Sponsor

Novartis

Generic Drug Name

Vildagliptin/Metformin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Type 2 diabetes

Study Number

CLMF237A2309

Title

A multicenter, double-blind, randomized study to compare the efficacy of 24 weeks treatment with fixed combination therapy of vildagliptin and metformin (25/1000 mg bid) versus metformin monotherapy (1000 mg bid) in patients with type 2 diabetes inadequately controlled with metformin monotherapy

Phase of Development

Phase III

Study Start/End Dates

26 June 2008 to 10 February 2010

Study Design/Methodology

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled study. Patients with T2DM inadequately controlled on metformin monotherapy (HbA1c 7.0-9.5%) were included in the trial. Following a run-in period during which all patients received treatment with metformin 1000 mg bid (Period I), eligible patients were randomized equally to fixed dose combination therapy of vildagliptin and metformin (25/1000 mg bid) or metformin monotherapy (1000 mg bid).

Each patient attended one screening visit (Week −4) where the inclusion/exclusion criteria were assessed. Eligible patients were randomized at visit 2 (Baseline; Day 1) and completed six additional visits over a period of 24 weeks of blinded treatment with either the fixed dose combination therapy of vildagliptin and metformin (25/1000 mg bid) or metformin monotherapy (1000 mg bid). When warranted for safety reasons, patients were recalled to the clinic for additional visits to obtain appropriate samples and instructions. In addition, starting at visit 3 (week 4) rescue medication could be prescribed in addition to blinded study medication .

Centres

61 centers in 5 countries: France (2), Germany (11), Hungary (12), Poland (8), and United States (15).

Publication

Ongoing

Objectives

Primary Objective

- To demonstrate that the HbA_{1c} reduction with fixed dose combination therapy of vildagliptin and metformin (25/1000 mg bid) is superior to that with metformin monotherapy (1000 mg bid) after 24 weeks of treatment in patients with T2DM inadequately controlled with prior metformin monotherapy.

Secondary objectives

- To demonstrate that the FPG reduction with fixed dose combination therapy of vildagliptin and metformin (25/1000 mg bid) is superior to that with metformin monotherapy (1000 mg bid) after 24 weeks of treatment in patients with T2DM inadequately controlled with prior metformin monotherapy.
- To evaluate the safety and tolerability of the fixed dose combination therapy of vildagliptin and metformin (25/1000 mg bid) compared to metformin monotherapy (1000 mg bid) over 24 weeks of treatment in patients with T2DM inadequately controlled with prior metformin monotherapy.
- To evaluate the body weight change from baseline with the fixed dose combination therapy of vildagliptin and metformin (25/1000 mg bid) compared to metformin monotherapy (1000 mg bid) after 24 weeks of treatment in patients with T2DM inadequately controlled with prior metformin monotherapy.
- To evaluate changes in the fasting lipid profile with the fixed dose combination therapy of vildagliptin and metformin (25/1000 mg bid) compared to metformin monotherapy (1000 mg bid) after 24 weeks of treatment in patients with T2DM inadequately controlled with prior metformin monotherapy.

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

Vildagliptin/metformin 25/1000 mg bid were supplied as oral tablets

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

Metformin 1000 mg bid were supplied as oral tablets

Criteria for Evaluation

Primary Efficacy Parameter

The primary efficacy variable was HbA_{1c}, measured by National Glycohemoglobin Standardization Program (NGSP), specifically, ion exchange High Performance Liquid Chromatography (HPLC).

Secondary Efficacy Parameters

The secondary efficacy variables were:

- fasting plasma glucose (FPG)
- fasting lipids
- body weight

Safety and tolerability

Safety assessments consisted of monitoring and recording all AEs and serious adverse events (SAEs) with their severity and relationship to study drug, all pregnancies, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs, and the performance of physical examinations and ECG.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The primary efficacy variable was the change from baseline in HbA1c at Week 24 or at the final post-baseline visit. The primary hypothesis tested was the superiority of vildagliptin 25 mg bid/metformin combination to metformin. An analysis of covariance (ANCOVA) model was fitted including terms for treatment, baseline HbA1c and region. The least squares mean change from baseline for each treatment group, the difference between the two treatment groups (vildagliptin/metformin – metformin), and the two sided 95% confidence intervals along with the p-value for the treatment difference were obtained from the primary analysis model and presented. The primary population was the Full Analysis Set (FAS) and robustness of the results was assessed in the Per Protocol Set (PPS).

The percentage of patients meeting each of the pre-defined responder criteria (categorical changes in HbA1c) was summarized in both the FAS and PPS.

The analysis of the secondary efficacy variables (FPG, fasting plasma lipid profile, and body weight) was performed in the FAS using the same ANCOVA model as specified for the primary efficacy variable.

Demographic and background data as well as safety data were summarized by treatment group.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population included patients with T2DM inadequately controlled on metformin monotherapy and were, therefore, candidates for combination therapy with a second oral antidiabetic agent. Patients with T2DM treated with metformin for at least three months and at a stable dose of at least 1500 mg daily for a minimum of 4 weeks prior to visit 1, and with HbA1c 7.0 to 9.5%, were eligible to participate in the trial. Patients treated with a maximally tolerated dose of metformin < 2000 mg daily (i.e., were previously unable to tolerate a dose that was ≤2000 mg daily) were excluded. In addition, treatment with a metformin dose of > 2000 mg daily at visit 1 precluded participation in the study.

Patients treated with metformin >1500 mg but < 2000 mg daily who had not been previously titrated to a higher dose of metformin were started on metformin 1000 mg bid at visit 1. Patients already receiving treatment with metformin 1000 mg bid continued on metformin 1000 mg bid at visit 1. Patients who were unable to tolerate treatment with metformin 1000 mg bid during the 4 week run-in period (Period I) were not eligible for randomization.

The population consisted of males and females (non-fertile or of childbearing potential using a medically approved birth control method) aged 18-78 years, with an HbA1c of 7.0-9.5%.

Exclusion criteria were: Pregnant or lactating female; a history of type 1 diabetes, acute metabolic diabetic complications within the past 6 months, patients taking vildagliptin, other DPP-4 inhibitors, GLP-1 mimetics, GLP-1 analogues within six months prior to visit 1, acute infections; any of the following within the past 6 months:MI, unstable angina, coronary artery bypass surgery or percutaneous coronary intervention, stroke; congestive heart failure requiring pharmacologic treatment; certain ECG abnormalities, malignancy including leukemia and lymphoma within the last 5 years; liver disease such as cirrhosis or chronic active hepatitis B and C; acromegaly or treatment with growth hormone or similar drugs, donation of one unit (500 mL) or more of blood, contraindications and warnings according to the country specific label for metformin; treatment with any oral anti-diabetic other than metformin within 3 months prior to visit 1; chronic insulin treatment within the past 6 months; chronic oral or parenteral corticosteroid treatment within 8 weeks prior to visit 1; treatment with class Ia, Ib and Ic or III anti-arrhythmics; use of other investigational drugs at visit 1, or within 30 days or 5 half-lives of visit 1; history of hypersensitivity to any of the study drugs or to drugs with similar chemical structures; any of the following significant laboratory abnormalities:ALT and/or AST greater than 2 times the upper limit of the normal (ULN) at visit 1, total bilirubin > 2 xULN and/or direct bilirubin > 1 xULN at visit 1, a positive Hepatitis B test at visit 1, a positive Hepatitis C test at visit 1, clinically significant TSH values outside of normal range at visit 1, clinically significant renal dysfunction as indicated by serum creatinine levels, or abnormal creatinine clearance as indicated by calculated GFR < 60

mL/min at visit 1, clinically significant laboratory abnormalities, confirmed by repeat measurement, that may interfere with the assessment of safety and/or efficacy of the study drug, other than hyperglycemia, hyperinsulinemia, and glycosuria at visit 1, fasting triglycerides >500 mg/dL (>5.6 mmol/L) at visit 1, history of active substance abuse (including alcohol) within the past 2 years; potentially unreliable patients, and those judged by the investigator to be unsuitable for the study

Number of Subjects

	FDC Vilda 25mg bid/ Met 1000mg bid N=161	Met 1000mg bid N=156	Total N=317
Randomized	161 (100%)	156 (100%)	317 (100%)
Safety	161 (100%)	156 (100%)	317 (100%)
Intent to treat	161 (100%)	156 (100%)	317 (100%)
Per protocol	145 (90.1%)	123 (78.8%)	268 (84.5%)
Completed	149 (92.5%)	132 (84.6%)	281 (88.6%)
Discontinued	12 (7.5%)	24 (15.4%)	36 (11.4%)
Abnormal laboratory value(s)	1 (0.6)	2 (1.3)	3 (0.9)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	1 (0.6)	1 (0.3)

Demographic and Background Characteristics

	FDC Vilda 25mg bid/ Met 1000mg bid	Met 1000mg bid	Total
N (randomized)	161	156	317
Females : males	85:76	88:68	173:144
Mean age, years (SD)	56.4 (9.19)	57.2 (9.71)	56.8 (9.8)
Mean body weight, kg (SD)	88.1 (15.61)	87.2 (16.10)	87.7 (15.61)
Mean BMI, kg/m^2 (SD)	31.1 (4.27)	31.3 (4.47)	31.2 (4.37)
Race Caucasian	151 (93.8%)	147 (94.2%)	288 (94.0%)
Black	2 (1.2%)	3 (1.9%)	5 (1.6%)
Asian (non indian subcontinent)	0 (0.0)	2 (1.3)	2 (0.6)
Other	4 (2.5%)	3 (1.9%)	7 (2.2%)
Mean HbA_{1c} % (SD)	7.8 (0.85)	7.9 (0.88)	7.9 (0.87)
Mean FPG, mmol/L (SD)	9.4 (2.08)	9.5 (2.53)	9.5 (2.31)
Mean duration of diabetes, years (SD)	5.6 (5.00)	5.3 (4.06)	5.5 (4.80)

Primary Efficacy Result(s)

ANCOVA results for change in HbA_{1c} (%) from baseline to endpoint (Full analysis set)

Treatment	Baseline			Adjusted mean change from baseline		Difference in adjusted mean change (FDC Vilda/Met - Met)			
	n	mean	SE	mean	SE	mean	SE	95% CI	p-Value
FDC Vilda 25mg bid/Met 1000mg bid	159	7.84	0.07	-0.35	0.07	-0.34	0.10	-0.54, 0.13	0.001*
Met 1000mg bid	147	7.92	0.07	-0.02	0.08				

ANCOVA results for change in HbA1c (%) from baseline to endpoint (Per protocol set)

Treatment	Baseline			Adjusted mean change from baseline		Difference in adjusted mean change (FDC Vilda/Met - Met)			
	n	mean	SE	mean	SE	mean	SE	95% CI	p-Value
FDC Vilda 25mg bid/Met 1000mg bid	145	7.80	0.07	-0.38	0.08	-0.37	0.11	-0.59, -0.16	<0.001*
Met 1000mg bid	123	7.89	0.07	-0.01	0.08				

Secondary Efficacy Results

ANCOVA results for change in FPG (mmol/L) from baseline to endpoint (Full analysis set)

		Baseline		Adjusted mean change from baseline		Difference in adjusted mean change (FDC Vilda/Met - Met)			
Treatment	N	mean	SE	mean	SE	mean	SE	95% CI	P Value
FDC Vilda 25mg bid/Met 1000mg bid	160	9.43	0.16	-0.58	0.17	-0.39	0.24	-0.86, 0.09	0.108
Met 1000mg bid	150	9.54	0.21	-0.19	0.18				

ANCOVA results for change in fasting lipid parameters (mmol/l) at endpoint (Full analysis set)

		Baseline		Adjusted mean change from baseline		Difference in adjusted mean change (FDC Vilda/Met - Met)			
Treatment	N	mean	SE	mean	SE	mean	SE	95% CI	P Value
Triglycerides									
FDC Vilda 25mg bid/Met 1000mg bid	156	2.29	0.10	-0.22	0.08	-0.13	0.11	-0.33, 0.08	0.235
Met 1000mg bid	144	2.35	0.12	-0.09	0.08				
Total Cholesterol									
FDC Vilda 25mg bid/Met 1000mg bid	154	4.95	0.08	-0.11	0.06	-0.16	0.09	-0.34, 0.02	0.073
Met 1000mg bid	140	5.19	0.11	0.06	0.07				
LDL Cholesterol									
FDC Vilda 25mg bid/Met 1000mg bid	139	2.68	0.08	-0.01	0.06	-0.11	0.09	-0.28, 0.06	0.216
Met 1000mg bid	122	2.94	0.09	0.09	0.06				
HDL Cholesterol									
FDC Vilda 25mg bid/Met 1000mg bid	150	1.25	0.03	-0.01	0.01	-0.01	0.02	-0.05, 0.03	0.618
Met 1000mg bid	138	1.23	0.03	0.00	0.02				
Non-HDL Cholesterol									
FDC Vilda 25mg bid/Met 1000mg bid	150	3.71	0.09	-0.10	0.06	-0.16	0.09	-0.34, 0.02	0.074
Met 1000mg bid	138	3.96	0.10	0.06	0.07				

ANCOVA results for change in body weight (kg) from baseline to endpoint (Full analysis set)

		Baseline		Adjusted mean change from		Difference in adjusted mean change (FDC Vilda/Met - Met)			
Treatment	n	mean	SE	baseline	SE	mean	SE	95% CI	P Value
FDC Vilda 25mg bid/Met 1000mg bid	160	87.93	1.22	-1.04	0.23	0.08	0.32	-0.55, 0.71	0.801
Met 1000mg bid	150	87.13	1.32	-1.12	0.24				

* indicates statistical significance at 5% level.

Safety Results

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

Primary system organ class	FDC Vilda 25mg bid/ Met 1000mg bid N=161 n (%)	Met 1000mg bid N=156 n (%)
Any primary system organ class	51 (31.7)	61 (39.1)
Blood and lymphatic system disorders	3 (1.9)	3 (1.9)
Cardiac disorders	2 (1.2)	4 (2.6)
Ear and labyrinth disorders	0 (0.0)	1 (0.6)
Eye disorders	2 (1.2)	2 (1.3)
Gastrointestinal disorders	12 (7.5)	17 (10.9)
General disorders and administration site conditions	8 (5.0)	2 (1.3)
Infections and infestations	20 (12.4)	17 (10.9)
Injury, poisoning and procedural complications	9 (5.6)	4 (2.6)
Investigations	8 (5.0)	11 (7.1)
Metabolism and nutrition disorders	7 (4.3)	6 (3.8)
Musculoskeletal and connective tissue disorders	9 (5.6)	9 (5.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2)	1 (0.6)
Nervous system disorders	8 (5.0)	10 (6.4)
Psychiatric disorders	1 (0.6)	2 (1.3)
Renal and urinary disorders	0 (0.0)	1 (0.6)
Reproductive system and breast disorders	1 (0.6)	2 (1.3)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	6 (3.8)
Skin and subcutaneous tissue disorders	4 (2.5)	8 (5.1)
Vascular disorders	4 (2.5)	7 (4.5)

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

Preferred term	FDC Vilda 25mg bid/ Met 1000mg bid N=161 n (%)	Met 1000mg bid N=156 n (%)
Headache	4 (2.5)	2 (1.3)
Abdominal pain upper	3 (1.9)	2 (1.3)
Anaemia	3 (1.9)	3 (1.9)
Influenza	3 (1.9)	1 (0.6)
Abdominal discomfort	2 (1.2)	0 (0.0)
Abdominal distension	2 (1.2)	0 (0.0)
Abdominal pain	2 (1.2)	2 (1.3)
Alanine aminotransferase increased	2 (1.2)	3 (1.9)
Back pain	2 (1.2)	4 (2.6)
Bronchitis	2 (1.2)	2 (1.3)
Diarrhea	2 (1.2)	7 (4.5)
Foot deformity	2 (1.2)	0 (0.0)
Gastrooesophageal reflux disease	2 (1.2)	0 (0.0)
Hyperglycaemia	2 (1.2)	3 (1.9)
Hypertriglyceridaemia	2 (1.2)	3 (1.9)
Liver function test abnormal	2 (1.2)	0 (0.0)
Migraine	2 (1.2)	0 (0.0)
Myalgia	2 (1.2)	0 (0.0)
Nasopharyngitis	2 (1.2)	0 (0.0)
Nausea	2 (1.2)	2 (1.3)
Oedema peripheral	2 (1.2)	0 (0.0)
Pharyngitis	2 (1.2)	3 (1.9)
Upper respiratory tract infection	2 (1.2)	4 (2.6)
Vomiting	2 (1.2)	1 (0.6)
Weight decreased	2 (1.2)	0 (0.0)

Number (%) of subjects with serious or other significant events

	FDC Vilda 25mg bid/ Met 1000mg bid N=161 n (%)	Met 1000mg bi N=156 n (%)
Deaths	0 (0.0)	0 (0.0)*
SAEs	1 (0.6)	5 (3.2)
AEs leading to discontinuation	2 (1.2)	8 (5.1)
Other clinically significant AEs	11 (6.8)	5 (3.2)

Other Relevant Findings Not applicable
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