Full Novartis CTRD Template

Sponsor

Novartis

Generic Drug Name

Vildagliptin/Metformin (LMF237)

Therapeutic Area of Trial

Type 2 Diabetes Mellitus

Approved Indication

Vildagliptin/Metformin is indicated in the treatment of type 2 diabetes mellitus:

- Vildagliptin/Metformin is indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.
- Vildagliptin/Metformin is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea.
- Vildagliptin/Metformin is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

Protocol Number

CLMF237ADE03

Title

A randomized, open-label, cross-over study to evaluate patient preferences for Eucreas® versus Victoza® as add-on to Metformin in Type 2 Diabetes mellitus patients who did not have adequate glycemic control with metformin

Study Phase

Phase IV

Study Start/End Dates

Study initiation date: 04-Jan-2012 (first patient screened)

Study completion date: 17-Oct-2012 (last patient / completed)

Study Design/Methodology

This was a randomized, open-label, cross-over study to evaluate patient preference for vildagliptin/metformin versus liraglutide/metformin in T2DM patients who did not have adequate glycemic control on stable metformin therapy. To evaluate the preference of the patient for one treatment, patients experienced both treatments for 12 weeks each. An open-label, cross-over design with two treatment sequences was used in this study (vildagliptin/metformin followed by liraglutide/metformin versus liraglutide/metformin followed by vildagliptin/metformin).

Centers

This was an outpatient multi-center clinical study conducted in Germany. About 100 patients were expected to be screened in order to randomize approximately 60 patients in about 8 centers in Germany.

Publication

Pending

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

Based on the suggested therapeutic guidelines, the standard dose of vildagliptin was 50 mg twice daily and liraglutide 1.2 mg once daily. Also, if patients were not responding to the 1.2 mg liraglutide dose, patients could be up-titrated to 1.8 mg liraglutide once daily based on the investigator's judgment. Due to the limited duration of this trial and similar efficacy parameters (HbA1c, FPG) after 12 weeks of treatment (Pratley et al., 2010) only the 1.2 mg

Statistical Methods

The hypothesis in this trial was that the proportion of patients with a preference for vildagliptin and metformin was greater than 50%. This hypothesis was tested on a two sided 5% significance level using the exact test for a binomial distribution in SAS PROC FREQ. The corresponding exact two-sided 95% confidence interval (Clopper Pearson) for the proportion of patients preferring vildagliptin and metformin was also provided. FPG and HbA1c after 12 and 24 weeks of treatment were compared using an analysis of variance model with factors center, period, patient within center, and treatment. No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Both male and female patients with a confirmed diagnosis of type 2 diabetes,
- Aged 18 to less than 80 years, stabilized on metformin monotherapy (stable dose of 1000 mg bid for at least 12 weeks prior to randomization.
- HbA1c 6.5 – 9.0% at Visit 1;
- BMI between 19 and 35 kg/m² at Visit 1,
- Agree to maintain their current diet and exercise habits during the full course of the study;
- Signed informed consent to participate in the study.

Exclusion criteria:

- FPG ≥ 270mg/dL (15mmol/L) at Visit 1;
- Prior use of DPP-4 inhibitors or GLP-1 analogs;
- Prior use of insulin or sulfonylurea for 7 consecutive days or more in the preceding 12 weeks;
- Use of weight control products in the last 12 weeks, use of oral (for 7 consecutive day or more) or chronic parenteral or intra-articular corticosteroid treatment within the last 8 weeks, treatment with growth hormone within the previous 6 months and treatment with any drug of known and frequent toxicity to a major organ, or that may interfere with the interpretation of the efficacy and safety data during the study.
- A history or evidence of any of the following at Visit 1:
    - Acute metabolic conditions such a ketoacidosis, lactic acidosis or hyperosmolar state (including diabetic precoma and coma) within the past 6 months;
    - current diagnosis of congestive heart failure, myocardial infarction, coronary-artery bypass surgery or percutaneous coronary interventions, stroke, transient ischemic attack, or reversible ischemic neurologic deficit within the past 6 months;
    - unstable angina within the past 3 months; sustained and clinically relevant ventricular arrhythmia;
    - active substance abuse, alcohol abuse and history of alcohol-related diseases within the past 2 years;
    - type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes (e.g. Cushing's syndrome or acromegaly-associated diabetes);
    - malignancy of an organ system (other than localized basal cell carcinoma of the skin) treated or untreated, within the past 5 years;
    - hepatic disorder defined as acute or chronic liver disease, evidence of hepatitis, cirrhosis or portal hypertension or history of imaging abnormalities that suggest liver disease (except hepatic steatosis), such as portal hypertension, capsule scalloping, cirrhosis;
    - acute infections which could affect blood glucose control within the past 4 weeks;
    - acute conditions with the potential to alter renal function within the past 6 months (such as dehydration. severe infection, shock, intravascular administration of iodinated contrast agents, acute or chronic inflammatory bowel diseases, acute or chronic diabetic gastroparesis, acute or chronic thyroid diseases.
- significant laboratory abnormalities at Visit 1 defined as clinically significant renal dysfunction (glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x upper limit of normal at Visit 1, confirmed by repeated measurements within 3 working days; or total bilirubin > 2 x ULN and/or direct bilirubin > 1 x ULN confirmed by repeated measurements within 3 working days; or clinically significant laboratory abnormalities which, in the opinion of the investigator, caused the patient to be

considered inappropriate for inclusion in the study. Women of childbearing potential not using hormonal contraceptives with a pearl index < 1, as well as women who were breastfeeding were excluded as well.

Participant Flow

Patient disposition – (%) of patients – safety set

	Vildagliptin	Liraglutide	Total
Patients			
Treated in period 1	32/32 (100.0%)	30/30 (100.0%)	62/62 (100.0%)
Treated in period 2	28/30 (93.3%)	32/32 (100.0%)	60/62 (96.8%)
Completed period 1[§]	32/32 (100.0%)	27/30 (90.0%)	59/62 (95.2%)
Completed period 2[§]	25/30 (83.3%)	29/32 (90.6%)	54/62 (87.1%)
Discontinued period 1[§]	0/32 (0.0%)	3/30 (10.0%)	3/62 (4.8%)
Discontinued period 2[§]	3/30 (10.0%)	3/32 (9.4%)	6/62 (9.7%)
Main cause of discontinuation[§]			
Unsatisfactory therapeutic effect (period 2)	3	0	3
Patient withdrew consent (period 1)	0	2	2
Patient withdrew consent (period 2)	0	1	1
Adverse event (period 1)	0	1§	1
Abnormal laboratory value (period 1)	0	1	1
Subject's condition no longer requires study drug (period 2)	0	1	1

§ One patient who discontinued due to an adverse event discontinued only period 1 but completed period 2.

Baseline Characteristics

Demographic summary by treatment group - Safety population

	Vildagliptin - Liraglutide (N=32)	Liraglutide - Vildagliptin (N=30)	Total (N=62)
Age (years)			
Mean	60.5	60.1	60.3
SD	11.23	11.15	11.10
Range	33-78	36-80	33-80
Age group – n (%)			
< 65 years	20 (62.5%)	20 (66.7%)	40 (64.5%)
65 - < 75 years	10 (31.3%)	8 (26.7%)	18 (29.0%)
≥ 75 years	2 (6.3%)	2 (6.7%)	4 (6.5%)
Sex – n (%)			
Male	18 (56.3%)	11 (36.7%)	29 (46.8%)
Female	14 (43.8%)	19 (63.3%)	33 (53.2%)

Race – n (%)			
Caucasian	31 (96.9%)	30 (100.0%)	61 (98.4%)
Other	0	1 (3.1%)	1 (1.6%)
BMI (kg/m^2) – n (%)			
Mean	30.5	32.1	31.3
SD	3.80	3.19	3.57

Outcome Measures

Primary Outcome Result(s)

Patient preference at Week 24 – primary analysis - Efficacy population

	Vildagliptin – Liraglutide (N = 32)		**Liraglutide – Vildagliptin** (N = 28)		**Total** (N = 60)	
	n (%)	95% CI/ p-value*	n (%)	95% CI/ p-value*	n (%)	95% CI/ p-value*
Preference for vildagliptin	14 (43.8%)	[26.4%-62.3%]	17 (60.7%)	[40.6%-78.5%]	31 (51.7%)	[38.4%-64.8%]
Preference for liraglutide	18 (56.3%)	[37.7%-73.6%]	11 (39.3%)	[21.5%-59.4%]	29 (48.3%)	[35.2%-61.6%]
Exact binomial test 1-sided p-value| preference for vildagliptin ≤ 50%		0.811		0.172		0.449

*Exact 2-sided 95%-confidence interval for the rate (Clopper-Pearson) / one sided p-value for H_0 that preference for vildagliptin ≤50%

Secondary Outcome Result(s)

Reason for patient preference at week 24 - Efficacy population

	Total (N=60)		**Patients who preferred liraglutide** (N=29)		**Patients who preferred vildagliptin** (N= 31)	
	n	%				
How you take the medication (oral or injection)						
Very unimportant (1)	5	(8.3%)	4	(13.8%)	1	(3.2%)
Unimportant (2)	15	(25.0%)	10	(34.5%)	5	(16.1%)
Undecided (3)	5	(8.3%)	2	(6.9%)	3	(9.7%)
Important (4)	22	(36.7%)	11	(37.9%)	11	(35.5%)
Very important (5)	13	(21.7%)	2	(6.9%)	11	(35.5%)
Side effects (nausea, vomiting and diarrhea)						
Very unimportant (1)	4	(6.7%)	3	(10.3%)	1	(3.2%)
Unimportant (2)	13	(21.7%)	8	(27.6%)	5	(16.1%)
Undecided (3)	10	(16.7%)	6	(20.7%)	4	(12.9%)
Important (4)	15	(25.0%)	8	(27.6%)	7	(22.6%)
Very important (5)	18	(30.0%)	4	(13.8%)	14	(45.2%)

	Total (N=60)		Patients who preferred liraglutide (N=29)		Patients who preferred vildagliptin (N= 31)	
	n	%				
Blood sugar lowering						
Very unimportant (1)	3	(5.0%)	2	(6.9%)	1	(3.2%)
Unimportant (2)	8	(13.3%)	5	(17.2%)	3	(9.7%)
Undecided (3)	3	(5.0%)	0	(0.0%)	3	(9.7%)
Important (4)	9	(15.0%)	2	(6.9%)	7	(22.6%)
Very important (5)	37	(61.7%)	20	(69.0%)	17	(54.8%)
Other effects (weight loss and blood pressure decrease)						
Very unimportant (1)	2	(3.3%)	2	(6.9%)	0	(0.0%)
Unimportant (2)	10	(16.7%)	4	(13.8%)	6	(19.4%)
Undecided (3)	9	(15.0%)	4	(13.8%)	5	(16.1%)
Important (4)	18	(30.0%)	8	(27.6%)	10	(32.3%)
Very important (5)	21	(35.0%)	11	(37.9%)	10	(32.3%)

Fasting plasma glucose (mg/dL) after 12 weeks of treatment: vildagliptin versus liraglutide – Safety population

	Vildagliptin (N=58)	Liraglutide (N=58)	Difference Liraglutide - Vildagliptin (N=58)
Unadjusted mean (SD)	140.9 (31.80)	130.6 (24.50)	-10.3 (28.71)
Least-square mean	141.2	130.5	-10.8
2-sided 95% CI			[-18.2, -3.3]
ANOVA p value| Diff=0			0.005

SD: Standard deviation; CI: confidence interval

ANOVA: analysis of variance model with factors center, period, patient within center, and treatment

Descriptive analysis of the TSQM-9 questionnaire by domain - Safety population

		Vildagliptin			Liraglutide			Difference Vildagliptin - Liraglutide
		Period 1	Period 2	Total	Period 1	Period 2	Total	
	N	n=32	n=28	n=60	n=28	n=32	n=60	n=60
Convenience	Mean	83.2	88.5	85.6	82.9	82.1	82.5	3.1
	SD	18.26	16.28	17.43	14.65	17.27	15.97	22.32
	Range	44-100	39-100	39-100	56-100	28-100	28-100	-56-50
	Median	88.9	100.0	94.4	83.3	86.1	83.3	5.6

		Vildagliptin			Liraglutide			Difference Vildagliptin - Liraglutide
		Period 1	Period 2	Total	Period 1	Period 2	Total	
	N	n=32	n=28	n=60	n=28	n=32	n=60	n=60
Effectiveness	Mean	71.0	62.9	67.2	70.4	74.1	72.4	-5.2
	SD	23.43	30.43	27.00	28.41	22.82	25.43	34.61
	Range	11-100	0-100	0-100	0-100	0-100	0-100	-100-89
	Median	66.7	66.7	66.7	72.2	77.8	77.8	-2.8
Global Satisfaction	Mean	78.8	61.7	70.8	78.1	74.6	76.2	-5.4
	SD	14.23	30.57	24.65	21.38	19.62	20.36	31.91
	Range	57-	0-100	0-100	14-100	21-100	14-100	-100-64
	Median	71.4	75.0	71.4	85.7	78.6	78.6	0.0

HbA1c (%) after 12 weeks of treatment: vildagliptin versus liraglutide - Safety population

	Vildagliptin (N=58)	Liraglutide (N=58)	Difference Liraglutide - Vildagliptin (N=58)
Unadjusted mean (SD)	6.7 (0.57)	6.5 (0.52)	-0.2 (0.38)
Least-square mean	6.7	6.5	-0.2
2-sided 95% CI			[-0.3, -0.1]
ANOVA p value| Diff=0			<0.001

Physician's preference at week 24 - Efficacy population

	Vildagliptin – Liraglutide (N = 32)		Liraglutide – Vildagliptin (N = 28)		Total (N = 60)	
	n (%)	95% CI/ p-value*	n (%)	95% CI/ p-value*	n (%)	95% CI/ p-value*
Preference for vildagliptin	15 (46.9%)	[29.1%-65.3%]	18 (64.3%)	[44.1%-81.4%]	33 (55.0%)	[41.6%-67.9%]
Preference for liraglutide	17 (53.1%)	[34.7%-70.9%]	10 (35.7%)	[18.6%-55.9%]	27 (45.0%)	[32.1%-58.4%]
Exact binomial test 1-sided p-value| preference for vildagliptin ≤ 50%		0.702		0.092		0.259

*Exact 2-sided 95%-confidence interval for the rate (Clopper-Pearson) / one sided p-value for H_0 that preference for vildagliptin ≤50%

Reason for physician's preference at week 24 - Safety population

	Total (N=62)		Physician's preference was liraglutide (N= 27)		Physician's preference was vildagliptin (N= 33)	
	n	%	n	%	n	%
Blood sugar lowering						
Very unimportant (1)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Unimportant (2)	4	(12.5%)	2	(7.4%)	4	(12.1%)
Undecided (3)	1	(3.1%)	0	(0.0%)	4	(12.1%)
Important (4)	4	(12.5%)	4	(14.8%)	8	(24.2%)
Very important (5)	23	(71.9%)	21	(77.8%)	17	(51.5%)
How the medication is applied (oral or injection)						
Very unimportant (1)	1	(3.1%)	4	(14.8%)	1	(3.0%)
Unimportant (2)	6	(18.8%)	8	(29.6%)	4	(12.1%)
Undecided (3)	2	(6.3%)	1	(3.7%)	2	(6.1%)
Important (4)	14	(43.8%)	12	(44.4%)	16	(48.5%)
Very important (5)	9	(28.1%)	2	(7.4%)	10	(30.3%)
Other effects (weight loss and blood pressure decrease)						
Very unimportant (1)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Unimportant (2)	5	(15.6%)	2	(7.4%)	6	(18.2%)
Undecided (3)	7	(21.9%)	5	(18.5%)	6	(18.2%)
Important (4)	12	(37.5%)	9	(33.3%)	16	(48.5%)
Very important (5)	8	(25.0%)	11	(40.7%)	5	(15.2%)
Side effects (nausea, vomiting and diarrhea)						
Very unimportant (1)	2	(6.3%)	2	(7.4%)	2	(6.1%)
Unimportant (2)	6	(18.8%)	4	(14.8%)	4	(12.1%)
Undecided (3)	6	(18.8%)	7	(25.9%)	5	(15.2%)
Important (4)	11	(34.4%)	11	(40.7%)	11	(33.3%)
Very important (5)	7	(21.9%)	3	(11.1%)	11	(33.3%)

Safety Results

Adverse events overall and by affected system organ classes – number of adverse events and n (%) of patients - Safety population

MedDRA System Organ Class and Preferred Term	Vildagliptin (N=60)		Liraglutide (N=62)		Total (N=62)	
	No. of AEs	No. (%) of patients	No. of AEs	No. (%) of patients	No. of AEs	No. (%) of patients
All AEs	16	9 (15.0%)	46	23 (37.1%)	62	28 (45.2%)
Gastrointestinal disorders	2	2 (3.3%)	20	15 (24.2%)	22	17 (27.4%)
Infections and infestations	2	2 (3.3%)	5	4 (6.5%)	7	6 (9.7%)
Metabolism and nutrition disorders	1	1 (1.7%)	9	5 (8.1%)	10	5 (8.1%)
Nervous system disorders	2	2 (3.3%)	5	4 (6.5%)	7	5 (8.1%)
Musculoskeletal and connective tissue disorders	2	2 (3.3%)	2	2 (3.2%)	4	4 (6.5%)
Cardiac disorders	1	1 (1.7%)	2	2 (3.2%)	3	3 (4.8%)
Skin and subcutaneous tissue disorders	2	2 (3.3%)	0	0	2	2 (3.2%)
Blood and lymphatic system disorders	0	0 (0.0%)	1	1 (1.6%)	1	1 (1.6%)
Ear and labyrinth disorders	1	1 (1.7%)	0	0	1	1 (1.6%)
General disorders and administration site conditions	1	1 (1.7%)	0	0	1	1 (1.6%)
Hepatobiliary disorders	0	0	1	1 (1.6%)	1	1 (1.6%)
Injury, poisoning and procedural complications	0	0	1	1 (1.6%)	1	1 (1.6%)
Psychiatric disorders	1	1 (1.7%)	0	0	1	1 (1.6%)
Renal and urinary disorders	1	1 (1.7%)	0	0	1	1 (1.6%)

The columns vildagliptin and liraglutide refer to the last treatment received before the onset of an AE.

Treatment emergent AEs by maximum severity - Safety population

	Vildagliptin (N=60)		Liraglutide (N=62)		Total (N=62)	
	No. of AEs	No. (%) of patients	No. of AEs	No. (%) of patients	No. of AEs	No. (%) of patients
All AE's	16	9 (15.0%)	46	23 (37.1%)	62	28 (45.2%)
Mild	12	8 (13.3%)	30	17 (27.4%)	42	23 (37.1%)
Moderate	4	3 (5.0%)	15	10 (16.1%)	19	11 (17.7%)
Severe	0	0	1	1 (1.6%)	1	1 (1.6%)

The columns vildagliptin and liraglutide refer to the last treatment received before the onset of an AE.

Treatment emergent serious adverse events by system organ class and preferred term - Safety population

MedDRA Preferred Term	Vildagliptin (N=60) No. (%) of patients	Liraglutide (N=62) No. (%) of patients	Total (N=62) No. (%) of patients
All serious AE's	0	2 (3.2%)	2 (3.2%)
Coronary artery disease	0	1 (1.6%)	1 (1.6%)
Cholelithiasis	0	1 (1.6%)	1 (1.6%)

The columns vildagliptin and liraglutide refer to the last treatment received before the onset of an AE.

Treatment emergent adverse events leading to study drug discontinuation by system organ class and preferred term - Safety population

MedDRA Preferred Term	Vildagliptin (N=60) No. (%) of patients	Liraglutide (N=62) No. (%) of patients	Total (N=62) No. (%) of patients
Total	0	1 (1.6%)	1 (1.6%)
Diarrhea	0	1 (1.6%)	1 (1.6%)

The columns vildagliptin and liraglutide refer to the last treatment received before the onset of an AE.

Other Relevant Findings

None

Date of Clinical Trial Report

15 AUG 2013

Date Inclusion on Novartis Clinical Trial Results Database

10 NOV 2013

Date of Latest Update

14 OCT 2013