Sponsor

Novartis

Generic Drug Name

Vildagliptin plus Metformin, LMF237

Therapeutic Area of Trial

Diabetes mellitus type 2

Approved Indication

- Indicated for the treatment of Diabetes mellitus type 2:
    - In adults without adequate glycaemic control despite the maximal tolerated dose of metformin or if the current treatment already exists of the free combination of vildagliptin and metformin
    - In combination with a sulphonylurea (triple-combination) in addition to diet and exercise, if glyceamic control is inadequate under combination of metformin with sulphonylurea.
    - In combination with insulin (triple-combination) in addition to diet and exercise to improve gylcaemic control, when treatment with a stable insulin dose in addition to metformin does not lead to an adequate glycaemic control.

Protocol Number

CLMF237ADE02

Title

Cross-over study to assess the difference in fasting plasma glucose (FPG) between vildagliptin (Galvus®/Eucreas®) and sitagliptin (Januvia®/Janumet®) after two weeks (FGP-VISIT)

Study Phase

Phase IV

Study Start/End Dates

Example: 29 Jun 2011 to 07 Jun 2012

Study Design/Methodology

This was a cross-over, open label, active-controlled trial to assess the FPG lowering properties of a vildagliptin-metformin single-pill combination (SPC) (50/1000 mg b.i.d. [twice daily]) compared to a sitagliptin-metformin SPC (50/1000 mg b.i.d.) after a 2-week treatment with either medication in type 2 diabetes patients uncontrolled on a stable metformin therapy (1000 : 2000 mg/day).

Centers

15 centers in Germany

Publication

None

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

- Vildagliptin/Metformin (50/1000 mg) SPC tablets
- Sitagliptin/Metformin (50/1000 mg) SPC tablets

Statistical Methods

The primary analysis was performed comparing treatments with respect to the primary efficacy variable in an analysis of variance (ANOVA) model with the factors center, period, patient within center, and treatment.

Raw (arithmetic) means as well as adjusted (LS-) means were provided as point estimates for the pair-wise treatment contrast. The point estimate and the corresponding two-sided 95% confidence interval for the difference in LS-means were provided. In addition, the p-value for the null hypothesis of no treatment difference was calculated on the model. The significance level was 5% two-sided.

Patients who dropped out prior to the scheduled observation period were included in the FAS, the primary analysis data set for the primary variable. Missing values of the primary variable were replaced by the baseline FPG measurement of the respective period if the patient received at least one dose of randomized study medication within that period. Otherwise the missing value was not replaced.

In addition, the primary objective was analyzed descriptively by visit and treatment and by visit, age group and treatment.

For all pair-wise comparisons, the p-values from the primary ANOVA model were compared to those obtained by applying a non-parametric test (Wilcoxon signed rank test) as supportive analyses.

The analysis of safety related data was based on the safety set.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion criteria

1. Type 2 diabetes patients stabilized on metformin monotherapy (stable dose for at least 4 weeks prior to screening) ≥ 1000 mg/day and ≤ 2000 mg/day.
2. Patients diagnosed with type 2 diabetes mellitus at least 3 months prior to screening.
3. HbA1c 7.0 – 9.5% (metformin ≥ 1000 mg/day and < 2000 mg/day) or HbA1c 6.5 – 9.5% (metformin 2000 mg/day) at screening.
4. FPG 126 – 270 mg/dL (7.0 – 15.0 mmol/L) at screening and at randomization.
5. Male and female patients aged 18 to 85 years inclusive.
6.

Key Exclusion criteria

1. FPG ≥ 270 mg/dL (15 mmol/L) at Visit 1 and Visit 102.
2. Use of any of the following medications as assessed at Visit 1:
   a. use of any anti-diabetes medication within the last 12 weeks, except metformin.
   b. use of weight-control products including weight-loss medications in the last 12 weeks.
   c. use of oral (≥ 7 consecutive days) or chronic parenteral or intra-articular corticosteroid treatment within the last 8 weeks. Inhaled or topical steroids without systemic effects were allowed.
   d. treatment with growth hormone within the previous 6 months.
3. Treatment with any drug of known and frequent toxicity to a major organ, or that could 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:
   a. acute metabolic conditions such a ketoacidosis, lactic acidosis or hyperosmolar state (including precoma and coma) within the past 6 months.
   b. current diagnosis of congestive heart failure (NYHA III or IV).
   c. myocardial infarction within the past 6 months.
   d. other acute or chronic disease which may cause tissue hypoxic (e.g. respiratory insufficiency, shock) within the past 6 months.
   e. coronary artery bypass surgery or percutaneous coronary intervention within the past 6 months.
   f. stroke, transient ischemic attack, or reversible ischemic neurologic deficit within the past 6 months.
   g. unstable angina within the past 3 months.

h. sustained and clinically relevant ventricular arrhythmia (patients with premature ventricular contractions if deemed not clinically significant could be enrolled).

i. active substance abuse, alcohol abuse and history of alcohol-related diseases within the past 2 years.

j. type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes (e.g. Cushing's syndrome or acromegaly-associated diabetes).

k. malignancy of an organ system (other than localized basal cell carcinoma of the skin) treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

l. hepatic disorder defined as:

- acute or chronic liver disease, evidence of hepatitis, cirrhosis or portal hypertension.
- history of imaging abnormalities that suggest liver disease (except hepatic steatosis), such as portal hypertension, capsule scalloping, cirrhosis.

m. acute infections which could affect blood glucose control within the past 4 weeks.

n. 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.

Participant Flow

Patient disposition – n (%) of patients (screened patients)

	Vildagliptin - Sitagliptin	Sitagliptin - Vildagliptin	Total
Patients			
Screened			187
Randomized	53	46	99
Exposed	53 (100.0%)	46 (100.0%)	99 (100.0%)
Completed	52 (98.1%)	46 (100.0%)	98 (99.0%)
Discontinued	1 (1.9%)	0	1 (1.0%)
Main cause of discontinuation			
Adverse event(s)	1 (1.9%)	0	1 (1.0%)

Baseline Characteristics

Demographic summary by treatment group (full analysis set)

	Total (N=99)	Vildagliptin - Sitagliptin (N=53)	Sitagliptin - Vildagliptin (N=46)
Age (years)	99	53	46
Mean	61.2	60.9	61.5
SD	10.14	10.68	9.60
Median	63.0	62.0	63.0
Max	81	80	81
Age group – n (%)			
< 65 years	64 (64.6%)	33 (62.3%)	31 (67.4%)
65 - < 75 years	25 (25.3%)	13 (24.5%)	12 (26.1%)
≥ 75 years	10 (10.1%)	7 (13.2%)	3 (6.5%)
Sex – n (%)			
Male	64 (64.6%)	37 (69.8%)	27 (58.7%)
Female	35 (35.4%)	16 (30.2%)	19 (41.3%)
Race – n (%)			
Caucasian	98 (99.0%)	53 (100.0%)	45 (97.8%)
Other	1 (1.0%)	0 (0.0%)	1 (2.2%)

Outcome Measures

Primary Outcome Results

Fasting blood glucose after 14 days of treatment [mg/dL] (full analysis set)

	Vildagliptin (N = 98)	Sitagliptin (N = 98)	Difference Sitagliptin-Vildagliptin (N = 98)
Unadjusted mean (SD)	137.8 (28.52)	140.1 (26.5)	2.3 (19.78)
Least-square mean	139.1	141.3	2.2
2-sided 95% CI			[-1.8 ,6.2]
ANOVA p value| Diff=0			0.2788
Wilcoxon signed rank test p-value			0.0498
SD: Standard deviation; CI: confidence interval ANOVA: analysis of variance model with factors center, period, patient within center, and treatment			

Change in fasting blood glucose after 14 days of treatment [mg/dL] (full analysis set)

	Vildagliptin (N = 97)	Sitagliptin (N = 97)	Difference Sitagliptin-Vildagliptin (N = 97)
Unadjusted mean (SD)	-21.9 (26.96)	-14.5 (22.96)	7.4 (33.73)
Least-square mean	-21.2	-14.2	7.0
2-sided 95% CI			[0.2, 13.7]
ANOVA p value| Diff=0			0.0425
Wilcoxon signed rank test p-value			0.0196
SD: Standard deviation; CI: confidence interval ANOVA: analysis of variance model with factors center, period, patient within center, and treatment			

Secondary Outcome Result

Fasting blood glucose at Day 15 (after missed dose) [mg/dl] (full analysis set)

	Vildagliptin (N = 98)	Sitagliptin (N = 98)	Difference Sitagliptin-Vildagliptin (N = 98)
Unadjusted mean (SD)	147.6 (29.24)	143.4 (27.88)	-4.2 (21.28)
Least-square mean	147.6	143.3	-4.3
2-sided 95% CI			[-8.6 , 0.0]
ANOVA p value| Diff=0			0.0512
Wilcoxon signed rank test p-value			0.0473
SD: Standard deviation; CI: confidence interval ANOVA: analysis of variance model with factors center, period, patient within center, and treatment			

Safety Results

Adverse Events by System Organ Class

Adverse events overall and by affected system organ classes – number of adverse events and n (%) of patients (safety set)

	Total (N=99)		Vildagliptin (N=99)		Sitagliptin (N=98)	
	No. of AEs	No. (%) of patients	No. of AEs	No. (%) of patients	No. of AEs	No. (%) of patients
All AE's	70	34 (34.3%)	48	26 (26.3%)	22	12 (12.2%)
Gastrointestinal disorders	12	11 (11.1%)	6	6 (6.1%)	6	5 (5.1%)
Infections and infestations	20	17 (17.2%)	15	14 (31.3%)	5	4 (4.1%)
Nervous system disorders	10	9 (9.1%)	8	7 (7.1%)	2	2 (2.0%)
Skin and subcutaneous tissue disorders	10	4 (4.0%)	9	3 (3.0%)	1	1 (1.0%)
Metabolism and nutrition disorders	7	2 (2.0%)	4	1 (1.0%)	3	2 (2.0%)
General disorders and administration site conditions	3	3 (3.0%)	2	2 (2.0%)	1	1 (1.0%)
Musculoskeletal and connective tissue disorders	3	2 (2.0%)	1	1 (1.0%)	2	1 (1.0%)
Cardiac disorders	1	1 (1.0%)	1	1 (1.0%)	0	0
Ear and labyrinth disorders	1	1 (1.0%)	1	1 (1.0%)	0	0
Injury, poisoning and procedural complications	1	1 (1.0%)	0	0	1	1 (1.0%)
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	1	1 (1.0%)	0	0	1	1 (1.0%)
Renal and urinary disorders	1	1 (1.0%)	1	1 (1.0%)	0	0
The columns vildagliptin and sitagliptin refer to the last treatment received before the onset of an AE.						

Serious Adverse Events and Deaths

Treatment emergent serious AEs by system organ class and preferred term (safety set)

	Total (N=99)		Vildagliptin (N=99)		Sitagliptin (N=98)	
Preferred term	No. (%) of AEs	No. (%) of patients	No. (%) of AEs	No. (%) of patients	No. (%) of AEs	No. (%) of patients
All serious AE's	4	3 (3.0)	1	1(1.0)	2	2 (2.0)
Anal abscess	2	1 (1.0)	0	0	2	1 (1.0)
Breast cancer	1	1 (1.0)	0	0	1	1 (1.0)
Incontinence	1	1 (1.0)	1	1 (1.0)	0	0

No deaths reported during this study.

Other Relevant Findings

None

Date of Clinical Trial Report

11 March 2013

Date Inclusion on Novartis Clinical Trial Results Database

31 MAY 2013

Date of Latest Update

21 MAY 2013