Sponsor

Novartis

Generic Drug Name

Combination of Vildagliptin and Metformin

Trial Indication(s)

Type 2 diabetes (T2DM)

Protocol Number

CLMF237A2302S1

Protocol Title

A multicenter, open-label sub-study to LMF237A2302 to assess the effect of 24 weeks treatment with initial combination of vildagliptin 100mg qd plus metformin 1000mg bid in drug naïve patients with type 2 diabetes with very poor glycemic control

Clinical Trial Phase

Phase III

Study Start/End Dates

06-Mar-2007 to 06-Jun-2008

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a multicenter, open-label study in drug-naïve patients with T2DM (Hemoglobin A1c (HbA_{1c}) >11%, and/or fasting plasma glucose (FPG) >270mg/dL (15mmol/L). Patients not eligible for the core study CLMF237A2302 at Visit 1 because of their elevated HbA_{1c} and/or FPG levels but meeting the inclusion/exclusion criteria of this sub-study were offered to enter this open-label sub-study and invited to attend a baseline visit (Visit 2; Day 1) and to complete three further visits over a period of 24 weeks of initial combination treatment with vildagliptin 100mg qd plus metformin 1000mg bid.

Centers

40 centers in 4 countries: Germany (1), Poland (3), Spain (3) and United States (33).

Objectives:

Primary Objective:

- To demonstrate the effect of initial combination with vildagliptin 100mg qd plus metformin 1000mg bid in poor glycemic controlled, drug-naïve patients with T2DM (HbA_{1c} >11%, and/or FPG >270mg/dL (15mmol/L)) on HbA_{1c} reduction after 24 weeks of treatment.

Secondary Objective:

- To provide evidence of the safety of initial combination treatment with vildagliptin 100mg qd plus metformin 1000mg bid in drug-naïve patients with T2DM.

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

Oral Vildagliptin 50mg tablets (2 tablets was taken before the breakfast meal [i.e. 100 mg once daily]) and metformin 500mg tablets 1 tablet was to be taken before the breakfast meal and 1 tablet before the evening meal (i.e. 500 mg twice daily).

Statistical Methods

The primary efficacy variable was change form baseline in HbA_{1c} at endpoint. The primary analysis was testing the hypothesis that the mean change from baseline in HbA_{1c} is significantly different from zero. An analysis of covariance (ANCOVA) model was used with pooled center as factor and baseline HbA_{1c} as covariate. The primary analysis was performed in the Intent to Treat (ITT) population. Analysis in the Per protocol population was also performed as supplementary analysis. Secondary efficacy variables such as FPG and body weights were analyzed using similar ANCOVA models as used for HbA_{1c}. Responder rates were summarized.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male or female (non-fertile or of childbearing potential using a medically approved birth control method) patients with type 2 diabetes
- Diagnosis of type 2 diabetes for at least 4 weeks prior to study entry
- Body mass index 22-40 kg/meter squared
- HbA_{1c} > 11% and/or FPG >270 mg/dL

Exclusion Criteria:

- Pregnant or lactating female
- History of type 1 diabetes
- Evidence of significant diabetic complications
- Treatment with insulin or any other oral antidiabetic agent

Participant Flow Table

Patient disposition (Open Label population)

Disposition Reason	Vilda 100mg qd + Met N=94 n (%)
Completed [1]	55 (58.5)
Discontinued	39 (41.5)
Adverse event(s)	7 (7.4)
Abnormal laboratory value(s)	1 (1.1)
Abnormal test procedure result(s)	0 (0.0)
Unsatisfactory therapeutic effect	3 (3.2)
Subject's condition no longer requires study drug	0 (0.0)
Protocol violation	0 (0.0)
Subject withdrew consent	11 (11.7)
Lost to follow-up	16 (17.0)
Administrative problems	1 (1.1)
·Death·	0 (0.0)

[1] Completed patients must have remained in the study through the final visit (Visit 6, Week 24).

Baseline Characteristics

Patient baseline demographic characteristics (Open label population)

Baseline Characteristic	Statistics	Vilda 100mg qd + Met N=94 n (%)
Sex		
Male		56 (59.6)
Female		38 (40.4)
Race		
Caucasian		41 (43.6)
Black		7 (7.4)
Asian (non Indian Subcontinent)		1 (1.1)
Asian (Indian Subcontinent)		1 (1.1)
Hispanic or Latino		43 (45.7)
Japanese		0 (0.0)
Native American		1 (1.1)
Pacific Islander		0 (0.0)
Other		0 (0.0)
Age (years)	n	94
	Mean (SD)	45.6 (10.67)
	Median	46.0
	(Min, Max)	(24, 72)
Age Groups		
< 65 years		90 (95.7)
≥ 65 years		4 (4.3)
< 75 years		94 (100)
≥ 75 years		0 (0.0)

Baseline Characteristic	Statistics	Vilda 100mg qd + Met N=94 n (%)
Height (cm)	n	93
	Mean (SD)	167.86 (10.869)
	Median	166.00
	(Min, Max)	(142.0, 193.0)
Weight (kg)	n	93
	Mean (SD)	86.62 (19.563)
	Median	84.50
	(Min, Max)	(46.3, 144.0)
BMI (kg/m^2)	n	93
	Mean (SD)	30.48 (4.791)
	Median	30.27
	(Min, Max)	(21.3, 39.9)
BMI Categories		
< 30 kg/m^2		46 (48.9)
≥ 30 kg/m^2		47 (50.0)
≥ 35 kg/m^2		21 (22.3)
Missing		1 (1.1)

Demography information is collected on the day of the screening measurement (Week -2, Visit 1).

Summary of Efficacy

Primary Outcome Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to endpoint (ITT) population, Per Protocol population)

Population	Treatment	n	Baseline Mean (SE)	Adjusted Mean Change (SE)	95% CI	p-value*
ITT	Vilda 100mg qd + Met	86	12.14 (0.132)	-3.72 (0.253)	(-4.22, -3.22)	<0.001*
Per Protocol	Vilda 100mg qd + Met	58	12.11 (0.173)	-3.99 (0.281)	(-4.55, -3.43)	<0.001*

Baseline is measurement on sample obtained on Visit 2 (Day 1), or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if Day 1 (Visit 2) measurement is missing.Endpoint is the final available on-treatment assessment up to the last regular scheduled visit. n is the number of patients with observations at both baseline and endpoint.Adjusted mean change and associated standard error (SE), confidence interval (CI) and p-value were obtained from an ANCOVA model containing terms for pooled study center and baseline HbA_{1c}.
* indicates statistical significance at 5% level.

Number (%) of patients who responded at endpoint (ITT population, Per Protocol population)

Population	Responder Criterion	Vilda 100mg qd + Met n (%)
ITT	N [1]	86 (100)
	At least one criterion met	74 (86.0)
	Reduction of HbA_{1c} ≥ 1.5% [1]	66 (76.7)
	Reduction of HbA_{1c} ≥ 1% [1]	71 (82.6)
	Reduction of HbA_{1c} ≥ 0.7% [1]	74 (86.0)
Per Protocol	N [1]	58 (100)
	At least one criterion met	52 (89.7)
	Reduction of HbA_{1c} ≥ 1.5% [1]	47 (81.0)
	Reduction of HbA_{1c} ≥ 1% [1]	51 (87.9)
	Reduction of HbA_{1c} ≥ 0.7% [1]	52 (89.7)

[1] Number of patients with both baseline and endpoint HbA_{1c} measurements, which is used as the denominator.
Baseline is the measurement obtained on Visit 2 (Day 1), or on the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if the Day 1 (Visit 2) measurement is missing.
Week 24 endpoint is the final available on-treatment assessment up to the last regular scheduled visit.

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

		Vilda 100mg qd + Met N=86		
Subgroup	**Category**	**n**	**BL mean**	**Change (SE)**
HbA_{1c} at Baseline (%)	≤11%	12	10.38	-2.28 (0.467)
	>11%	74	12.43	-3.75 (0.298)
FPG at Baseline (mmol/L)	≤15mmol/L	24	12.18	-3.98 (0.495)
	>15 mmol/L	62	12.13	-3.38 (0.321)
BMI at Baseline (kg/m^2)	<30 kg/m^2	43	12.44	-3.94 (0.397)
	≥30kg/m^2	43	11.85	-3.14 (0.360)
	≥35kg/m^2	20	12.16	-3.39 (0.627)
Age at Baseline	<65 years	82	12.16	-3.49 (0.281)
	≥65 years	4	11.85	-4.58 (0.338)
Gender	Males	51	12.18	-3.80 (0.359)
	Females	35	12.09	-3.17 (0.405)

Baseline is measurement on sample obtained on Visit 2 (Day 1), or on sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if Day 1 (Visit 2) measurement is missing. Endpoint is the final available on-treatment assessment up to the last regular scheduled visit. $ The baseline value for those patients having measurement at this visit.

Secondary Outcome Result(s)

Refer to Safety Result section for safety secondary outcome result

Summary of Safety

Safety Results

Number (%) of patients with SAEs up to and including Week 24 visit by preferred term (Safety population)

Preferred term	Vilda 100mg qd + Met N=92 n (%)
Any SAE	5 (5.4)
Back pain	1 (1.1)
Diverticulitis	1 (1.1)
Gangrene	1 (1.1)
Gastric cancer	1 (1.1)
Gastric polyps	1 (1.1)
Gastritis	1 (1.1)
Osteomyelitis	1 (1.1)
Supraventricular tachycardia	1 (1.1)

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

Other Adverse Events by System Organ Class

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

Primary system organ class	Vilda 100mg qd + Met N=92 n (%)
Any Primary system organ class	40 (43.5)
Blood and lymphatic system disorders	2 (2.2)
Cardiac disorders	2 (2.2)
Eye disorders	2 (2.2)
Gastrointestinal disorders	19 (20.7)
General disorders and administration site conditions	2 (2.2)
Infections and infestations	12 (13.0)
Injury, poisoning and procedural complications	2 (2.2)
Investigations	3 (3.3)
Musculoskeletal and connective tissue disorders	7 (7.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.2)
Nervous system disorders	7 (7.6)
Psychiatric disorders	2 (2.2)
Reproductive system and breast disorders	1 (1.1)
Respiratory, thoracic and mediastinal disorders	3 (3.3)
Skin and subcutaneous tissue disorders	2 (2.2)
Vascular disorders	2 (2.2)

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

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

Preferred term	Vilda 100mg qd + Met N=92 n (%)
Diarrhea	11 (12.0)
Nausea	5 (5.4)
Headache	4 (4.3)
Abdominal pain	3 (3.3)
Arthralgia	2 (2.2)
Back pain	2 (2.2)
Cellulitis	2 (2.2)
Dizziness	2 (2.2)
Hypertension	2 (2.2)
Nasopharyngitis	2 (2.2)
Tremor	2 (2.2)
Upper respiratory tract infection	2 (2.2)

A patient with multiple occurrences of an AE is counted only once in the AE category.
Preferred terms are sorted by descending order of incidence.

Number (%) of patients with other clinically significant adverse events (Safety population)

Preferred term Maximum severity	Vilda 100mg qd + Met N=92 n (%)
Any event category	3 (3.3)
Mild	1 (1.1)
Moderate	1 (1.1)
Severe	1 (1.1)
Muscle event related term	3 (3.3)
Mild	1 (1.1)
Moderate	1 (1.1)
Severe	1 (1.1)
Blood creatine phosphokinase increased	
Severe	1 (1.1)
Muscle spasms	
Moderate	1 (1.1)
Muscular weakness	
Mild	1 (1.1)
Myalgia	
Mild	1 (1.1)
Pain in extremity	
Mild	1 (1.1)

A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple severity ratings for an AE is only counted under the maximum rating.
Events with missing severity are included only in the total row.

Serious Adverse Events and Deaths

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

	Vilda 100mg qd + Met N=92 n (%)
Deaths	0 (0.0)
SAEs	5 (5.4)
Discontinuation due to AEs	7 (7.6)
Discontinuation due to laboratory abnormalities	0 (0.0)
AEs causing dose adjustment or study drug interruption	1 (1.1)
Clinically significant CCV AEs	1 (1.1)
Clinically significant IM AEs	0 (0.0)
Other clinically significant AEs	3 (3.3)

These categories are not mutually exclusive.
Outside of those defined in the protocol, the study does not allow dose adjustment of study medication.

Other Relevant Findings

Number (%) of patients with hematological abnormalities based on notable ranges up to and including Week 24 (Safety population)

Laboratory test	Criterion	Vilda 100mg qd + Met N=92	
		Total	n (%)
Any notable abnormality		87	3 (3.4)
Eosinophils	≥14%	87	0 (0.0)
Hematocrit	(m) ≤0.37 V/V	52	2 (3.8)
	(f) ≤0.32 V/V	35	1 (2.9)
Hemoglobin	(m) ≤115 g/L	52	1 (1.9)
	(f) ≤95 g/L	35	0 (0.0)
Platelet count (direct)	≤75 10^9/L ≥700 10^9/L	87	0 (0.0)
Total leukocytes	≤2.8 $10E^9$/L ≥16 $10E^9$/L	87	0 (0.0)

(m) = Male; (f) = Female
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 hematological variables (Safety population)

			Vilda 100mg qd + Met N=92	
Laboratory test	Criterion		n	(%)
Any relevant percent change		Total Number	87	(100)
		No. of patients meeting criterion^	15	(17.2)
Hematocrit (1)	>25% decrease	Total Number	87	(100)
		No. of patients meeting criterion^	1	(1.1)
		High (#)	0	(0.0)
		Normal (#)	0	(0.0)
		Low (#)	1	(1.1)
	>50% increase	Total Number	87	(100)
		No. of patients meeting criterion^	0	(0.0)
		High (#)	0	(0.0)
		Normal (#)	0	(0.0)
		Low (#)	0	(0.0)
Hemoglobin (g/L)	>25% decrease	Total Number	87	(100)
		No. of patients meeting criterion^	1	(1.1)
		High (#)	0	(0.0)
		Normal (#)	0	(0.0)
		Low (#)	1	(1.1)
	>50% increase	Total Number	87	(100)
		No. of patients meeting criterion^	0	(0.0)
		High (#)	0	(0.0)
		Normal (#)	0	(0.0)
		Low (#)	0	(0.0)

Laboratory test	Criterion		Vilda 100mg qd + Met N=92 n	(%)
Platelet count (direct) (10E9/L)	>25% decrease	Total Number	85	(100)
		No. of patients meeting criterion^	3	(3.5)
		High (#)	0	(0.0)
		Normal (#)	2	(2.4)
		Low (#)	1	(1.2)
	>50% increase	Total Number	85	(100)
		No. of patients meeting criterion^	3	(3.5)
		High (#)	0	(0.0)
		Normal (#)	2	(2.4)
		Low (#)	1	(1.2)
WBC (total) (10E9/L)	>25% decrease	Total Number	87	(100)
		No. of patients meeting criterion^	5	(5.7)
		High (#)	0	(0.0)
		Normal (#)	5	(5.7)
		Low (#)	0	(0.0)
	>50% increase	Total Number	87	(100)
		No. of patients meeting criterion^	4	(4.6)
		High (#)	2	(2.3)
		Normal (#)	2	(2.3)
		Low (#)	0	(0.0)

^ 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 laboratory normal ranges. Baseline is the measurement obtained on Visit 2 (Day 1), or the screening measurement (Visit 1, Week -2) if the Visit 2 measurement is missing.

Number (%) of patients with biochemistry abnormalities based on notable ranges up to and including Week 24 (Safety population)

Laboratory test	Criterion	Vilda 100mg qd + Met N=92	
		Total	n (%)
Any notable abnormality		87	4 (4.6)
Alkaline phosphatase, serum (U/L)	≥3*ULN	87	0 (0.0)
SGPT (ALT) (U/L)	≥3*ULN	87	0 (0.0)
SGOT (AST) (U/L)	≥3*ULN	87	0 (0.0)
Bilirubin (direct/conjugated) (µmol/L)	≥3*ULN	87	0 (0.0)
Blood urea nitrogen (BUN) (mmol/L)	≥9.99 mmol/L	87	0 (0.0)
Creatinine (µmol/L)	≥176.8 mmol/L	87	0 (0.0)
Creatine kinase (U/L)	≥5*ULN	87	3 (3.4)
Potassium (mmol/L)	≤3 mmol/L ≥6 mmol/L	87	1 (1.1)
Sodium (mmol/L)	≤125 mmol/L ≥160 mmol/L	87	0 (0.0)

(m) = Male; (f) = Female
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)

Laboratory test	Criterion		Vilda 100mg qd + Met N=92 n	(%)
Any relevant percent change		Total Number	87	(100)
		No. of patients meeting criterion^	11	(12.6)
Creatinine (µmol/L)	> 40% increase	Total Number	87	(100)
		No. of patients meeting criterion^	1	(1.1)
		High (#)	1	(1.1)
		Normal (#)	0	(0.0)
		Low (#)	0	(0.0)
Potassium (mmol/L)	> 20% decrease	Total Number	87	(100)
		No. of patients meeting criterion^	2	(2.3)
		High (#)	0	(0.0)
		Normal (#)	2	(2.3)
		Low (#)	0	(0.0)
	> 20% increase	Total Number	87	(100)
		No. of patients meeting criterion^	8	(9.2)
		High (#)	2	(2.3)
		Normal (#)	6	(6.9)
		Low (#)	0	(0.0)
Sodium (mmol/L)	> 10% decrease	Total Number	87	(100)
		No. of patients meeting criterion^	0	(0.0)
		High (#)	0	(0.0)
		Normal (#)	0	(0.0)
		Low (#)	0	(0.0)
	> 10% increase	Total Number	87	(100)
		No. of patients meeting criterion^	0	(0.0)
		High (#)	0	(0.0)
		Normal (#)	0	(0.0)
		Low (#)	0	(0.0)

^ 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 laboratory normal ranges. Baseline is the measurement obtained on Visit 2 (Day 1), or the screening measurement (Visit 1, Week -2) if the Visit 2 measurement is missing.

Publications

Bosi E, Dotta F, Jia Y, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2009 May;11(5):506-15. doi: 10.1111/j.1463-1326.2009.01040.x. Epub 2009 Mar 23.

Date of Clinical Trial Report

26-Feb-2009