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Sponsor Novartis
Generic Drug Name Vildagliptin
Therapeutic Area of Trial Type 2 Diabetes Mellitus
Approved Indication Type 2 Diabetes Mellitus
Protocol Number CLAF237AFR02
Title: Prospective, randomized pilot study comparing the 72-hour continuous glucose monitoring (CGM) glycemic profiles of vildagliptin versus sitagliptin after 8 weeks of treatment in T2DM patients inadequately controlled by metformin monotherapy
Phase of Development Phase IV
Study Start/End Dates First patient enrolled: 03-June-2010 Last patient completed: 17-June-2011
Study Design/Methodology This was a pilot, multicenter, prospective, randomized, active-controlled, parallel group trial, conducted using Prospective Randomized Open Label with Blinded Endpoint (PROBE) methodology for the main efficacy end points (all CGM data). A first 72-hour CGM recording (CGMS® iPro™, Medtronic/MiniMed, Northridge, CA) was performed while the included patients were still on metformin alone. Patients with a successful recording were then randomized on a one-to-one basis to receive either vildagliptin (50 mg twice daily) or sitagliptin (100 mg once daily) for the next 8 weeks, in addition to ongoing metformin

(the dose of which remained unchanged). A second 72-hour CGM profile was then recorded after 8 weeks of add-on therapy. For valid analysis of a patient on a given day, CGM data had to be available for the entire 24-hour period. Patients were also asked to record 6 SMBG readings on each of these days to calibrate the CGM.

Centers

7 centers in France

Publication

None

Outcome measures

Primary outcome measures(s)

Primary efficacy variables were CGM parameters analyzed centrally in a blinded fashion:

- Glycemic variability assessed by the change in the mean amplitude of glucose excursions (MAGE) index, and the standard deviation (SD) of the mean 24-hour blood glucose concentration.
- Daily glycaemic control assessed by the mean (M) daily CGM value, by the times (in minutes/day) spent in optimal glycemic range (70-140 mg/dL) and above pre-defined hyperglycemic thresholds (140 and 180 mg/dL) together with the corresponding area under the curve (AUC) values. Overall hyperglycemia (defined as AUC≥ 100 mg/dl over the full 24-hour period); postprandial hyperglycemia (AUC[0-4h], i.e. for four-hour periods after each of the main meals and, if considered relevant by the core laboratory, after additional snacks); and basal hyperglycemia, i.e. overall hyperglycaemia – post-prandial hyperglycaemia, were also calculated.

Secondary outcome measures(s)

Secondary efficacy variables were HbA1c, FPG and SMBG readings.

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

Vildagliptin) 50 mg twice daily, as commercially available, taken orally

Sitagliptin 100 mg once daily, as commercially available, taken orally

Statistical Methods

The primary analysis was conducted on the Per Protocol (PP) population. For consistency, all efficacy analyses were repeated in the ITT population which comprised all patients who received at least one dose of study medication and in whom both CGM recordings were successful (n=33).

Primary and secondary endpoint changes from BL were compared between groups by analysis of covariance (ANCOVA), with treatment as classification variable and BL value as covariate. The statistical significance of changes from BL was assessed within groups by Wilcoxon signed-rank tests for continuous variables and all tests were adjusted with a significance level of 5%.

For this pilot study, without reliable historical data, sample size was essentially set on the basis of practical considerations and patient availability. In the only prior cross-sectional study with a similar CGM end point, an overall sample of 38 patients was sufficient to show a significant difference in MAGE index between 2 treatment groups (Marfella et all, 2009).

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients who were:

- Infertile or using a medically approved birth control method
- 18-80 years of age with a body mass index (BMI) of 22–45 kg/m2,
- Diagnosed with T2DM (HbA1c 6.5–8.0%),
- Took metformin for at least 3 months (a stable, maximum tolerated daily dose of at least 1500 mg)
- Willing to perform SMBG at least 6 times daily and use the CGMS® (iPro™, Medtronic/MiniMed, Northridge, CA) for 3 consecutive days on 2 different occasions, were eligible to participate.

Exclusion criteria

Patients who had:

- A history of type 1 diabetes or any secondary form of as were those with acute metabolic diabetic complications within the past 6 months,
- An acute infection that might affect blood glucose control in the four weeks prior to Visit 1,
- Serious cardiac conditions, clinically significant liver or kidney disease, or alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of normal or creatinine clearance < 50 ml/min.
- Chronic oral (> 7 consecutive days) or parenteral corticosteroids were prohibited in the eight weeks before inclusion and during the study.

Other protocol defined inclusion/exclusion criteria applied

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Participant Flow

	Vildagliptin n (%)	*Sitagliptin* n (%)	Total n (%)
Screenings	-	-	50
Patients			
Randomized	19 (100.0)	19 (100.0)	38 (100.0)
Expose	19 (100.0)	19 (100.0)	38 (100.0)
Completed	18 (94.7)	17 (89.5)	35 (92.1)
Discontinued	1 (5.3)	2 (10.5)	3 (7.9)
Primary reason for premature discontinuation			
Adverse event(s)	0 (0)	2 (10.5)	2 (5.0)
Subject withdrew consent	1 (5.3)	0 (0.0)	1 (3.0)
Protocol deviation	0	0	0
Abnormal test procedure result(s)	0)	0 (0.0)	0
Unsatisfactory therapeutic effect	0	0	0
Lost to follow-up	0	0	0
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)

Baseline Characteristics

Patient demographic and baseline characteristics (randomized population)

Demographic	*Vildagliptin (50 mg twice daily)* N = *19*	*Sitagliptin (100 mg once daily)* N = *19*	*Total* N = *38*
Age (years)			
Mean ± SD	59.1 ± 7.9	53.5 ± 14.5	56.3 ± 11.8
Age group (years)			
< 65	13 (%)	14 (%)	27 (%)
≥ 65	6 (%)	5 (26.3%)	11 (28.9%)
Sex			
Male	10 (52.6%)	11 (57.9%)	21 (55.3%)
Female	9 (47.4%)	8 (42.1%)	17 (44.7%)
Weight (kg)			
Mean ± SD	85.1 ± 11.5	87.6 ± 15.2	86.3 ± 13.4
BMI (kg/m^2)			
Mean ± SD	31.2 ± 3.9	30.9 ± 5.2	31.7 ± 4.5
HbA_{1c} (%)			
Mean ± SD Median (range)	7.16 ± 0.41 7.14 (6.6-7.8)	7.09 ± 0.42 7.0 (6.5-7.9)	7.13 ± 0.41 7.09 (6.5-7.9)
At least one diabetic complication			
N (%)	6 (31.6)	8 (42.1)	14 (36.8)
Duration of T2DM (years)			
Mean ± SD Median (range)	7.6 ± 7.5 7.0 (0.6-25)	6.3 ± 5.1 5.0 (1.0-20)	6.9 ± 6.4 5.0 (0.6-25)
Duration of metformin use at randomization (years)			

Mean ± SD Median (range)	4.4 ± 5.8 3.0 (0.3-25)	4.4 ± 4.0 4.0 (0.3-15.0)	4.4 ± 4.9 3.0 (0.3-25)
Total daily metformin dosage at randomization (mg/day)			
Mean ± SD	2115 ± 611.9	2113 ± 542.3	2114 ± 570.3
Cardiovascular (CV) risk factors			
Obese (BMI ≥ 30 kg/m^2)	11 (57.9%)	10 (52.6%)	21 (55.2%)
Morbidly obese (BMI ≥ 35 kg/m^2)	4 (21.1%)	3 (15.8%)	7 (18.4%)
Smokers	3 (15.8%)	2 (10.5%)	5 (13.2%)
Hypertension	10 (64.6%)	12 (68.5%)	22 (57.9%)
Dyslipidaemia	13 (49.3%)	9 (50.0%)	22 (57.9%)
At least 3 associated CV risk factors			
N (%)	8 (42.2%)	9 (47.5%)	17 (44.8%)
At least 1 concomitant treatment			
N (%)	18 (94.7%)	16 (84.2%)	34 (89.5%)

Outcome measures

Primary Outcome Result(s)

Primary Outcome Results (blinded analysis at core lab, PROBE) : CGM data on variability and Circadian glycemic control at baseline and after 8 weeks of adjunctive vildagliptin or sitagliptin treatment, Per-Protocol population

	Vildagliptin			Sitagliptin			P change vilda vs. sita*
	n	Mean ± SD	P vs. baseline	n	Mean ± SD	P vs. baseline	
Glycemic variability							
Mean amplitude of glucose excursions (MAGE) (mg/dL)							
Baseline	14	67.0 ± 21.3		16	67.9 ± 17.3		
Week 8	14	52.6 ± 16.4	0.03	16	51.4 ± 16.2	0.02	0.83
Standard deviation of mean 24-hour CGMS blood glucose readings (mg/dL)							
Baseline	14	29.3 ± 8.0		16	29.1 ± 5.6		
Week 8	14	24.2 ± 6.0	0.20	16	23.1 ± 5.5	0.02	0.61
Mean of daily differences (MoDD)							
Baseline	14	27.9 ± 13.9		14	26.1 ± 11.1		
Week 8	14	22.1 ± 4.9	0.32	14	23.5 ± 6.2	0.68	0.89
Glycemic control							
Mean 24-hour blood glucose reading (M) (mg/dL) mean (± SD)							
Baseline	14	130.6 ± 12.0		16	131.0 ± 14.7		
Week 8	14	118.5 ± 12.5	0.01	16	129.4 ± 18.2	0.62	0.07
Time (min) spent in ideal range (70-140 mg/dL) mean (± SD)							

Baseline	14	917 ± 167		16	872 ± 260		
Week 8	14	1139 ± 231	0.02	16	958 ± 315	0.33	0.11
AUC ideal range (70-140 mg/dL) (mg/dL*h) mean (± SD)							
Baseline	14	1255 ± 187		16	1207 ± 223		
Week 8	14	1038 ± 223	0.02	16	1230 ± 258	0.78	0.02
Time spent above 140 mg/dL per day (min) mean (± SD)							
Baseline	14	501 ± 179		16	533 ± 274		
Week 8	14	273 ± 242	0.02		469 ± 328	0.46	0.09
AUC > 140 mg/dL per day (mg/dL*h) mean (± SD)							
Baseline	14	208 ± 115		16	243 ± 154		
Week 8	14	103 ± 120	0.01	16	165 ± 164	0.18	0.24
Time above 180 mg/dL per day (min) mean (± SD)							
Baseline	14	120 ± 90		16	170 ± 227		
Week 8	14	51 ± 73	0.01	16	92 ± 146	0.07	0.54
Minimum blood glucose reading during the night (mg/dL) mean (± SD)							
Baseline	14	95 ± 20		16	91 ± 19		
Week 8	14	84 ± 16	0.15	16	99 ± 23	0.35	0.05
Post-prandial Hyperglycemia* AUC[0-4h]X3 (mg/dL*h) mean (± SD)							
Baseline	14	443 ± 133		16	444 ± 133		
Week 8	14	294 ± 127	<0.01	16	339 ± 140	0.04	0.37
Overall Hyperglycemia AUC[24h]≥100 mg/dL (mg/dL*h) mean (± SD)							
Baseline	14	795 ± 227		16	794 ± 308		
Week 8	14	504 ± 274	0.01	16	721 ± 353	0.50	0.07
Basal Hyperglycemia (Overall Hyperglycemia – Postprandial Hyperglycemia) (mg/dL*h) mean (± SD)							
Baseline	14	352 ± 175		16	349 ± 279		
Week 8	14	209 ± 198	0.04	16	381 ± 318	0.98	0.08

P versus baseline, Wilcoxon test

*Difference in adjusted mean change between groups from Ancova model.
* All three 4-hour post prandial periods throughout the day

Secondary Outcome Result(s)

Secondary Outcome results (not blinded): Conventional Parameters of glucose control - Per Protocol population

	Vildagliptin			Sitagliptin			P change vilda vs. sita*
	n	Mean ± SD	P vs. baseline	n	Mean ± SD	P vs. baseline	
HbA1c (%)							
Baseline	14	**7.14 ± 0.40**		15	7.12 ± 0.45		
Week 8	14	6.65 ± 0.51	<0.001	16	6.78 ± 0.55	0.09	0.42
Fasting plasma glucose (mg/dL)							
Baseline	14	135 ± 18		16	138 ± 30		
Week 8	14	120 ± 14	<0.01	16	123 ± 19	0.03	0.73
Glycaemia (mean of 6 self-monitoring readings) (mg/dL)							
Baseline	14	139 ± 12		16	140 ± 16		
Week 8	14	127 ± 15	<0.01	16	131 ± 18	0.06	0.54

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Safety Results

Adverse Events by System Organ Class

Most frequently reported Adverse Events overall by system organ class and by severity n (%) – safety population

		Vildagliptine (N= 19)			Sitagliptine (N= 19)			Total (N= 38)		
		mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
At least one EI		6 (31.6%)	5 (26.3%)	0	7 (36.8%)	2 (10.5%)	2 (10.5%)	13 (34.2%)	7 (18.4%)	2 (5.3%)
Gastrointestinal disorders	Total	2 (10.5%)	1 (5.3%)	0	2 (10.5%)	0 (0.0%)	2 (10.5%)	4 (10.5%)	1 (2.6%)	2 (5.3%)
	Abdominal pain	0 (0.0%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Abdominal pain upper	0 (0.0%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Constipation	0 (0.0%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Diarrhoea	2 (10.5%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	3 (7.9%)	0 (0.0%)	0 (0.0%)
	Nausea	0 (0.0%)	1 (5.3%)	0	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (2.6%)	1 (2.6%)
	Toothache	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
	Vomiting	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	1 (5.3%)	1 (2.6%)	0 (0.0%)	1 (2.6%)
General disorders and administration site conditions	Total	1 (5.3%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)	0 (0.0%)
	Implant site haemorrhage	0 (0.0%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Malaise	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Pyrexia	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Infections and infestations	Total	2 (10.5%)	0 (0.0%)	0	1 (5.3%)	1 (5.3%)	0 (0.0%)	3 (7.9%)	1 (2.6%)	0 (0.0%)
	Gastroenteritis	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Influenza	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Lower respiratory tract infection	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Nasopharyngitis	0 (0.0%)	0 (0.0%)	0	1 (5.3%)	1 (5.3%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	0 (0.0%)
	Peritonsillar abscess	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Tonsillitis	1	0 (0.0%)	0	0	0 (0.0%)	0	1	0 (0.0%)	0 (0.0%)

		(5.3%)			(0.0%)		(0.0%)	(2.6%)		
Injury, poisoning and procedural complications	Total	0 (0.0%)	1 (5.3%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	0 (0.0%)
	Joint dislocation	0 (0.0%)	1 (5.3%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
	Overdose	0 (0.0%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Investigations	Total	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Lipase increased	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	Total	2 (10.5%)	0 (0.0%)	0	2 (10.5%)	0 (0.0%)	0 (0.0%)	4 (10.5%)	0 (0.0%)	0 (0.0%)
	Hypoglycaemia	2 (10.5%)	0 (0.0%)	0	2 (10.5%)	0 (0.0%)	0 (0.0%)	4 (10.5%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Total	1 (5.3%)	2 (10.5%)	0	1 (5.3%)	0 (0.0%)	1 (5.3%)	2 (5.3%)	2 (5.3%)	1 (2.6%)
	Intervertebral disc protrusion	0 (0.0%)	1 (5.3%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
	Muscle spasms	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
	Neck pain	1 (5.3%)	0 (0.0%)	0	1 (5.3%)	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)	0 (0.0%)
	Tendonitis	0 (0.0%)	1 (5.3%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Nervous system disorders	Total	3 (15.8%)	1 (5.3%)	0	1 (5.3%)	1 (5.3%)	1 (5.3%)	4 (10.5%)	2 (5.3%)	1 (2.6%)
	Dizziness	3 (15.8%)	1 (5.3%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.9%)	1 (2.6%)	0 (0.0%)
	Headache	0 (0.0%)	0 (0.0%)	0	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (2.6%)	1 (2.6%)	1 (2.6%)
Reproductive system and breast disorders	Total	0 (0.0%)	1 (5.3%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
	Genital pruritus male	0 (0.0%)	1 (5.3%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Total	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
	Lung disorder	1 (5.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)

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

	Vildagliptin (N = 19)	Sitagliptin (N = 19)	Total (N = 38)
Dizziness	4 (21.1%)	0 (0.0%)	4 (10.5%)
Hypoglycaemia	2 (10.5%)	2 (10.5%)	4 (10.5%)
Diarrhoea	2 (10.5%)	1 (5.3%)	3 (7.9%)
Headache	0 (0.0%)	3 (15.8%)	3 (7.9%)
Nasopharyngitis	0 (0.0%)	2 (10.5%)	2 (5.3%)
Nausea	1 (5.3%)	1 (5.3%)	2 (5.3%)
Neck pain	1 (5.3%)	1 (5.3%)	2 (5.3%)
Vomiting	1 (5.3%)	1 (5.3%)	2 (5.3%)
Abdominal pain	0 (0.0%)	1 (5.3%)	1 (2.6%)
Abdominal pain upper	0 (0.0%)	1 (5.3%)	1 (2.6%)
Constipation	0 (0.0%)	1 (5.3%)	1 (2.6%)
Gastroenteritis	1 (5.3%)	0 (0.0%)	1 (2.6%)
Genital pruritus male	1 (5.3%)	0 (0.0%)	1 (2.6%)
Implant site haemorrhage	0 (0.0%)	1 (5.3%)	1 (2.6%)
Influenza	1 (5.3%)	0 (0.0%)	1 (2.6%)
Intervertebral disc protrusion	1 (5.3%)	0 (0.0%)	1 (2.6%)
Joint dislocation	1 (5.3%)	0 (0.0%)	1 (2.6%)
Lipase increased	1 (5.3%)	0 (0.0%)	1 (2.6%)
Lower respiratory tract infection	1 (5.3%)	0 (0.0%)	1 (2.6%)
Lung disorder	1 (5.3%)	0 (0.0%)	1 (2.6%)
Malaise	1 (5.3%)	0 (0.0%)	1 (2.6%)
Muscle spasms	0 (0.0%)	1 (5.3%)	1 (2.6%)
Overdose	0 (0.0%)	1 (5.3%)	1 (2.6%)
Peritonsillar abscess	1 (5.3%)	0 (0.0%)	1 (2.6%)
Pyrexia	1 (5.3%)	0 (0.0%)	1 (2.6%)
Tendonitis	1 (5.3%)	0 (0.0%)	1 (2.6%)
Tonsillitis	1 (5.3%)	0 (0.0%)	1 (2.6%)
Toothache	0 (0.0%)	1 (5.3%)	1 (2.6%)

Serious Adverse Events and Deaths

Summary / overview of relevant Averse Events

	Vildagliptin (50 mg twice daily) **N = *19*** ***n (%)***	***Sitagliptine (100 mg/day)*** **N = *19*** ***n (%)***
Any AE	11 (57.9)	11 (57.9)
Mild	6 (31.6)	7 (36.8)
Moderate	5 (26.3)	2 (10.5)
Severe	0 (0)	2 (10.5)
Drug-related AEs	4 (21.1)	8 (42.1)
Hypoglycemia	1 (7.1)	2 (15.4)
Discontinuation due to AEs	0 (0)	2 (10.5)
Serious AEs	0 (0)	1 (5.3)

Date of Clinical Trial Report Content final Date- 29th May 2012
Date Inclusion on Novartis Clinical Trial Results Database 15 JUNE 2012
Date of Latest Update