94)	−17.0 (3.49)	−18.8 (4.60)	−17.4 (1.87)
95%CI [c)]	(−21.6, −6.4)	(−25.5, −13.7)	(−24.0, −10.0)	(−28.0, −9.6)	(−21.1, −13.7)

FPG unit: mg/dL;
Baseline was defined as the first day (Day 0, Visit 2) of the treatment period. If the value at Visit 2 was missing, a value at a time immediately prior to Visit 2 (at a scheduled or unscheduled visit) was handled as a baseline value.
The last evaluation was performed with last values obtained during a period between the first day of the treatment period and the day of scheduled visit at Week 52.

a) n represents the number of subjects from whom values both at baseline and at the time of last evaluation could be obtained.

b) SE: standard error

c) CI: confidence interval based on 1-sample t-distribution

Changes in fasting insulin and fasting C-peptide from baseline at the time of last evaluation (FAS)

Parameter	Vilda + Met N = 58	Vilda + TZD N = 62	Vilda + α-GI N = 62	Vilda + glinides N = 63	Total Vilda N = 245
Fasting insulin (μU/mL)					
n [a)]	58	62	62	63	245
Baseline mean (SE) [b)]	8.33 (0.616)	6.43 (0.536)	7.58 (0.691)	7.13 (0.638)	7.35 (0.313)
Mean change (SE) [b)]	−0.23 (0.478)	−0.56 (0.298)	0.02 (0.383)	−0.04 (0.459)	−0.20 (0.204)
95% CI [c)]	(−1.18, 0.73)	(−1.16, 0.04)	(−0.74, 0.79)	(−0.96, 0.88)	(−0.60, 0.20)
Fasting C-peptide (ng/mL)					
n [a)]	58	62	62	63	245
Baseline mean (SE) [b)]	1.53 (0.084)	1.34 (0.073)	1.49 (0.078)	1.38 (0.070)	1.43 (0.038)
Mean change (SE) [b)]	−0.04 (0.061)	−0.13 (0.043)	−0.05 (0.049)	0.01 (0.052)	−0.05 (0.026)
95% CI [c)]	(−0.16, 0.08)	(−0.22, −0.05)	(−0.15, 0.04)	(−0.09, 0.12)	(−0.10, −0.00)

Baseline was defined as the first day (Day 0, Visit 2) of the treatment period. If the value at Visit 2 was missing, a

value at a time immediately prior to Visit 2 (at a scheduled or unscheduled visit) was handled as a baseline value. The last evaluation was performed with last values obtained during a period between the first day of the treatment period and the day of scheduled visit at Week 52.

a) n represents the number of subjects from whom values both at baseline and at the time of last evaluation could be obtained.

b) SE: standard error

c) CI: confidence interval based on 1-sample t-distribution

Changes in HOMA-β and HOMA-R from baseline at the time of last evaluation (FAS)

Parameter	Vilda + Met N = 58	Vilda + TZD N = 62	Vilda + α-GI N = 62	Vilda + glinides N = 63	Total Vilda N = 245
HOMA-β					
n [a]	58	62	62	63	245
Baseline mean (SE) [b]	35.092 (3.2842)	28.134 (2.6656)	32.834 (4.0817)	25.663 (2.3932)	30.335 (1.5908)
Mean change (SE) [b]	6.755 (3.3414)	5.791 (1.9447)	4.635 (2.0575)	4.501 (1.6079)	5.395 (1.1388)
95% CI [c]	(0.064, 13.446)	(1.902, 9.680)	(0.521, 8.749)	(1.287, 7.715)	(3.152, 7.638)
HOMA-R					
n [a]	58	62	62	63	245
Baseline mean (SE) [b]	3.306 (0.2911)	2.420 (0.1994)	2.886 (0.2462)	3.259 (0.3908)	2.964 (0.1468)
Mean change (SE) [b]	−0.362 (0.1874)	−0.526 (0.1220)	−0.230 (0.1724)	−0.433 (0.2634)	−0.388 (0.0967)
95% CI [c]	(−0.737, 0.013)	(−0.770, −0.282)	(−0.575, 0.115)	(−0.960, 0.093)	(−0.579, −0.198)

Baseline was defined as the first day (Day 0, Visit 2) of the treatment period. If the value at Visit 2 was missing, a value at a time immediately prior to Visit 2 (at a scheduled or unscheduled visit) was handled as a baseline value.

HOMA-β = [20 × fasting insulin (μU/L)]/[FPG (mg/dL)/18.016 – 3.5]

HOMA-R = [fasting insulin (μU/L)] × [FPG (mg/dL)/18.016]/22.5

The last evaluation was performed with last values obtained during a period between the first day of the treatment period and the day of scheduled visit at Week 52.

a) n represents the number of subjects from whom values both at baseline and at the time of last evaluation could be obtained.

b) SE: standard error

c) CI: confidence interval based on 1-sample t-distribution

Safety Results

Adverse Events by System Organ Class (safety analysis population)

AE by SOC	Vilda + Met* N = 58 n (%)	Vilda + TZD N = 62 n (%)	Vilda + α-GI N = 62 n (%)	Vilda + glinides N = 63 n (%)	Total Vilda N = 245 n (%)
Total	55(94.8)	52(83.9)	53(85.5)	52(82.5)	212(86.5)
Blood and lymphatic system disorders	1(1.7)	1(1.6)	2(3.2)	0(0.0)	4(1.6)
Cardiac disorders	1(1.7)	3(4.8)	4(6.5)	1(1.6)	9(3.7)
Ear and labyrinth disorders	2(3.4)	3(4.8)	1(1.6)	0(0.0)	6(2.4)
Endocrine disorders	1(1.7)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Eye disorders	7(12.1)	10(16.1)	4(6.5)	10(15.9)	31(12.7)
Gastrointestinal disorders	23(39.7)	18(29.0)	17(27.4)	12(19.0)	70(28.6)
General disorders and administration site conditions	7(12.1)	6(9.7)	6(9.7)	5(7.9)	24(9.8)
Hepatobiliary disorders	3(5.2)	3(4.8)	3(4.8)	2(3.2)	11(4.5)
Immune system disorders	0(0.0)	0(0.0)	0(0.0)	1(1.6)	1(0.4)
Infections and infestations	36(62.1)	27(43.5)	33(53.2)	28(44.4)	124(50.6)
Injury, poisoning and procedural complications	12(20.7)	9(14.5)	6(9.7)	10(15.9)	37(15.1)
Investigations	20(34.5)	12(19.4)	8(12.9)	3(4.8)	43(17.6)
Metabolism and nutrition disorders	3(5.2)	1(1.6)	3(4.8)	2(3.2)	9(3.7)
Musculoskeletal and connective tissue disorders	15(25.9)	14(22.6)	13(21.0)	10(15.9)	52(21.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2(3.4)	2(3.2)	1(1.6)	0(0.0)	5(2.0)
Nervous system disorders	11(19.0)	9(14.5)	6(9.7)	11(17.5)	37(15.1)

Psychiatric disorders	1(1.7)	0(0.0)	1(1.6)	1(1.6)	3(1.2)
Renal and urinary disorders	3(5.2)	4(6.5)	1(1.6)	1(1.6)	9(3.7)
Reproductive system and breast disorders	1(1.7)	1(1.6)	1(1.6)	0(0.0)	3(1.2)
Respiratory, thoracic and mediastinal disorders	3(5.2)	3(4.8)	4(6.5)	3(4.8)	13(5.3)
Skin and subcutaneous tissue disorders	10(17.2)	11(17.7)	8(12.9)	9(14.3)	38(15.5)
Vascular disorders	3(5.2)	3(4.8)	3(4.8)	3(4.8)	12(4.9)

Displayed in alphabetical order
A subject who experienced multiple onset of an adverse event is counted as 1 subject.
*Vilda = Vildagliptin, Met = Metformin, TZD = Thiazolidinedione, α-GI = α- glucosidase inhibitor, glinides = Rapid-acting insulin secretagogues

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

Number of subjects with adverse events by preferred term and the incidence of them (safety analysis population)

Preferred Term	Vilda + Met N = 58 n (%)	Vilda + TZD N = 62 n (%)	Vilda + α-GI N = 62 n (%)	Vilda + glinides N = 63 n (%)	Total Vilda N = 245 n (%)
Total	55 (94.8)	52 (83.9)	53 (85.5)	52 (82.5)	212 (86.5)
Nasopharyngitis	17 (29.3)	13 (21.0)	25 (40.3)	20 (31.7)	75 (30.6)
Constipation	9 (15.5)	3 (4.8)	4 (6.5)	5 (7.9)	21 (8.6)
Back pain	3 (5.2)	4 (6.5)	5 (8.1)	3 (4.8)	15 (6.1)
Pharyngitis	10 (17.2)	3 (4.8)	1 (1.6)	1 (1.6)	15 (6.1)
Gastritis	5 (8.6)	4 (6.5)	2 (3.2)	1 (1.6)	12 (4.9)
Upper respiratory tract infection	3 (5.2)	4 (6.5)	1 (1.6)	4 (6.3)	12 (4.9)
Dizziness	2 (3.4)	2 (3.2)	2 (3.2)	5 (7.9)	11 (4.5)
Contusion	3 (5.2)	1 (1.6)	1 (1.6)	5 (7.9)	10 (4.1)
Bronchitis	5 (8.6)	0 (0.0)	3 (4.8)	1 (1.6)	9 (3.7)
Gastroenteritis	2 (3.4)	3 (4.8)	1 (1.6)	3 (4.8)	9 (3.7)

Displayed in decreasing order of incidence in "Total Vilda"
A subject who experienced multiple onset of an adverse event is counted as 1 subject.

Serious Adverse Events and Deaths (SAF)

Deaths, other serious adverse events, and other significant adverse events N (%)

	Vilda + Met N = 58 n (%)	Vilda + TZD N = 62 n (%)	Vilda + α-GI N = 62 n (%)	Vilda + glinides N = 63 n (%)	Total Vilda N = 245 n (%)
Deaths	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Serious adverse events	4(6.9)	5(8.1)	4(6.5)	2(3.2)	15(6.1)
Adverse events leading to treatment discontinuation	3(5.2)	4(6.5)	4(6.5)	6(9.5)	17(6.9)
Adverse events requiring interruption or dose reduction of the study drug	0(0.0)	0(0.0)	1(1.6)	2(3.2)	3(1.2)

Other Relevant Findings

Not applicable

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