Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes with impaired glucose tolerance (IGT)

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

CLAF237A2357

Title

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of 12 week treatment with vildagliptin (LAF237) 50 mg qd in subjects with impaired glucose tolerance (IGT)

Phase of Development

Phase III

Study Start/End Dates

03 Oct 2005 to 05 Jul 2006

Study Design/Methodology

This was a multicenter, randomized, double-blind, placebo-controlled study. Subjects with impaired glucose tolerance (IGT) as defined by the revised American Diabetes Association (ADA) criteria were randomized equally to vildagliptin 50 mg once daily (qd) or placebo.

Each patient attended a pre-screening visit (Week -4) where an oral glucose tolerance test (OGTT) was performed. Subjects with confirmed IGT then attended the main screening visit (Week -2) where all the inclusion/exclusion criteria were assessed. Eligible patients were then randomized at visit 3 (Baseline, Day 1) and completed 2 further visits over a period of 12 weeks of treatment with vildagliptin or placebo.

Centers

28 centers in 6 countries: Great Britain (4), Sweden (3), Finland (4), Spain (5), Germany (2), and US (10)

Publication

Rosenstock J, Foley J, Rendell M, Landin-Olsson M, Holst J, Deacon C, Rochotte E, Baron M. Effects of the diapeptidyl peptidase-IV inhibitor vildagliptin on incretin hormones, islet function, and postprandial glycemia in subjects with impaired glucose tolerance. Diabetes Care 2008;31(1):30-5.

http://www.ncbi.nlm.nih.gov/pubmed/17947341?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Outcome Measures

Primary Outcome Measure

- Change in Prandial Plasma Glucose Area Under the Curve from 0 to 2 hours (AUC_{0-2h}) from Baseline at Week 12

Secondary Outcome Measures

- Change in Adjusted Prandial Plasma Glucose AUC_{0-2h} from Baseline at Week 12
- Change in 2-hour Prandial Plasma Glucose Level from Baseline at Week 12
- Change in Peak Prandial Excursion of Glucose from Baseline at Week 12
- Change in Prandial Insulin AUC_{0-2h} from Baseline at Week 12
- Change in Adjusted Prandial Insulin AUC_{0-2h} from Baseline at Week 12
- Change in Prandial C-peptide AUC_{0-2h} from Baseline at Week 12
- Change in Adjusted Prandial C-peptide AUC_{0-2h} from Baseline at Week 12

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

One oral tablet of vildagliptin 50 mg before breakfast

Statistical Methods

The primary hypothesis tested was the superiority of vildagliptin 50 mg once daily (qd) over placebo for the effect of reducing the area under the 0-2 hour prandial plasma glucose curve (AUC_{0-2h}) after 12 weeks of treatment. Change from baseline in primary and secondary endpoints was analyzed using analysis of covariance (ANCOVA) with treatment and pooled center as classification variables and baseline value as a covariate. The estimated treatment difference (vildagliptin - placebo) and its 95% confidence interval were derived from the least square mean change from baseline ('adjusted mean') of each treatment group. For all efficacy variables treatment comparisons were made at an individual 2-sided 5% significance level.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Male or female (non-fertile or using a medically approved birth control method).
- Age in the range of 18 to 80 years inclusive.
- Body mass index (BMI) of 23-45 kg/m2 inclusive at Visit 1 (Week -4).
- Impaired glucose tolerance (IGT) as defined as fasting plasma glucose (FPG) < 126 mg/dL (7.0 mmol/L) and 2-hour post-challenge plasma glucose (after a 75 g oral glucose tolerance test [OGTT]) ≥ 140 mg/dL (7.8 mmol/L) and < 200 mg/dL (11.1 mmol/L)
- Agreement to maintain prior diet and exercise habits during the full course of the study.

Exclusion Criteria

- Pregnant or lactating female.
- Diabetes, defined as any of the following:
  - FPG ≥ 126mg/dL (7.0 mmol/L) at Visit 1 (Week -4).
  - 2-hour post-challenge plasma glucose (after a 75-g OGTT) ≥ 200 mg/dL (11.1 mmol/L) at Visit 1 (Week -4).
  - Diabetes diagnosed by a physician and confirmed by other clinical data, other than gestational diabetes.
  - Use of insulin or any oral antidiabetic agents prior to Visit 1 (Week -4), other than during pregnancy.
- Acute infections which may have had affected blood glucose control within 4 weeks prior to Visit 1 (Week -4).
- A history of:
  - Torsades de Pointes, sustained and clinically relevant ventricular tachycardia or ventricular fibrillation.
  - Percutaneous coronary intervention within the past 3 months.
  - Any of the following within the past 6 months: myocardial infarction, coronary artery bypass surgery, unstable angina, or stroke.
- Congestive heart failure New York Heart Association (NYHA) class III or IV.
- Second degree atrioventricular (AV) block (Mobitz 1 and 2), third degree AV block, prolonged QTc.
- Malignancy including leukemia and lymphoma (not including basal cell skin cancer) within the last 5 years.
- Liver disease.
- Acromegaly or treatment with growth hormone or similar drugs.
- Concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study.
- Donation of one unit (500 ml) or more of blood, significant blood loss equaling to at least one unit of blood within the past 2 weeks, or a blood transfusion within the past 8 weeks.
- Chronic insulin treatment (> 4 weeks of treatment in the absence of an intercurrent illness) within the past 6 months.
- Chronic oral or parenteral corticosteroid treatment (> 7 consecutive days of treatment) within 8 weeks prior to Visit 1 (Week -4).
- Treatment with class Ia, Ib and Ic, or III anti-arrhythmics.
- Thyroid hormone replacement was allowed if the dosage had been stable for at least 3 months, use of other investigational drugs at Visit 1 (Week -4), or within 30 days or 5 half-lives of Visit 1 (Week -4), whichever was longer, unless local health authority guidelines mandate a longer period.
- Treatment with any drug with a known and frequent toxicity to a major organ system within the past 3 months.
- Any of the following significant laboratory abnormalities:
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) greater than 3 times the upper limit of the normal range.

- Direct bilirubin greater than 1.3 times the upper limit of the normal range at Visit 2 (Week -2).
- Serum creatinine levels ≥ 2.5 mg/dL (220 µmol/L) at Visit 2 (Week -2).
- Thyroid stimulating hormone (TSH) outside normal range at Visit 2 (Week -2).
- Clinically significant laboratory abnormalities confirmed by repeat measurement at Visit 2 (Week -2).
- Fasting triglycerides > 700 mg/dL (>7.9 mmol/L) at Visit 2 (Week -2).

- 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.

Participant Flow

Disposition Reason	Vilda 50 mg qd N=90		Placebo N=89		Total N=179	
	n	(%)	n	(%)	n	(%)
Completed	84	(93.3)	84	(94.4)	168	(93.9)
Discontinued	6	(6.7)	5	(5.6)	11	(6.1)
Adverse Event(s)	3	(3.3)	2	(2.2)	5	(2.8)
Protocol violation	1	(1.1)	2	(2.2)	3	(1.7)
Subject withdrew consent	1	(1.1)	1	(1.1)	2	(1.1)
Lost to follow up	1	(1.1)	0	(0.0)	1	(0.6)

Baseline Characteristics

Demographic variable	Vilda 50 mg qd N=90	Placebo N=89	Total N=179
Age (years)			
n	90	89	179
Mean ± SD	57.1 ± 10.72	58.8 ± 11.51	58.0 ± 11.12
Sex			
Male	43 (47.8%)	38 (42.7%)	81 (45.3%)
Female	47 (52.2%)	51 (57.3%)	98 (54.7%)

Outcome Measure Results

Primary Outcome Measure

Change in Prandial Plasma Glucose Area Under the Curve from 0 to 2 hours (AUC_{0-2h}) from Baseline at Week 12

Treatment	n	Baseline mean (SE)	Adjusted mean change from baseline (SE)	Mean difference to placebo (SE)	95% CI	p-value
ITT population						
Vilda 50 mg qd	83	15.82 (0.272)	-0.87 (0.184)	-0.96 (0.261)	(-1.48, -0.44)	<0.001*
Placebo	82	15.89 (0.267)	0.09 (0.186)			

Secondary Outcome Measures

Change in Adjusted Prandial Plasma Glucose AUC_{0-2h} from Baseline at Week 12

Change in 2-hour Prandial Plasma Glucose Level from Baseline at Week 12

Change in Peak Prandial Excursion of Glucose from Baseline at Week 12

Change in Prandial Insulin AUC_{0-2h} from Baseline at Week 12

Change in Adjusted Prandial Insulin AUC_{0-2h} from Baseline at Week 12

Change in Prandial C-peptide AUC_{0-2h} from Baseline at Week 12

Change in Adjusted Prandial C-peptide AUC_{0-2h} from Baseline at Week 12

Treatment group	n	Baseline mean (SE)	Adjusted mean change from baseline (SE)	Mean difference to placebo (SE)	95% CI	p-value
Adjusted prandial plasma glucose AUC_{0-2hr} (mmol x hr/L)						
Vilda 50 mg qd	83	3.17 (0.217)	-0.71 (0.180)	-1.00 (0.256)	(-1.50, -0.49)	<0.001*
Placebo	82	3.53 (0.245)	0.29 (0.183)			
2-hour prandial plasma glucose level (mmol/L)						
Vilda 50 mg qd	84	6.78 (0.169)	-0.17 (0.118)	-0.31 (0.168)	(-0.64, 0.02)	0.067
Placebo	82	6.83 (0.147)	0.14 (0.120)			
Peak prandial excursion of glucose (mmol/L)						
Vilda 50 mg qd	85	3.03 (0.148)	-0.57 (0.115)	-0.63 (0.162)	(-0.95, -0.31)	<0.001*
Placebo	85	3.26 (0.146)	0.06 (0.116)			
Prandial insulin AUC_{0-2hr} (pmol x hr/L)						
Vilda 50 mg qd	74	653.0 (42.60)	-29.4 (26.18)	36.8 (37.35)	(-37.1, 110.6)	0.327
Placebo	73	750.2 (51.90)	-66.1 (26.80)			
Adjusted prandial insulin AUC_{0-2hr} (pmol x hr/L)						
Vilda 50 mg qd	74	523.8 (37.43)	-37.6 (25.02)	20.8 (35.72)	(-49.8, 91.4)	0.561
Placebo	73	618.7 (45.06)	-58.4 (25.59)			
Prandial C-peptide AUC_{0-2hr} (nmol x hr/L)						
Vilda 50 mg qd	77	5.75 (0.203)	0.15 (0.135)	0.25 (0.190)	(-0.12, 0.63)	0.186
Placebo	78	5.95 (0.232)	-0.10 (0.135)			
Adjusted prandial C-peptide AUC_{0-2hr} (nmol x hr/L)						
Vilda 50 mg qd	77	3.34 (0.137)	0.08 (0.108)	0.17 (0.152)	(-0.13, 0.47)	0.271
Placebo	78	3.52 (0.160)	-0.09 (0.107)			

Safety Results

Adverse Events by System Organ Class

	Vilda 50 mg qd N=90		Placebo N=89	
Primary system organ class	**n**	**(%)**	**n**	**(%)**
Any Primary system organ class	49	(54.4)	44	(49.4)
Cardiac disorders	1	(1.1)	2	(2.2)
Ear and labyrinth disorders	2	(2.2)	0	(0.0)
Eye disorders	1	(1.1)	1	(1.1)
Gastrointestinal disorders	7	(7.8)	5	(5.6)
General disorders and administration site conditions	8	(8.9)	6	(6.7)
Infections and infestations	15	(16.7)	20	(22.5)
Injury, poisoning and procedural complications	1	(1.1)	2	(2.2)
Investigations	2	(2.2)	0	(0.0)
Metabolism and nutrition disorders	3	(3.3)	1	(1.1)
Musculoskeletal and connective tissue disorders	9	(10.0)	9	(10.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(1.1)	1	(1.1)
Nervous system disorders	9	(10.0)	8	(9.0)
Psychiatric disorders	1	(1.1)	1	(1.1)
Renal and urinary disorders	1	(1.1)	0	(0.0)
Reproductive system and breast disorders	1	(1.1)	2	(2.2)
Respiratory, thoracic and mediastinal disorders	4	(4.4)	3	(3.4)
Skin and subcutaneous tissue disorders	3	(3.3)	5	(5.6)
Vascular disorders	1	(1.1)	2	(2.2)

Adverse Events Occurring in 2% or More of Patients in Any Treatment Group by Preferred Term

	Vilda 50 mg qd N=90		Placebo N=89	
Preferred term	**n**	**(%)**	**n**	**(%)**
Headache	4	(4.4)	4	(4.5)
Dizziness	4	(4.4)	2	(2.2)
Influenza	4	(4.4)	2	(2.2)
Nasopharyngitis	3	(3.3)	5	(5.6)
Back pain	3	(3.3)	2	(2.2)
Diabetes mellitus non-insulin-dependent	3	(3.3)	1	(1.1)
Arthralgia	2	(2.2)	1	(1.1)
Diarrhoea	2	(2.2)	1	(1.1)
Generalised oedema	2	(2.2)	0	(0.0)
Tooth infection	2	(2.2)	0	(0.0)
Tremor	2	(2.2)	2	(2.2)
Urinary tract infection	2	(2.2)	3	(3.4)
Asthenia	1	(1.1)	2	(2.2)
Joint swelling	1	(1.1)	2	(2.2)
Pharyngolaryngeal pain	1	(1.1)	2	(2.2)
Upper respiratory tract infection	1	(1.1)	4	(4.5)
Hunger	0	(0.0)	2	(2.2)
Hyperhidrosis	0	(0.0)	2	(2.2)

Serious Adverse Events and Deaths

No deaths were reported in this study.

	Vilda 50 mg qd N=90		Placebo N=89	
Preferred term	**n**	**(%)**	**n**	**(%)**
Any SAE	1	(1.1)	2	(2.2)
Cardiac failure congestive	1	(1.1)	0	(0.0)
Appendicitis	0	(0.0)	1	(1.1)
Cellulitis	0	(0.0)	1	(1.1)

Other Relevant Findings

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

Date of Clinical Trial Report

24 Aug 2007

Date Posted to the Novartis Clinical Trial Results Database

29 OCT 2007

Date of Latest Update

19 Jun 2012