Sponsor

Novartis

Generic Drug Name

Vildagliptin

Therapeutic Area of Trial

Type 2 diabetes

Approved Indication

According to the Summary of Product Characteristics (SPC) in Germany:
Treatment of type 2 diabetes in combination therapy with

- Metformin, in patients inadequately controlled with maximal tolerated doses of metformin
- Sulfonylureas, in patients having intolerability of metformin and being inadequately controlled with maximal tolerated doses of sulfonylureas
- Thiazolidindiones, in patients being inadequately controlled and being eligible for thiazolidindione treatment

Study Number

CLAF237ADE02

Title

A multicenter, randomized, double-blind, parallel-group study to investigate the glucose lowering effect, safety and tolerability of a 24 week treatment with Vildagliptin 100 mg o.a.d. versus placebo followed by a 12 week treatment period with open-label Vildagliptin 100 mg o.a.d. as add-on therapy in patients with type 2 diabetes inadequately controlled with Metformin monotherapy

Phase of Development

Phase IIIb

Study Start/End Dates

11-Jun-2007 to 07-Jul-2008

Study Design/Methodology

Multicenter, randomized, double-blind study with open-label follow-up. Patients with T2DM and prior therapy with metformin for at least 3 months prior to screening who were inadequately controlled (HbA1c 6.5-8.0%) were randomized into this study. Eligible patients have been random-

ized into 2 treatment arms (ratio 2: 1 for vildagliptin 100 mg o.a.d.: placebo o.a.d.) for a period of 24 weeks. Within the treatment arms patients were randomized to morning or evening administration. After this 24 weeks double-blind phase all patients were treated with open-label vildagliptin 100 mg o.a.d. according to the previous dosing regime.

Centres

94 centers in Germany

Publication

Vollmer M, Abletshauser C, Pennartz C, Meier JJ. Wirksamkeit und Sicherheit der frühen Kombination von Vildagliptin mit Metformin im Vergleich zu Placebo bei Patienten mit Typ 2 Diabetes.

Diabetologie und Stoffwechsel S1 2009; 4: S83

Objectives

Primary objective(s)

To confirm the efficacy of vildagliptin 100 mg add-on therapy in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the HbA_{1c} reduction with vildagliptin 100 mg o.a.d. (hierarchically testing of pooled data of a.m. and p.m. dose as well as within a.m. and p.m. dosing groups) is superior to that with placebo after 24 weeks of treatment.

Secondary objective(s)

To confirm the efficacy of add-on therapy with vildagliptin in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the FPG reduction with vildagliptin 100 mg o.a.d. (pooled data of a.m. and p.m dose as well as within a.m. and p.m. dosing groups) is superior to that with placebo after 24 weeks of treatment.

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

Oral tablets of vildagliptin 100 mg once daily

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

Placebo oral tablets matching vildagliptin 100 mg once daily

Criteria for Evaluation

Primary variables

Primary parameter is HbA_{1c} after 24 weeks measured by certified methodology.

Secondary variables

Secondary parameters: Fasting plasma glucose after 24 weeks of treatment.

Safety and tolerability

Hypoglycemia during 24 weeks of treatment. Biochemistry.

Pharmacology

None

Other

None

Statistical Methods

The **primary analysis** was performed comparing treatments with respect to the primary efficacy variable in an analysis of covariance (ANCOVA) model with the factors treatment and center and baseline HbA_{1c} as a covariate. The raw- as well as the adjusted (LS) group means are presented together with a 95% confidence interval and a p-value.

Multiplicity issues: The factorial design of this trial with 2 treatments (vildagliptin and placebo), each given in 2 different dosing schedules (a.m.-and p.m.-dosing) yields 4 different treatment arms. The resulting multiplicity was dealt with by applying a closed test procedure. In a first step, vildagliptin was compared to placebo pooled over dosing schedules. The null hypothesis of no difference in HbA_{1c} reduction was tested by applying a linear contrast with weights -0.25 for the two placebo arms and with weights +0.25 for the vildagliptin arms.

Significance Level: Both null hypothesis tested in step 2 are hierarchically nested within the pooled null hypothesis of step 1 and can't both be true, once the pooled null hypothesis of step 1 has been rejected. Therefore no further adjustment for multiplicity is required, all tests were performed at the two-sided 5% level.
No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male, non-fertile female or female of childbearing potential using a medically approved birth control method.
2. Patients with T2DM who have received metformin for at least three months prior visit 1 and have been on a stable (maximal tolerated) dose for a minimum of 8 weeks prior to visit 1.
3. Agreement to maintain the same dose of metformin throughout the study.
4. Age in the range of 18-85 years inclusive.
5. HbA_{1c} in the range of 6.5 – 8.0 % (inclusive) at visit 1.

Exclusion criteria

1. A history of:
   - type 1 diabetes, diabetes that is 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 (coma) within the past 6 months.
2. Evidence of significant diabetic complications, e.g. symptomatic autonomic neuropathy or gastroparesis.
3. Acute infections which may affect blood glucose control within 4 weeks prior to visit 1 and other concurrent medical conditions that may interfere with the interpretation of efficacy and safety data during the study.
4. ALT, AST greater than 2 times the upper limit of the normal range (ULN) at visit 1.
5. Total bilirubin greater than 2 times ULN and direct bilirubin greater than the upper limit of the normal range at visit 1.

Number of Subjects

	Vildagliptin	Placebo
Planned N	268	134
Randomised n	274	131
Intent-to-treat population (ITT) n (%)	268 (97.8)	127 (96.9)
Completed n (%)	239 (87.2)	107 (81.7)
Withdrawn n (%)	35 (12.8)	24 (18.3)
Withdrawn due to adverse events n (%)	10 (3.6)	2 (1.5)
Withdrawn due to lack of efficacy n (%)	8 (2.9)	12 (9.2)
Withdrawn for other reasons n (%)	17 (6.2)	10 (7.6)

Demographic and Background Characteristics

	Viladgliptin	**Placebo**
N (ITT)	268	127
Females: males (%)	124 (45.3)	64 (48.9)
Mean age, years (SD)	61.5 (10.1)	61.4 (9.8)
Mean weight, kg (SD)		
Race White n (%) Black n (%) Oriental n (%) Other n (%)	 268 (97.8) 0 2 (0.7) 4 (1.5)	 122 (93.1) 0 2 (1.5) 7 (5.3)
HbA1c (SD)	7.2 (0.4)	7.2 (0.5)

Primary Objective Result(s)

Mean Change in HbA1c over 24 weeks pooled over dosing schedules for the ITT population

Variable: change from baseline

		Unadjusted	Results from ANCOVA model *)		
	N	Mean (SD)	LS-Mean	95% CL	p|Diff=0
Vildagliptin	268	-0.4 (0.67)	-0.4		
Placebo	127	0.2 (0.59)	0.2		
Diff. Vildagliptin - Placebo		-0.5	-0.5	[-0.7 , -0.4]	<.0001

Secondary Objective Result(s)

Mean Fasting Plasma Glucose comparison pooled over dosing schedules for the ITT population

Variable: laboratory result (value)

			Unadjusted	Results from ANCOVA model *)		
vis1n		N	Mean (SD)	LS-Mean	95% CL	p|Diff=0
Day 1 Baseline	Vildagliptin	268	122.9 (23.88)	123.2		
	Placebo	127	123.8 (26.11)	123.2		
	Diff. Vildagliptin - Placebo		-0.9	0.0	[. , .]	.
Week 12	Vildagliptin	260	111.0 (23.46)	111.6		
	Placebo	123	123.2 (26.58)	124.5		
	Diff. Vildagliptin - Placebo		-12.2	-12.8	[-18.0 , -7.7]	<.0001
Week 24	Vildagliptin	248	113.7 (22.95)	114.5		
	Placebo	113	121.8 (26.38)	124.0		
	Diff. Vildagliptin - Placebo		-8.0	-9.4	[-14.5 , -4.4]	0.0003

Safety Results

The incidence of SAEs was 5.2% under vildagliptin versus 9.4% under placebo. Mild hypoglycemia occurred in 0.4% of vildagliptin patients versus 0.8% of the placebo group. No severe hypoglycemia and no death occurred during the study.

Adverse Events by System Organ Class

Number of AEs / patients with AEs with suspected drug relation, by system organ class and preferred term

System organ class	Vildagliptin			Placebo		
Preferred term	n	% of all AEs	% of pats(n=274)	n	% of all AEs	% of pats(n=131)
Randomized patients	274			131		
All System Organ Classes						
No. of Patients with AEs	16		(5.8)	8		(6.1)
Total no. of AEs	23	(100.0)		14	(100.0)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
No. of Patients with AEs	1		(0.4)	0		(0.0)
Total no. of AEs	1	(4.3)		0	(0.0)	
LEUKOCYTOSIS	1	(4.3)	(0.4)	0	(0.0)	(0.0)
CARDIAC DISORDERS						
No. of Patients with AEs	0		(0.0)	1		(0.8)
Total no. of AEs	0	(0.0)		1	(7.1)	
TACHYARRHYTHMIA	0	(0.0)	(0.0)	1	(7.1)	(0.8)
GASTROINTESTINAL DISORDERS						
No. of Patients with AEs	6		(2.2)	4		(3.1)
Total no. of AEs	9	(39.1)		4	(28.6)	
ABDOMINAL DISTENSION	1	(4.3)	(0.4)	0	(0.0)	(0.0)
ABDOMINAL PAIN UPPER	1	(4.3)	(0.4)	0	(0.0)	(0.0)
DIARRHOEA	1	(4.3)	(0.4)	1	(7.1)	(0.8)
FLATULENCE	0	(0.0)	(0.0)	1	(7.1)	(0.8)
GASTROINTESTINAL DISORDERS (cont.)						
FREQUENT BOWEL MOVEMENTS	1	(4.3)	(0.4)	0	(0.0)	(0.0)
GINGIVITIS	0	(0.0)	(0.0)	1	(7.1)	(0.8)
NAUSEA	3	(13.0)	(1.1)	1	(7.1)	(0.8)
VOMITING	2	(8.7)	(0.7)	0	(0.0)	(0.0)
HEPATOBILIARY DISORDERS						
No. of Patients with AEs	0		(0.0)	1		(0.8)

Total no. of AEs	0	(0.0)		1	(7.1)	
HYPERBILIRUBINAEMIA	0	(0.0)	(0.0)	1	(7.1)	(0.8)
INVESTIGATIONS						
No. of Patients with AEs	1		(0.4)	2		(1.5)
Total no. of AEs	1	(4.3)		2	(14.3)	
BLOOD CREATINE PHOSPHOKINASE INCREASED	0	(0.0)	(0.0)	2	(14.3)	(1.5)
GLYCOSYLATED HAEMOGLOBIN INCREASED	1	(4.3)	(0.4)	0	(0.0)	(0.0)
METABOLISM AND NUTRITION DISORDERS						
FOOD CRAVING	2	(8.7)	(0.7)	0	(0.0)	(0.0)
METABOLISM AND NUTRITION DISORDERS (cont.)						
INCREASED APPETITE	1	(4.3)	(0.4)	0	(0.0)	(0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
No. of Patients with AEs	1		(0.4)	0		(0.0)
Total no. of AEs	1	(4.3)		0	(0.0)	
ARTHRALGIA	1	(4.3)	(0.4)	0	(0.0)	(0.0)
NERVOUS SYSTEM DISORDERS						
No. of Patients with AEs	1		(0.4)	4		(3.1)
Total no. of AEs	1	(4.3)		4	(28.6)	
DIABETIC NEUROPATHY	0	(0.0)	(0.0)	1	(7.1)	(0.8)
DIZZINESS	1	(4.3)	(0.4)	0	(0.0)	(0.0)
DIZZINESS EXERTIONAL	0	(0.0)	(0.0)	1	(7.1)	(0.8)
HEADACHE	0	(0.0)	(0.0)	1	(7.1)	(0.8)
TREMOR	0	(0.0)	(0.0)	1	(7.1)	(0.8)
PSYCHIATRIC DISORDERS						
BIPOLAR DISORDER	1	(4.3)	(0.4)	0	(0.0)	(0.0)
PSYCHIATRIC DISORDERS (cont.)						
INSOMNIA	1	(4.3)	(0.4)	0	(0.0)	(0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
No. of Patients with AEs	5		(1.8)	2		(1.5)
Total no. of AEs	5	(21.7)		2	(14.3)	
DERMATITIS ALLERGIC	1	(4.3)	(0.4)	0	(0.0)	(0.0)

ECZEMA	1	(4.3)	(0.4)	0	(0.0)	(0.0)
HYPERHIDROSIS	1	(4.3)	(0.4)	2	(14.3)	(1.5)
PRURITUS	1	(4.3)	(0.4)	0	(0.0)	(0.0)
URTICARIA	1	(4.3)	(0.4)	0	(0.0)	(0.0)

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

	Vildagliptin	Placebo
Nasopharyngitis	18 (5.5)	5 (3.9)
Headache	14 (4.3)	3 (2.3)
Diarrhoea	12 (3.7)	3 (2.3)
Gastroenteritis	8 (2.4)	2 (1.6)
Nausea	8 (2.4)	2 (1.6)
Urinary tract infection	5 (1.5)	3 (2.3)
Glycosylated haemoglobin increased	2 (0.6)	3 (2.3)
Osteoarthritis	5 (1.5)	3 (2.3)
Insomnia	6 (1.8)	3 (2.3)
Back pain	6 (1.8)	5 (3.9)

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	Vildagliptin		Placebo	
	No. (%) of AEs	No. (%) of patients	No. (%) of AEs	No. (%) of patients
Number of Patients		274		131
All AEs	327 (100.0)	143 (52.2)	128 (100.0)	60 (45.8)
with suspected drug relation	23 (7.0)	16 (5.8)	14 (10.9)	8 (6.1)
leading to dose adjustment or temp. interruption	5 (1.5)	4 (1.5)	7 (5.5)	5 (3.8)
leading to permanent discontinuation	20 (6.1)	12 (4.4)	4 (3.1)	4 (3.1)
requiring concomitant medication/non-drug therapy	153 (46.8)	93 (33.9)	88 (68.8)	49 (37.4)
Serious AEs	17 (5.2)	15 (5.5)	12 (9.4)	9 (6.9)
Deaths		0 (0.0)		0 (0.0)
SAEs with suspected drug relation	1 (0.3)	1 (0.4)	1 (0.8)	1 (0.8)
SAEs leading to permanent discontinuation	3 (0.9)	3 (1.1)	0 (0.0)	0 (0.0)

Other Relevant Findings

None

Date of Clinical Trial Report

12 February 2009

Date Inclusion on Novartis Clinical Trial Results Database

01 July 2009

Date of Latest Update

26 June 2009