Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Vildagliptin is approved in the EU for the treatment of Type 2 Diabetes Mellitus for use as monotherapy in patients who cannot take metformin and in combination with some of the most frequently prescribed oral anti-diabetes medicines - metformin, sulfonylureas (SUs) or thiazolidinediones (TZDs).

Protocol Number

CLAF237A23137

Title

A multi-center, randomized, double-blind, clinical trial to evaluate the safety and tolerability of 24 weeks treatment with vildagliptin (50 mg once daily [qd]) versus placebo in patients with type 2 diabetes and moderate or severe renal insufficiency

Phase of Development

Phase IIIb

Study Start/End Dates

05 Mar 2008 to 20 Oct 2010

Study Design/Methodology

This was a multicenter, randomized, double-blind, clinical trial to evaluate the safety and tolerability of vildagliptin 50 mg once daily (qd) versus placebo when given as monotherapy or as an add-on to other anti-diabetic drugs for 24 weeks in patients with type 2 diabetes mellitus and moderate or severe renal insufficiency.

After a 2-week, single-blind, placebo run-in period, patients were randomized to receive either vildagliptin 50 mg qd or placebo in a ratio of 2:1 (changed from originally 1:1) for 24 weeks. Patients were to continue their current anti-diabetic treatment (if any at study entry). Treatment was stratified by renal impairment severity (moderate or severe), combined age and gender factor (≥ 65 year old females or other) and background anti-diabetic therapy (thiazolidinedione, or insulin, or sulfonylurea/alpha-glucosidase inhibitor/meglitinides, or untreated). Rescue medication was allowed from Week 4 onwards.

Centers

95 centers in 13 countries: Argentina (7), Australia (4), Canada (5), Costa Rica (4), Finland (2), France (6), Germany (22), Guatemala (3), India (7), Norway (1), Russia (17), Spain (12), Sweden (5)

Outcome Measures

Primary Outcome Measure

The primary objective of the study was to evaluate the safety and tolerability of vildagliptin (50 mg qd) versus placebo in patients with T2DM and moderate or severe renal sufficiency over 24 weeks of treatment.

Secondary Outcome Measure

No secondary measures

Test Product, Dose, and Mode of Administration

One oral tablet of vildagliptin 50 mg before breakfast

Statistical Methods

Safety evaluation was the primary objective of the study. Safety data were summarized by renal impairment severity and treatment. Safety data includes treatment emergent adverse events (including hypoglycemia events and events of special interest), serious adverse events, AEs leading to study drug discontinuation, deaths, events confirmed by adjudication committee, biochemistry and hematology laboratory test results, urine laboratory tests, electrocardiogram (ECG) findings, vital signs, and body weight. For each treatment group within each renal impairment severity, the rates of events of special interest by event category were estimated with an exact binomial 95% confidence interval and compared between vildagliptin and placebo by Fisher's exact test.

Efficacy evaluation was an exploratory objective of the study.

Study Population: Inclusion/Exclusion Criteria

Inclusion Criteria

- Age in the range of 18 - 85 years inclusive at Visit 1 (Week -2).
- Patients treated with anti-diabetic therapy had to be on a stable dose for the past 4 weeks prior to Visit 1 (Week -2) (stable insulin therapy defined as ± 20% of total daily units).
- GFR < 50 mL/min/ 1.73 m2 at Visit 1 (Week -2).
- HbA1c of ≥ 6.5 and ≤ 10% at Visit 1 (Week -2).
- Body mass index (BMI) 18 - 42 kg/m^2 at Visit 1 (Week -2).
- Male, non-fertile female or female of childbearing potential using a medically approved birth control method by the country health authorities.
- Patients who agreed to continue their current diet/exercise regimen and sulfonylurea, AGI, TZD, insulin, or meglitinide therapy throughout the duration of the study or to remain untreated if were not taking anti-diabetic therapy, unless otherwise instructed by the trial physician.
- Patients who gave written informed consent to participate in the study and had the ability

to comply with all study requirements.

Exclusion Criteria

- Fasting plasma glucose (FPG) ≥ 270 mg/dL (≥ 15 mmol/L).
- Pregnant or lactating female.
- History of:
  - Type 1 diabetes, diabetes that was a result of pancreatic injury, or secondary forms of diabetes (eg, Cushing's syndrome and acromegaly).
  - Acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (with coma) within the past 6 months.
- Congestive heart failure (New York Heart Association (NYHA) class III-IV).
- Any of the following within the past 6 months:
  - myocardial infarction (MI) (if the Visit 1 [Week -2] ECG revealed patterns consistent with a MI and the date of the event could not be determined, then the patient could enter the clinical trial at the discretion of the investigator and/or local medical monitor)
  - unstable angina
  - coronary artery bypass surgery or percutaneous coronary intervention
  - stroke
- Any of the following ECG abnormalities:
  - Torsades de pointes, sustained and clinically relevant ventricular tachycardia, or ventricular fibrillation
  - second degree atrioventricular (AV) block (Mobitz 1 and 2)
  - third degree AV block
  - prolonged QTc (> 500 ms)
- Liver disease such as cirrhosis or chronic active hepatitis B and C.
- Concurrent medical condition that could have interfered with the interpretation of efficacy and safety data during the study.
- Any of the following significant laboratory abnormalities:
  - clinically significant thyroid stimulating hormone (TSH) outside of normal range at Visit 1 (Week -2)
  - clinically significant laboratory abnormalities at the opinion of the investigator
  - elevated fasting triglycerides > 500 mg/dL at Visit 1 (Week -2), confirmed by a repeat measure within 3 working days
  - alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2x upper limit of normal (ULN) at Visit 1 (Week -2), confirmed by a repeat measure within 3 working days
  - total bilirubin > 2x ULN and/or direct bilirubin greater than the ULN at Visit 1 (Week -2), confirmed by a repeat measure within 3 working days
  - history of spontaneous or drug induced muscle symptoms (not associated with exercise and/or physical activity), and/or elevated creatine phosphokinase (CPK) (> 3x ULN) confirmed by a repeat measure within 3 working days
  - a positive hepatitis B surface test (antigen HbsAg)
  - a positive hepatitis C test (HCV antibodies)

Participant Flow

Renal impairment: Moderate

Disposition Reason	Vilda 50mg qd N=165 n (%)	Placebo N=129 n (%)	Total N=294 n (%)
Completed	148 (89.7)	115 (89.1)	263 (89.5)
Discontinued	17 (10.3)	14 (10.9)	31 (10.5)
Abnormal test procedure result(s)	1 (0.6)	0 (0.0)	1 (0.3)
Administrative problems	1 (0.6)	0 (0.0)	1 (0.3)
Adverse event(s)	3 (1.8)	6 (4.7)	9 (3.1)
Death	1 (0.6)	1 (0.8)	2 (0.7)
Lost to follow-up	4 (2.4)	2 (1.6)	6 (2.0)
Patient withdrew consent	3 (1.8)	4 (3.1)	7 (2.4)
Protocol deviation	4 (2.4)	1 (0.8)	5 (1.7)

Renal impairment: Severe

Disposition Reason	Vilda 50mg qd N=124 n (%)	Placebo N=97 n (%)	Total N=221 n (%)
Completed	107 (86.3)	84 (86.6)	191 (86.4)
Discontinued	17 (13.7)	13 (13.4)	30 (13.6)
Abnormal laboratory value(s)	0 (0.0)	1 (1.0)	1 (0.5)
Abnormal test procedure result(s)	1 (0.8)	0 (0.0)	1 (0.5)
Adverse event(s)	8 (6.5)	2 (2.1)	10 (4.5)
Death	3 (2.4)	4 (4.1)	7 (3.2)
Lost to follow-up	2 (1.6)	2 (2.1)	4 (1.8)
Patient withdrew consent	3 (2.4)	4 (4.1)	7 (3.2)

Baseline Characteristics

Renal impairment: Moderate

Demographic variable	Vilda 50mg qd N=165	Placebo N=129	Total N=294
Age (years)			
N	165	129	294
Mean	67.7	69.7	68.6
SD	8.81	7.25	8.21
Sex			
Male	96 (58.2%)	80 (62.0%)	176 (59.9%)
Female	69 (41.8%)	49 (38.0%)	118 (40.1%)

Renal impairment: Severe

Age (years)			
N	124	97	221
Mean	64.1	64.5	64.3
SD	9.17	10.83	9.91
Sex			
Male	65 (52.4%)	53 (54.6%)	118 (53.4%)
Female	59 (47.6%)	44 (45.4%)	103 (46.6%)

Outcome Measure Results

Primary Outcome Measure (Please refer to "Safety Result" section)

Secondary Outcome Measure

There were no defined secondary outcomes.

Safety Results

Adverse Events by System Organ Class

Renal impairment: Moderate Primary system organ class	Vilda 50mg qd N=163 n (%)	Placebo N=129 n (%)
- Any primary system organ class	110 (67.5)	94 (72.9)
Blood and lymphatic system disorders	3 (1.8)	2 (1.6)
Cardiac disorders	8 (4.9)	11 (8.5)
Ear and labyrinth disorders	4 (2.5)	2 (1.6)
Endocrine disorders	1 (0.6)	0 (0.0)
Eye disorders	9 (5.5)	7 (5.4)
Gastrointestinal disorders	22 (13.5)	20 (15.5)
General disorders and administration site conditions	35 (21.5)	30 (23.3)
Immune system disorders	0 (0.0)	1 (0.8)
Infections and infestations	38 (23.3)	35 (27.1)
Injury, poisoning and procedural complications	10 (6.1)	10 (7.8)
Investigations	19 (11.7)	11 (8.5)
Metabolism and nutrition disorders	36 (22.1)	22 (17.1)
Musculoskeletal and connective tissue disorders	25 (15.3)	20 (15.5)
Nervous system disorders	37 (22.7)	30 (23.3)
Psychiatric disorders	10 (6.1)	8 (6.2)
Renal and urinary disorders	4 (2.5)	5 (3.9)
Reproductive system and breast disorders	2 (1.2)	2 (1.6)
Respiratory, thoracic and mediastinal disorders	9 (5.5)	10 (7.8)
Skin and subcutaneous tissue disorders	27 (16.6)	17 (13.2)
Vascular disorders	9 (5.5)	6 (4.7)
Renal impairment: Severe **Primary system organ class**	**Vilda 50mg qd N=124** **n (%)**	**Placebo N=97** **n (%)**
- Any primary system organ class	90 (72.6)	72 (74.2)
Blood and lymphatic system disorders	7 (5.6)	6 (6.2)
Cardiac disorders	15 (12.1)	12 (12.4)
Ear and labyrinth disorders	5 (4.0)	1 (1.0)
Endocrine disorders	0 (0.0)	1 (1.0)
Eye disorders	11 (8.9)	10 (10.3)
Gastrointestinal disorders	27 (21.8)	24 (24.7)
General disorders and administration site conditions	38 (30.6)	27 (27.8)
Hepatobiliary disorders	2 (1.6)	0 (0.0)
Immune system disorders	2 (1.6)	0 (0.0)
Infections and infestations	38 (30.6)	19 (19.6)
Injury, poisoning and procedural complications	9 (7.3)	2 (2.1)
Investigations	13 (10.5)	8 (8.2)
Metabolism and nutrition disorders	33 (26.6)	30 (30.9)
Musculoskeletal and connective tissue disorders	9 (7.3)	14 (14.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	0 (0.0)
Nervous system disorders	28 (22.6)	16 (16.5)
Psychiatric disorders	9 (7.3)	4 (4.1)
Renal and urinary disorders	8 (6.5)	8 (8.2)
Reproductive system and breast disorders	1 (0.8)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	12 (9.7)	13 (13.4)
Skin and subcutaneous tissue disorders	28 (22.6)	23 (23.7)
Vascular disorders	13 (10.5)	13 (13.4)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE

Adverse Events Affecting 5% or More of Patients in Any Treatment Group by Preferred Term

Renal impairment: Moderate Preferred term	Vilda 50mg qd N=163 n (%)	Placebo N=129 n (%)
- Any Preferred term	110 (67.5)	94 (72.9)
Hypoglycemia	28 (17.2)	15 (11.6)
Oedema peripheral	18 (11.0)	13 (10.1)
Dizziness	14 (8.6)	14 (10.9)
Blood glucose decreased	13 (8.0)	4 (3.1)
Hyperhidrosis	12 (7.4)	12 (9.3)
Tremor	11 (6.7)	10 (7.8)
Asthenia	9 (5.5)	6 (4.7)
Nasopharyngitis	9 (5.5)	13 (10.1)

Renal impairment: Severe Preferred term	Vilda 50mg qd N=124 n (%)	Placebo N=97 n (%)
- Any Preferred term	90 (72.6)	72 (74.2)
Oedema peripheral	21 (16.9)	18 (18.6)
Hypoglycemia	19 (15.3)	12 (12.4)
Hyperhidrosis	13 (10.5)	8 (8.2)
Hyperkalaemia	13 (10.5)	4 (4.1)
Dizziness	12 (9.7)	10 (10.3)
Diarrhea	11 (8.9)	8 (8.2)
Influenza	8 (6.5)	1 (1.0)
Asthenia	7 (5.6)	6 (6.2)
Blood glucose decreased	7 (5.6)	3 (3.1)
Fatigue	7 (5.6)	2 (2.1)
Nausea	7 (5.6)	6 (6.2)
Vomiting	7 (5.6)	4 (4.1)
Hypertension	6 (4.8)	9 (9.3)
Urinary tract infection	6 (4.8)	5 (5.2)
Dyspnoea	4 (3.2)	5 (5.2)
Nasopharyngitis	4 (3.2)	5 (5.2)
Hyperuricaemia	3 (2.4)	6 (6.2)
Back pain	1 (0.8)	5 (5.2)

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

Preferred terms are sorted by descending order of incidence in the vildagliptin 50mg qd group.

Serious Adverse Events and Deaths

Renal impairment: Moderate Event category	Vilda 50mg qd N=163 n (%)	Placebo N=129 n (%)
Deaths	1(0.6)	1(0.8)
SAEs	15 (9.2)	11 (8.5)
Discontinuation due to AEs	4 (2.5)	7 (5.4)
AEs causing dose adjustment or study drug interruption	0 (0.0)	5 (3.9)

Renal impairment: Severe Event category	Vilda 50mg qd N=124 n (%)	Placebo N=97 n (%)
Deaths	3(2.4)	4(4.1)
SAEs	23 (18.5)	20 (20.6)
Discontinuation due to AEs	11 (8.9)	6 (6.2)
AEs causing dose adjustment or study drug interruption	14 (11.3)	8 (8.2)

Other Relevant Findings

No other important or notable findings were reported in this study.

Date of Clinical Trial Report

18 April 2011

Date Inclusion on Novartis Clinical Trial Results Database

27 September 2011

Date of Latest Update

25 Jun 2012