NOVARTIS

Full Novartis CTRD Results Template

Sponsor Novartis
Generic Drug Name Vildagliptin
Therapeutic Area of Trial Type II Diabetes
Approved Indication • Indicated for the treatment of type 2 diabetes mellitus. It may be used alone or in combination with other anti-diabetic agents such as metformin, SUs and TZDs.
Protocol Number CLAF237A23151
Title Pilot study to assess the difference in glycemic profiles between vildagliptin and glimepiride using Continuous Glucose Monitoring device
Phase of Development Phase III
Study Start/End Dates 14 Oct 2010 to 18 Mar 2011
Study Design/Methodology This was an open-label, randomized, 2 period cross-over study in patients with type 2 diabetes mellitus (T2DM) who were on a stable dose of metformin. Eligible patients were randomized on Day -2 and completed baseline evaluations (Day -2 and Day 19), and two 5 day treatment periods with either vildagliptin 50 mg b.i.d or glimepiride 2 mg q.d. in a cross-over manner. The 2 treatment periods were separated by a 14 day (± 1 day) washout period, to explore the 24-hr glucose profiles using a CGM device at Baseline before treatment and during treatment

with vildagliptin or glimepiride. The metformin dosing regimen remained unchanged during the entire study period.

Centres

Germany (1)

Publication

N/A

Outcome measures

Primary outcome measures(s)

Changes in the mean 24-hour glucose concentrations measured using CGM device after 5 day treatment with vildagliptin or glimepiride

Secondary outcome measures(s)

Glucose fluctuation parameter, MAGE (mean amplitude of glycemic excursions), derived from 24-hour glucose versus time profiles

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

Oral tablets of Vildagliptin 50 mg twice a day and oral tablets of glimepiride 2 mg once daily

Statistical Methods

Based on the pilot nature of this mechanistic profiling study, the sample size of 20 completers was selected on the basis of practical consideration. A total of 24 patients planned to be enrolled, assuming a discontinuation rate of 15% or lower.

Primary endpoints were focused on the glycemic profiles (the glucose concentrations versus time courses over 24-hr from the CGM device) collected at Baseline and at Day 5 of each treatment period.

To visualize changes in glycemic parameters, the 24-hr CGM glucose profiles at Baseline and Day 5 of each treatment were plotted at median, 10^{th}, 25^{th}, 75^{th} and 90^{th} percentile of the data.

The glucose exposure was assessed by calculating the AUC_{0-24}, and the average glucose concentration over 24-hr was calculated as AUC_{0-24h}/24h. This was analyzed using a linear mixed effect model, with treatment, sequence, period included as fixed effects and patient as a random effect. The estimated mean difference between treatments was derived from the linear mixed effect model as well as the p-value for the treatment difference. Analysis was done on log-transformed data and back transformed to provide the ratio of geometric means and 90% confidence limits for comparison of vildagliptin vs. glimepiride.

Similar statistical analysis mentioned above was performed on the following parameters for the comparison of vildagliptin and glimepiride.

To evaluate the dynamics of glucose fluctuations on the time scale of minutes, blood glucose rate of change was calculated. The standard deviation (SD) of the rate of change as a measure of stability of glucose fluctuation was used in the inferential data analysis. Furthermore, IQR (interquartile range between the 25th and 75th percentile curves), and RCMC (rate of change in the median curve) was calculated and compared. The MAGE for Baseline and Day 5 CGM measurements was calculated for each patient by taking the arithmetic mean of the blood glucose increase or decrease (from blood glucose nadirs to peaks or vice versa) when such an ascending or descending segment exceeded the value of 1 SD of the blood glucose for the same 24-hr period. These were analyzed using a linear mixed effect model, with treatment, sequence, period included as fixed effects, and patient as a random effect. The estimated mean difference and 90% confidence interval were derived from the linear mixed effect model as well as the p-value for the treatment difference provided.

The urinary excretion rate of 8-iso-prostaglandin $F_{2\alpha}$ and creatinine were calculated by multiplying the volume of urine collected over 12-hr by the concentration then dividing by 12-hr. The ratio of urinary excretion rate of 8-iso-prostaglandin $F_{2\alpha}$ versus that of creatinine was calculated (pg/mg). The correlation between the above described ratio and glucose fluctuation (MAGE) was explored and linear regression was performed.

For Biomarker endpoints: The $AUC_{0\text{-}180}$ of GLP-1, glucose, insulin, c-peptide, and glucagon was calculated for baseline and post baseline on Day 5 for each treatment. Differences in these parameters between each treatment and Baseline were explored by comparing these parameters at Baseline and after treatment with vildagliptin or glimepiride.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

- Written informed consent must be obtained before any assessment is performed.
- Able to communicate well with the investigator, to understand and comply with the requirements of the study.
- Patients must be willing to comply with dietary recommendations throughout the study.
- Willingness to perform required study and data collection procedures and adhere to operating requirements CGMS iPro Systems.
- Willingness to perform at least 4 capillary blood glucose tests per day while wearing the Guardian REAL-Time and iPro Systems.
- Type 2 diabetics stabilized on metformin monotherapy (stable dose for at least 4 weeks prior to Screening). The metformin dose should not be expected to change during the course of the study.
- Agreement to maintain the same dose of metformin throughout the study.
- Patients must be diagnosed with type 2 diabetes mellitus at least 3 months prior to screening. Anti-GAD antibodies will be determined during the screening period. Patients with a positive anti-GAD antibodies assay will not be enrolled.
- HbA1c 7.0~8.5% % at screening.
- Male and female patients, age 18 to 70years of age inclusive

- Female patients of childbearing potential must be using two acceptable methods of contraception, (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion.
- Postmenopausal females must have had no regular menstrual bleeding for at least one (1) year prior to initial dosing. Menopause will be confirmed by a plasma FSH level (reference local lab value or >40 IU/L) at screening.
- Female patients who report surgical sterilization must have had the procedure at least six (6) months prior to initial dosing. Surgical sterilization procedures should be supported with clinical documentation made available to the sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the CRF.
- All female patients must have negative pregnancy test results at screening and at each baseline.
- Body mass index (BMI) within the range of 20 -42 kg/m2 at screening.
- At screening and baseline, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the subject has rested for at least three (3) minutes and again when required after three (3) minutes in the standing position. Sitting vital signs should be within the normal range:
    - oral body temperature between 35.0-37.5 °C
    - systolic blood pressure, 90-160 mm Hg
    - diastolic blood pressure, 50-95 mm Hg
    - pulse rate, >=50 - 90 bpm
- When blood pressure and pulse are taken after at least 3 minutes standing, there should be nomore than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure and increase in heart rate (>20 bpm) (compared to the sitting results) associated with clinical manifestation of postural hypotension. Any subject exhibiting clinical manifestations of postural hypotension should be excluded.

Exclusion criteria:

- All study patients meeting any of the following criteria will be excluded from entry into the study:
    - Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
    - Use of any other antidiabetic agents (including sulfonylureas, thiazolidinediones, repaglinide, netaglinide, exenatide, liruglutide, sitagliptin, saxagliptin and insulin) other than stable dose of metformin.
    - Use of any drugs that induce or inhibit CYP2C9 isozyme activity, including but not limited to Rifampicin , fluconazole, fluvoxamine, gemfibrozil and voriconazole amiodarone, fluorouracil, metronidazole, miconazole, sulfamethoxazole barbiturates and cambamazepine.
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
- History of tape allergies that have not been resolved.
- Skin abnormality (e.g. psoriasis, rash, staphylococcus infection) that has not been resolved

and would inhibit them from wearing the sensors.

- Significant unstable concomitant disease or complications of diabetes.
- Significant illness unresolved within two (2) weeks prior to initial dosing and/or acute infection(s) which may affect blood glucose control within 4 weeks prior to screening.
- Evidence of clinically significant diabetic organ disease (renal, retinal, neurological, vascular) or complications (e.g., symptomatic autonomic neuropathy or gastroparesis) that would preclude study participation.
- Patients with second degree AV block (Mobitz 1 and 2); patients with third degree AV block.
- Recent (within the last three [3] years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc).
- Fasting triglycerides >5.1 mmol/L (>450 mg/dL) within 4 weeks prior to screening.
- Treatment with systemic steroids and/or on an unstable dosage of thyroid hormone.
- Hemoglobin levels <11.0 g/dl for females and <12.0 g/dl for males at screening.
- CPK >1.5 x ULN at screening and baseline.

Patient Disposition (All Patients):

	Treatment	**Treatment**	**All Patients**
	Sequence I	**Sequence II**	
	N=12	**N=12**	**N=24**
Disposition	**n (%)**	**n (%)**	**n (%)**
Completed	12 (100)	12 (100)	24 (100)

Treatment Sequence I: vildagliptin 50 mg b.i.d for 5 days // glimepiride 2 mg q.d for 5 days
Treatment Sequence II: glimepiride 2 mg q.d for 5 days // vildagliptin 50 mg b.i.d for 5 days

Demographic summary by treatment group (Safety Analysis Set)

	Treatment		**Treatment**	**All Patients**
	Sequence I		**Sequence II**	
	N=12		**N=12**	**N=24**
Age (years)	Mean	60.1	56.6	58.3
	SD	4.98	5.76	5.56
	Median	60.0	57.5	59.0
	Range	52-67	46-65	46-67
Gender – n (%)	Male	9 (75.0)	10 (83.3)	19 (79.2)
	Female	3 (25.0)	2 (16.7)	5 (20.8)
Race – n (%)	Caucasian	12 (100)	12 (100)	24 (100)
Weight (kg)	Mean	97.47	94.94	96.20
	SD	12.6	16.7	14.53
	Median	92.45	95.0	93.3
	Range	79.8-122.1	72.4-131.5	72.4-131.5
Height (cm)	Mean	173.8	172.7	173.3
	SD	10.23	12.53	11.2

	Median	175.5	172.0	172.5
	Range	155-191	150-196	150-196
BMI (kg/m2)	Mean	32.26	31.63	31.95
	SD	3.29	2.37	2.82
	Median	32.45	32.31	32.45
	Range	27.6-38.28	27.25-34.23	27.25-38.28

BMI: Body mass index.

Treatment Sequence I: vildagliptin 50 mg b.i.d for 5 days // glimepiride 2 mg q.d for 5 days
Treatment Sequence II: glimepiride 2 mg q.d for 5 days // vildagliptin 50 mg b.i.d for 5 days

Outcome measures

Primary Outcome Result(s)

Summary of statistical analysis of $AUC_{0\text{-}24}$/24 (mmol/L) on CGM data on Day 5, Vildagliptin vs. Glimepiride

Treatment	N	Geometric mean	Ratio of geometric means	90% CI for ratio	p-value
Vildagliptin 50 mg	24	6.78	0.96	(0.81, 1.14)	0.6858
Glimepiride 2 mg	24	7.06			

Secondary Outcome Result(s)

Summary of the statistical analysis of glucose fluctuation parameters on CGM data on Day 5, vildagliptin vs. glimepiride

Glucose fluctuation parameter [unit]	Treatment	N	Adjusted mean (SE)	Mean difference	90% CI for ratio	P-value
SD of BG rate of change [mmol/L*hr]	Vildagliptin 50 mg	24	1.71 (0.12)	-0.20	(-0.42, 0.02)	0.1346
	Glimepiride 2 mg	24	1.91 (0.12)			
MAGE [mmol/L]	Vildagliptin 50 mg	24	3.24 (0.30)	-0.60	(-1.21, 0.01)	0.1076
	Glimepiride 2 mg	24	3.83 (0.30)			
IQR [mmol/L]	Vildagliptin 50 mg	24	1.67 (0.16)	-0.38	(-0.69, -0.07)	0.0462
	Glimepiride 2 mg	24	2.05 (0.16)			

Safety Results

Adverse Events by System Organ Class

	Vildagliptin	Glimepiride	All Patients
	50 mg b.i.d for 5 days	2 mg q.d for 5 days	
	N=24	N=24	N=24
	n (%)	n (%)	n (%)
Patients with at least one AE	4 (16.7)	8 (33.3)	10 (41.7)
Primary system organ class			
General disorders & administration site conditions	1 (4.2)	4 (16.7)	5 (20.8)
Infections & infestations	1 (4.2)	2 (8.3)	3 (12.5)
Skin & subcutaneous tissue disorders	0	3 (12.5)	3 (12.5)
Cardiac disorders	2 (8.3)	1 (4.2)	3 (12.5)
Nervous system disorders	1 (4.2)	1 (4.2)	2 (8.3)
Psychiatric disorders	1 (4.2)	1 (4.2)	2 (8.3)
Gastrointestinal disorders	0	1 (4.2)	1 (4.2)
Hepatobiliary disorders	1 (4.2)	0	1 (4.2)
Musculoskeletal & connective tissue disorders	1 (4.2)	0	1 (4.2)
Metabolism and nutrition disorders	0	1 (4.2)	1 (4.2)

Most Frequently Reported AEs Overall by Preferred Term n (%)

	Vildagliptin 50 mg b.i.d for 5 days N=24	Glimepiride 2 mg q.d for 5 days N=24	All Patients N=24
	n (%)	**n (%)**	**n (%)**
Patients with at least one AE	4 (16.7)	8 (33.3)	10 (41.7)
Preferred term			
Agitation	0	1 (4.2)	1 (4.2)
Angina pectoris	0	1 (4.2)	1 (4.2)
Appetite increased	0	1 (4.2)	1 (4.2)
Back pain	1 (4.2)	0	1 (4.2)
Chills	0	3 (12.5)	3 (12.5)
Diarrhea	0	1 (4.2)	1 (4.2)
Fatigue	1 (4.2)	0	1 (4.2)
Headache	1 (4.2)	1 (4.2)	2 (8.3)
Hepatic pain	1 (4.2)	0	1 (4.2)
Hyperhidrosis	0	3 (12.5)	3 (12.5)
Malaise	0	1 (4.2)	1 (4.2)
Nasopharyngitis	1 (4.2)	2 (8.3)	3 (12.5)
Nervousness	0	1 (4.2)	1 (4.2)
Palpitations	1 (4.2)	0	1 (4.2)
Restlessness	1 (4.2)	0	1 (4.2)
Tachycardia	1 (4.2)	0	1 (4.2)

Serious Adverse Events and Deaths

No serious adverse events or deaths occurred.

Other Relevant Findings

Parameter	**Arithmetic mean ± SD* (CV%) Vildagliptin (N= 24)**
T_{max} (h)*	1.00 (1.00 – 2.00)
$C_{max,ss}$ (ng/mL)	316 ± 105 (33.3%)
AUC_{tau} (h*ng/mL)	953 ± 248 (26.0%)
$t_{½}$ (h)	2.02 ± 0.483 (24.0%)
*: Median (Range) for t_{max}, $t_{1/2}$ (n=23)	

Date of Clinical Trial Report 02-Mar-2012
Date Inclusion on Novartis Clinical Trial Results Database 18-MAR-2012
Date of Latest Update 18-MAR-2012