Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

Type 2 diabetes

Study Number

CLAF237A23138

Title

A multi-center, randomized, double-blind, active-controlled clinical trial to evaluate the safety and tolerability of 24 weeks treatment with vildagliptin (50 mg qd) versus sitagliptin (25 mg qd) in patients with type 2 diabetes and severe renal insufficiency

Phase of Development

Phase IIIb

Study Start/End Dates

24-Jan-2008 to 06-Oct-2010

Study Design/Methodology

This was a multi-center, randomized, double-blind, active-controlled clinical trial to evaluate the safety and tolerability of vildagliptin 50 mg qd versus sitagliptin 25 mg qd when given as mono-therapy or as add on to other anti-diabetic drugs for 24 weeks in patients with T2DM and severe renal insufficiency (estimated GFR of < 30 mL/min/ 1.73 m^2).

After a 2-week single blind placebo run-in period, patients were randomized to receive either vildagliptin 50 mg qd or sitagliptin 25 mg qd in a ratio of 3:1 (changed from originally 1:1) for 24 weeks. Patients were to continue their current anti-diabetic treatment (if any at study entry). Rescue medication was allowed from week 4 onwards.

Centres

87 centers in two countries: Brazil (6), USA (81).

Objectives

Primary objective(s)

The primary objective was to evaluate the safety and tolerability of vildagliptin (50 mg qd) versus sitagliptin (25 mg qd) in patients with T2DM and severe renal insufficiency over 24 weeks of treatment.

Secondary objective(s)

There were no secondary objectives for this study.

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

Vildagliptin 50 mg tablets or matching placebo tablets (once daily)

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

Sitagliptin 25 mg capsules or 25 mg matching placebo capsules (once daily)

Criteria for Evaluation

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events, recording of hypoglycemic events, regular monitoring of hematology, blood chemistry and urine parameters, and regular assessments of vital signs, body weight and ECGs.

Other

Not applicable.

Statistical Methods

Safety data were summarized based on all data collected during the entire study regardless of rescue medication use. Selected safety data (e.g. events of special interest and hypoglycemic events) were also summarized for the rescue free data.

The number and percentage of patients with adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, program-wise predefined events of special interest and hypoglycemic events were summarized by treatment. Hematology and biochemistry data and changes in GFR MDRD from study entry value to endpoint value were also summarized by treatment. Vital signs, body weight and ECG findings by category were evaluated descriptively.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria

- Patients with T2DM either untreated or treated with anti-diabetic therapy defined as sulfonylurea, TZDs, insulin, and meglitinides as monotherapy or combination therapy. Patients treated with anti-diabetic therapy had to be on a stable dose for the 4 weeks prior to visit 1
- Male or female (non-fertile or using a medically approved birth control method)
- Age in the range of 18-85 years (inclusive)
- GFR of < 30 mL/min/ 1.73 m^2
- HbA_{1c} of ≥ 6.5 and ≤ 10%
- Body mass index (BMI) 18-42 kg/m^2

Key exclusion criteria

- FPG ≥ 270 mg/dL (≥15 mmol/L)
- Pregnant or lactating females
- A history of Type 1 diabetes, diabetes that was a result of pancreatic injury, or secondary forms of diabetes, e.g. 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 Health Association (NYHA) class III-IV)
- Any of the following within the past 6 months: myocardial infarction, 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 AV block (Mobitz 1 and 2), third degree AV block, prolonged QTc (> 500 ms)
- Any of the following significant laboratory abnormalities: clinically significant thyroid stimulating hormone (TSH) outside of normal range, elevated fasting triglycerides > 500 mg/dL, ALT and/or AST > 2 x upper limit of normal (ULN), total bilirubin > 2 x ULN and/or direct bilirubin > ULN, history of spontaneous or drug induced muscle symptoms (not associated with exercise and/or physical activity), and/or elevated CPK (>3 x ULN), a positive Hepatitis B test (surface antigen - HbsAg) or Hepatitis C test (HCV antibodies)

Number of Subjects

Patient disposition (Randomized set)

Disposition Reason	Vilda 50mg qd N=83 n (%)	Sita 25mg qd N=65 n (%)	Total N=148 n (%)
Completed	64 (77.1)	53 (81.5)	117 (79.1)
Discontinued	19 (22.9)	12 (18.5)	31 (20.9)
Adverse event (s)	4 (4.8)	4 (6.2)	8 (5.4)
Death	2 (2.4)	2 (3.1)	4 (2.7)
Lost to follow-up	1 (1.2)	1 (1.5)	2 (1.4)
Patient's condition no longer requires study drug	0 (0.0)	1 (1.5)	1 (0.7)
Patient withdrew consent	10 (12.0)	3 (4.6)	13 (8.8)
Protocol deviation	2 (2.4)	1 (1.5)	3 (2.0)

Demographic and Background Characteristics

Demographic variable	Vilda 50mg qd N=83	Sita 25mg qd N=65	Total N=148
Age (years)			
N	83	65	148
Mean	66.7	66.9	66.8
SD	8.80	9.62	9.14
Min	40.0	46.0	40.0
Median	68.0	68.0	68.0
Max	84.0	85.0	85.0
Age group			
< 65 yrs	32 (38.6%)	25 (38.5%)	57 (38.5%)
≥ 65 yrs	51 (61.4%)	40 (61.5%)	91 (61.5%)
< 75 yrs	67 (80.7%)	50 (76.9%)	117 (79.1%)
≥ 75 yrs	16 (19.3%)	15 (23.1%)	31 (20.9%)
Sex			
Male	42 (50.6%)	29 (44.6%)	71 (48.0%)
Female	41 (49.4%)	36 (55.4%)	77 (52. %)
Age/Gender			
≥ 65 yrs female	25 (30 1%)	21 (32.3%)	46 (31.1%)
Others	58 (69.9%)	44 (67.7%)	102 (68.9%)
Race			
Asian (Non Indian Subcontinent)	1 (1.2%)	0 (0.0%)	1 (0.7%)
Black	19 (22.9%)	15 (23.1%)	34 (23.0%)
Caucasian	51 (61.4%)	40 (61.5%)	91 61.5%)
His anic or latino	10 (12.0%)	7 (10.8%)	17 (11.5%)
Japanese	1 (1.2%)	0 (0.0%)	1 (0.7%)
Other	0 (0.0%)	2 (3.1%)	2 (1.4%)

Pacific islander	1 (1.2%)	1 (1.5%)	2 (1.4%)
Height (cm)			
N	82	65	147
Mean	166.5	164.4	165.5
SD	9.74	9.89	9.83
Min	143.0	144.0	143.0
Median	165.0	163.0	165.0
Max	188.0	189.0	189.0
Body weight (kg)			
N	82	65	147
Mean	90.8	91.7	91.2
SD	16.96	17.77	17.27
Min	58.1	55.0	55.0
Median	86.5	93.9	90.0
Max	140.9	147.5	147.5
BMI (kg/m^2)			
N	82	65	147
Mean	32.7	33.8	33.2
SD	5.03	4.83	4.95
Min	22.5	23.2	22.5
Median	32.3	34.4	33.7
Max	41.7	41.8	41.8
BMI group			
<30 (kg/m^2)	30 (36.1%)	16 (24.6%)	46 (31.1%)
≥ 30 (kg/m^2)	52 (62.7%)	49 (75.4%)	101 (68.2%)
≥ 35 (kg/m^2)	26 (31.3%)	30 (46.2%)	56 (37.8%)
Not recorded	1 (1 2%)	0 (0.0%	1 (0.7%)

Demography information is collected on the day of the screening measurement (Week -2, Visit 1).

Primary Objective Results

Safety Results

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

Primary system organ class	Vilda 50mg qd N=83 n (%)	Sita 25mg qd N=65 n (%)
- Any primary system organ class	68 (81.9)	56 (86.2)
Blood and lymphatic system disorders	6 (7.2)	5 (7.7)
Cardiac disorders	11 (13.3)	10 (15.4)
Ear and labyrinth disorders	1 (1.2)	2 (3.1)
Endocrine disorders	0 (0.0)	1 (1.5)
Eye disorders	0 (0.0)	10 (15.4)
Gastrointestinal disorders	20 (24.1)	22 (33.8)
General disorders and administration site conditions	31 (37.3)	31 (47.7)
Hepatobiliary disorders	0 (0.0)	1 (1.5)
Infections and infestations	29 (34.9)	25 (38.5)
Injury, poisoning and procedural complications	16 (19.3)	9 (13.8)
Investigations	9 (10.8)	16 (24.6)
Metabolism and nutrition disorders	32 (38.6)	19 (29.2)
Musculoskeletal and connective tissue disorders	18 (21.7)	15 (23.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.2)	2 (3.1)
Nervous system disorders	21 (25.3)	24 (36.9)
Psychiatric disorders	6 (7.2)	8 (12.3)
Renal and urinary disorders	12 (14.5)	10 (15.4)
Reproductive system and breast disorders	3 (3.6)	2 (3.1)
Respiratory, thoracic and mediastinal disorders	12 (14.5)	11 (16.9)
Skin and subcutaneous tissue disorders	21 (25.3)	18 (27.7)
Vascular disorders	7 (8.4)	7 (10.8)

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 category for that treatment.

Coded using MedDRA version13.0.

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

Preferred term	Vilda 50mg qd N=83 n (%)	Sita 25mg qd N=65 n (%)
Oedema peripheral	19 (22.9)	16 (24.6)
Dizziness	13 (15.7)	8 (12.3)
Hypoglycaemia	13 (15.7)	10 (15.4)
Constipation	8 (9.6)	4 (6.2)
Urinary tract infection	8 (9.6)	5 (7.7)
Tremor	7 (8.4)	11 (16.9)
Hyperhidrosis	6 (7.2)	9 (13.8)
Asthenia	5 (6.0)	14 (21.5)
Upper respiratory tract infection	5 (6.0)	6 (9.2)
Nausea	3 (3.6)	9 (13.8)

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 Vilda 50mg qd group.

Serious Adverse Events and Deaths

Number (%) of patients with serious or clinically significant AEs during the double-blind period (Safety set)

Event category	Vilda 50mg qd N=83 n (%)	Sita 25mg qd N=65 n (%)
Deaths	2 (2.4)	2 (3.1)
SAEs	20 (24.1)	15 (23.1)
Discontinuation due to AEs	6 (7.2)	6 (9.2)
AEs causing dose adjustment or study drug interruption	13 (15.7)	11 (16.9)

* Patients with events confirmed by the Cardiovascular and Cerebrovascular adjudication committee

** Patients with events confirmed by the Hepatic adjudication committee

*** Patients with events confirmed by the Skin, Vascular, Edema and Muscle adjudication committee

Deaths during the randomized double-blind period by primary system organ class, preferred term and treatment (Safety set)

Primary system organ class Principal cause of death	Vilda 50mg qd N=83 n (%)	Sita 25mg qd N=65 n (%)
-Any primary system organ class		
-Total	2 (2.4)	2 (3.1)
Cardiac disorders		

-Total	1 (1.2)	0 (0.0)
Cardiac arrest	1 (1.2)	0 (0.0)
Infections and infestations		
-Total	1 (1.2)	0 (0.0)
Septic shock	1 (1.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
-Total	0 (0.0)	2 (3.1)
Acute pulmonary oedema	0 (0.0)	1 (1.5)
Asphyxia	0 (0.0)	1 (1.5)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.

Number (%) of patients with SAEs by preferred terms (Safety set)

Preferred term	Vilda 50mg qd N=83 n (%)	Sita 25mg qd N=65 n (%)
- Any SAE	20 (24.1)	15 (23.1)
Acute myocardial infarction	0 (0.0)	1 (1.5)
Acute pulmonary oedema	0 (0.0)	1 (1.5)
Anaemia	0 (0.0)	2 (3.1)
Angina pectoris	0 (0.0)	1 (1.5)
Anoxic encephalopathy	0 (0.0)	1 (1.5)
Anxiety	1 (1.2)	0 (0.0)
Arteriovenous fistula thrombosis	1 (1.2)	0 (0.0)
Asphyxia	0 (0.0)	1 (1.5)
Aspiration	0 (0.0)	1 (1.5)
Azotaemia	0 (0.0)	1 (1.5)
Benign renal neoplasm	1 (1.2)	0 (0.0)
Cardiac arrest	1 (1.2)	2 (3.1)
Cardiac failure congestive	1 (1.2)	2 (3.1)
Cellulitis	0 (0.0)	1 (1.5)
Coronary artery disease	0 (0.0)	1 (1.5)
Coronary artery occlusion	1 (1.2)	0 (0.0)
Dehydration	1 (1.2)	2 (3.1)
Diabetes mellitus	1 (1.2)	0 (0.0)
Diverticulitis	1 (1.2)	0 (0.0)
Dyspnoea	1 (1.2)	2 (3.1)
Erosive oesophagitis	1 (1.2)	0 (0.0)
Gangrene	1 (1.2)	0 (0.0)
Gastritis	0 (0.0)	1 (1.5)
Gastroenteritis viral	1 (1.2)	0 (0.0)
Hydronephrosis	1 (1.2)	0 (0.0)
Hypercalcaemia	1 (1.2)	0 (0.0)
Hypercapnia	0 (0.0)	1 (1.5)

Hyperkalaemia	1 (1.2)	0 (0.0)
Hypertension	0 (0.0)	1 (1.5)
Hypoglycaemia	1 (1.2)	2 (3.1)
Hypoxia	0 (0.0)	1 (1.5)
Myocardial infarction	2 (2.4)	0 (0.0)
Non-cardiac chest pain	2 (2.4)	1 (1.5)
Osteomyelitis	1 (1.2)	0 (0.0)
Peripheral vascular disorder	1 (1.2)	0 (0.0)
Pneumonia	0 (0.0)	1 (1.5)
Prostatomegaly	1 (1.2)	0 (0.0)
Pulmonary oedema	1 (1.2)	1 (1.5)
Renal failure acute	1 (1.2)	2 (3.1)
Renal failure chronic	2 (2.4)	1 (1.5)
Sepsis	1 (1.2)	0 (0.0)
Septic shock	1 (1.2)	0 (0.0)
Urinary retention	0 (0.0)	1 (1.5)

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

Other Relevant Findings

Hypoglycemic events during the randomized double-blind period (Safety set)

Event category	Vilda 50 mg qd N=83 n (%)	Sita 25 mg qd N=65 n (%)
Number (%) of patients with at least one hypoglycemic event	13 (15.7)	10 (15.4)
Number (%) of patients who discontinued due to hypoglycemic events	0 (0.0)	0 (0.0)
Number (%) of patients with grade 2 hypoglycemic events	1 (1.2)	1 (1.5)
Number (%) of patients with suspected grade 2 hypoglycemic events	0 (0.0)	1 (1.5)

Hypoglycemic events are defined as a) symptoms suggestive of hypoglycemia, where the patient is able to initiate self-treatment and plasma glucose measurement is < 3.1 mmol/L (grade 1), b) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and plasma glucose measurement is < 3.1 mmol/L (grade 2), c) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and no plasma glucose measurement is available (suspected grade 2).
A patient may have had more than one type of event.

Date of Clinical Trial Report

14-April-2011

Date Inclusion on Novartis Clinical Trial Results Database

27-September-2011

Date of Latest Update

26-September-2011