Sponsor

Novartis

Generic Drug Name

Vildagliptin (LAF237)

Therapeutic Area of Trial

Renal impairment, Type 2 Diabetes Mellitus

Approved Indication

Type 2 Diabetes Mellitus

Study Number

CLAF237B2202

Title

An open-label, parallel-group study to determine the single and multiple dose pharmacokinetics of vildagliptin and its metabolites in mild, moderate and severe renal impaired patients compared to age, sex and weight-matched healthy volunteers following vildagliptin 25 mg and 50 mg qd for 14 days

Phase of Development

Phase I

Study Start/End Dates

08 Dec 2008 (first subject dosed)
30 April 2009 (last subject dosed)

Study Design/Methodology

This was multicenter (3 sites), multiple-dose, open-label, parallel-group study in mild, moderate or severe renal impaired patients and age (±5 years), gender and weight (±10% BMI) matched healthy volunteers

Centres

3 centers in 2 countries: Russia (2) and Germany (1)

Publication

None

Objectives

Primary objective(s)

To determine the pharmacokinetics of vildagliptin and its metabolites in patients with mild, moderate or severe renal impairment compared to gender, age and weight-matched healthy volunteers following single and multiple doses of vildagliptin 25 and 50 mg.

Secondary objective(s)

To assess the safety and tolerability of vildagliptin 25 and 50 mg in patients with mild, moderate or severe renal impairment

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

Oral tablets of vildagliptin 25 mg or 50 once daily each morning

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

N/A

Criteria for Evaluation

Primary variables, Pharmacology

Plasma samples were collected on Day 1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15 and 24 (Day 2) h post-dose. On Day 7, 11 – 13: daily trough samples taken just prior to drug administration. On Day 14: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24 (Day 15), 48 (Day 16), 72 (Day 17) h post-dose. Urine samples were collected on Day 1 and 14: pre-dose, 0-24 h. The analytes LAF237 and its metabolites LAY151 and BQS867 were determined in plasma and urine using a LC/MS/MS method.

Secondary variables , Safety and Tolerability

Safety and tolerability assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs) with their severity and relationship to study drug, concomitant medications/significant non-drug therapies and medications taken prior to first dosing. They also included regular monitoring of vital signs and body measurements (height, weight, temperature, blood pressure, and pulse rate), electrocardiogram (ECG) evaluation, hematology, blood chemistry and urinalysis.

Statistical Methods

The number and percentage of subjects with adverse events were tabulated by dose level for each renal insufficiency category, treatment, body system and preferred term. Pharmacokinetic parameters of LAF237, LAY151 and BQS867 were derived and summarized by dose level for each renal insufficiency category and study day. AUC_TAU (AUC0-24h) , Cmax , Tmax , CL/F , CLR , Vdss/F were determined using non-compartmental methods. Descriptive statistics of PK parameters included mean, SD, and CV, median, min and max. A repeated measures analysis of variance (ANOVA) with fixed effect for renal function group and random effect for matched pair was performed for the log-transformed AUC and C_{max} (Day 1 and Day 14, separately) by dose level to compare the renal impaired patients in each severity category with the age, gender, and BMI-matched healthy volunteers. In addition, an Analysis of Variance (ANOVA) with classification by renal function group was performed for the log-transformed AUC and C_{max} (Day 1 and Day 14, separately) to compare the PK parameters of the renal impaired subjects in each severity category with all age, gender, and BMI matched healthy volunteers pooled together

Study Population: Inclusion/Exclusion Criteria and Demographics

Consenting male and female subjects between 18 and 75 years of age (inclusive). Female subjects of childbearing potential must be using or agree to use double-barrier local contraception.

Renal impaired patients with mild (CrCl from 50 to ≤80 ml/min), moderate (CrCl from 30 to <50 ml/min) and severe (CrCl of <30 ml/min) renal function (aiming for ≥ 30% to be type 2 diabetic) who are otherwise in good health as determined by past medical history, physical examination, electrocardiogram, vital signs, laboratory tests and urinalysis.

Healthy volunteers must be matched by age (±5 years), gender and weight (±10% BMI) to the renal patients enrolled into the study. Subjects must be in good health as determined by past medical history, physical examination, electrocardiogram, vital signs, laboratory tests and urinalysis. Healthy subjects must have a CrCl of >80 ml/min.

Number of Subjects

	Novartis product	Comparator
Planned N	96	N/A
Randomised n	96	N/A
Intent-to-treat population (ITT) n (%)	96	N/A
Completed n (%)	96	N/A
Withdrawn n (%)	0	N/A
Withdrawn due to adverse events n (%)	0	N/A
Withdrawn due to lack of efficacy n (%)	0	N/A
Withdrawn for other reasons n (%)	0	N/A

Demographic and Background Characteristics

	25mg vildagliptin	50mg vildagliptin
N (ITT)	48	48
Females : males	23 : 25	24 : 24
Mean age, years (SD)	57.6 (10.5)	60.3 (7.4)
Mean weight, kg (SD)	79.4 (15.0)	74.9 (10.5)
Race White n (%) Asian n (%)	 46 (96) 2 (4)	 48 (100) 0 (0)

Primary Objective Result(s)

Statistical comparison of Day 1 vildagliptin PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 25 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	280.636	162.690	1.72	1.29	2.31
	Cmax (ng/mL)	46.958	36.470	1.29	1.02	1.62
Moderate	AUC_TAU (hr.ng/mL)	298.405	206.079	1.45	1.08	1.94
	Cmax (ng/mL)	50.373	39.398	1.28	1.02	1.61
Severe	AUC_TAU (hr.ng/mL)	443.411	179.672	2.47	1.85	3.30
	Cmax (ng/mL)	55.857	36.793	1.52	1.21	1.91

Test = Renal impaired patients, Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 1 vildagliptin PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 50 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	554.468	428.543	1.29	0.90	1.85
	Cmax (ng/mL)	79.772	64.047	1.25	0.96	1.62
Moderate	AUC_TAU (hr.ng/mL)	730.307	514.131	1.42	0.99	2.03
	Cmax (ng/mL)	98.954	74.023	1.34	1.03	1.74
Severe	AUC_TAU (hr.ng/mL)	768.563	384.530	2.00	1.40	2.86
	Cmax (ng/mL)	100.410	66.110	1.52	1.17	1.98

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 14 vildagliptin PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 25 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	298.395	205.571	1.45	0.99	2.13
	Cmax (ng/mL)	50.080	42.363	1.18	0.90	1.56
Moderate	AUC_TAU (hr.ng/mL)	322.068	208.900	1.54	1.05	2.26
	Cmax (ng/mL)	51.575	34.196	1.51	1.14	1.99

Severe	AUC_TAU (hr.ng/mL)	442.795	244.964	1.81	1.23	2.65
	Cmax (ng/mL)	61.505	42.450	1.45	1.10	1.91

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 14 vildagliptin PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 50 mg QD dosing regimen

		Adjusted geometric mean		-Geometric Mean ratio-		
Renal Impairment	PK variable (Unit)	Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	631.216	597.807	1.06	0.73	1.52
	Cmax (ng/mL)	95.346	79.107	1.21	0.91	1.59
Moderate	AUC_TAU (hr.ng/mL)	946.775	566.576	1.67	1.16	2.41
	Cmax (ng/mL)	106.692	82.212	1.30	0.98	1.71
Severe	AUC_TAU (hr.ng/mL)	1073.477	520.372	2.06	1.43	2.98
	Cmax (ng/mL)	118.567	78.030	1.52	1.15	2.01

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 1 BQS867 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 25 mg QD dosing regimen

		Adjusted geometric mean		-Geometric Mean ratio-		
Renal Impairment	PK variable (Unit)	Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	97.701	43.824	2.23	1.47	3.39
	Cmax (ng/mL)	16.784	11.602	1.45	1.09	1.92
Moderate	AUC_TAU (hr.ng/mL)	122.839	70.733	1.74	1.14	2.64
	Cmax (ng/mL)	18.966	14.619	1.30	0.98	1.72
Severe	AUC_TAU (hr.ng/mL)	382.208	50.623	7.55	4.97	11.48
	Cmax (ng/mL)	41.180	11.060	3.72	2.80	4.95

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 1 BQS867 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 50 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	258.054	167.045	1.54	0.80	2.98
	Cmax (ng/mL)	36.117	26.327	1.37	0.85	2.21
Moderate	AUC_TAU (hr.ng/mL)	500.311	223.963	2.23	1.16	4.31
	Cmax (ng/mL)	52.808	30.625	1.72	1.07	2.78
Severe	AUC_TAU (hr.ng/mL)	650.130	166.365	3.91	2.03	7.54
	Cmax (ng/mL)	54.796	27.456	2.00	1.24	3.22

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 14 BQS867 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 25 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	105.382	61.278	1.72	0.86	3.46
	Cmax (ng/mL)	18.408	14.683	1.25	0.76	2.08
Moderate	AUC_TAU (hr.ng/mL)	123.906	52.166	2.38	1.18	4.78
	Cmax (ng/mL)	17.289	12.183	1.42	0.86	2.35
Severe	AUC_TAU (hr.ng/mL)	401.361	84.158	4.77	2.37	9.59
	Cmax (ng/mL)	39.547	15.151	2.61	1.58	4.33

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 14 BQS867 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 50 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	258.044	278.160	0.93	0.54	1.59
	Cmax (ng/mL)	32.546	38.420	0.85	0.55	1.31
Moderate	AUC_TAU (hr.ng/mL)	673.287	223.495	3.01	1.76	5.16
	Cmax (ng/mL)	61.728	32.989	1.87	1.21	2.89
Severe	AUC_TAU (hr.ng/mL)	1215.253	214.732	5.66	3.31	9.69
	Cmax (ng/mL)	88.169	28.800	3.06	1.99	4.72

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 1 LAY151 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 25 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	1232.217	648.284	1.90	1.41	2.57
	Cmax (ng/mL)	77.259	41.768	1.85	1.38	2.47
Moderate	AUC_TAU (hr.ng/mL)	2186.816	816.194	2.68	1.98	3.62
	Cmax (ng/mL)	130.106	55.713	2.34	1.75	3.12
Severe	AUC_TAU (hr.ng/mL)	4722.273	727.468	6.49	4.75	8.86
	Cmax (ng/mL)	283.048	47.093	6.01	4.50	8.04

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 1 LAY151 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 50 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	1863.377	1195.602	1.56	1.21	2.00
	Cmax (ng/mL)	108.255	72.800	1.49	1.12	1.98
Moderate	AUC_TAU (hr.ng/mL)	3110.159	1318.511	2.36	1.84	3.03
	Cmax (ng/mL)	186.523	80.698	2.31	1.74	3.08
Severe	AUC_TAU (hr.ng/mL)	5970.727	1281.680	4.66	3.63	5.99
	Cmax (ng/mL)	361.595	79.227	4.56	3.43	6.07

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 14 LAY151 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 25 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	1705.670	982.603	1.74	1.23	2.45
	Cmax (ng/mL)	97.691	60.136	1.62	1.19	2.22
Moderate	AUC_TAU (hr.ng/mL)	3085.110	1016.248	3.04	2.15	4.29
	Cmax (ng/mL)	165.757	62.000	2.67	1.95	3.66
Severe	AUC_TAU (hr.ng/mL)	10297.69	1102.293	9.34	6.62	13.19
	Cmax (ng/mL)	481.404	67.762	7.10	5.19	9.72

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Statistical comparison of Day 14 LAY151 PK parameters between patients with renal impairment and matched healthy subjects for the LAF237 50 mg QD dosing regimen

Renal Impairment	PK variable (Unit)	Adjusted geometric mean		-Geometric Mean ratio-		
		Test	Reference	Estimate	90% Lower CL	90% Upper CL
Mild	AUC_TAU (hr.ng/mL)	2696.268	1893.910	1.42	1.07	1.90
	Cmax (ng/mL)	140.223	106.597	1.32	0.99	1.76
Moderate	AUC_TAU (hr.ng/mL)	5271.911	1711.901	3.08	2.31	4.11
	Cmax (ng/mL)	293.681	99.062	2.96	2.22	3.96
Severe	AUC_TAU (hr.ng/mL)	17062.37	1967.128	8.67	6.50	11.57
	Cmax (ng/mL)	811.184	111.759	7.26	5.44	9.69

Test = Renal impaired patients.

Reference = Age, sex weight- matched healthy volunteers.

Secondary Objective Result(s)

See Safety Results

Safety Results

Adverse Events by System Organ Class

Number and percentage of subjects with adverse events for vildagliptin 25mg qd treatment group

		Mild RI		Moderate RI		Severe RI		Pooled
Body system/ preferred term	AE Severity	Patients N=8	HV N=8	Patients N=8	HV N=8	Patients N=8	HV N=8	HVs N=24
- **Any Body System**								
-Total	Mild	3(37.5)	0(0.0)	2(25.0)	0(0.0)	3(37.5)	2(25.0)	2(8.3)
	Moderate	1(12.5)	0(0.0)	0(0.0)	1(12.5)	1(12.5)	0(0.0)	1(4.2)
Vascular disorders								
-Total	Mild	2(25.0)	0(0.0)	2(25.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Orthostatic hypotension	Mild	2(25.0)	0(0.0)	2(25.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Nervous system disorders								
-Total	Mild	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(12.5)	2(25.0)	2(8.3)
	Moderate	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Headache	Mild	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(12.5)	2(25.0)	2(8.3)
Headache	Moderate	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Cardiac disorders								
-Total	Mild	1(12.5)	0(0.0)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Atrioventricular block first degree	Mild	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Tachycardia	Mild	1(12.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Infections and infestations								
-Total	Moderate	1(12.5)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)	1(4.2)
Nasopharyngitis	Moderate	1(12.5)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)	1(4.2)
Investigations								
-Total	Mild	1(12.5)	0(0.0)	1(12.5)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Electrocardiogram QT prolonged	Mild	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Glomerular filtration rate decreased	Mild	1(12.5)	0(0.0)	1(12.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

RI: Renal Impairment, HV: Age, sex and weight-matched Healthy Volunteers, NA: Not applicable

A subject with multiple occurrences of an AE is counted once in the AE category. A subject with multiple AEs within a body system is counted once in the total row. N = number of subjects studied, n = number of subjects with at least one AE on the category. Only AEs occurring at or after first drug intake are included

Number and percentage of subjects with adverse events for vildagliptin 50mg qd treatment group

		Mild RI		Moderate RI		Severe RI		Pooled
Body system/ preferred term	AE Severity	Patients N=8	HV N=8	Patients N=8	HV N=8	Patients N=8	HV N=8	HVs N=24
- **Any Body System**								
-Total	Mild	3 (37.5)	1 (12.5)	4 (50.0)	0 (0.0)	2 (25.0)	1 (12.5)	2 (8.3)
	Moderate	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	1 (12.5)	1 (4.2)
Gastrointestinal disorders								
-Total	Mild	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders								
-Total	Moderate	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	Moderate	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	Mild	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations								
-Total	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Nasopharyngitis	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Investigations								
-Total	Mild	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Lipase increased	Mild	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Nervous system disorders								
-Total	Mild	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (4.2)
	Moderate	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	1 (4.2)
Headache	Mild	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (4.2)
Headache	Moderate	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	1 (4.2)
Vascular disorders								
-Total	Mild	2 (25.0)	0 (0.0)	4 (50.0)	0 (0.0)	3 (37.5)	0 (0.0)	0 (0.0)
Orthostatic hypotension	Mild	2 (25.0)	0 (0.0)	4 (50.0)	0 (0.0)	3 (37.5)	0 (0.0)	0 (0.0)

RI: Renal Impairment, HV: Age, sex and weight-matched Healthy Volunteers, NA: Not applicable

A subject with multiple occurrences of an AE is counted once in the AE category. A subject with multiple AEs within a body system is counted once in the total row. N = number of subjects studied, n = number of subjects with at least one AE on the category. Only AEs occurring at or after first drug intake are included

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

Number of subjects, who received 25 mg vildagliptin , experiencing one or more adverse events by patient population and diagnosis of T2DM

Adverse event	Subjects	Renal Impairment			All HVs	T2DM*
		Mild	Moderate	Severe		
	N=48	N=8	N=8	N=8	N=24	N=12
Orthostatic hypotension	5(10.4)	2(25.0)	2(25.0)	1(12.5)	0(0.0)	2(16.7)
Headache	4(8.3)	0(0.0)	0(0.0)	2(25.0)	2(8.3)	0(0.0)
Glomerular filtration rate de-creased	2(4.2)	1(12.5)	1(12.5)	0(0.0)	0(0.0)	2(16.7)
Nasopharyngitis	2(4.2)	1(12.5)	0(0.0)	0(0.0)	1(4.2)	1(8.3)
Progression of first AV block	1(2.1)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Tachycardia	1(2.1)	1(12.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
QTc prolongation	1(2.1)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Total subjects	13(27.1)	4(50.0)	2(25.0)	4(50.0)	3(12.5)	4(33.3)

* Twelve (12) patients with T2DM are a subset of the 24 renal impairment patients

Number of subjects, who received 50 mg vildagliptin , experiencing one or more adverse events by patient population and diagnosis of T2DM

Adverse event	Subjects	Renal Impairment			Pooled HVs	T2DM*
		Mild	Moderate	Severe		
	N=48	N=8	N=8	N=8	N=24	N=9
Orthostatic hypotension	9(18.7)	2(25.0)	4(50.0)	3(37.5)	0(0.0)	5(55.6)
Headache	6(12.5)	3(37.5)	1(12.5)	0(0.0)	2(8.3)	0(0.0)
Vomiting	2(4.2)	1(12.5)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Nausea	1(2.1)	1(12.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Elevated lipase levels	1(2.1)	0(0.0)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
Dental Pain	1(2.1)	0(0.0)	1(12.5)	0(0.0)	0(0.0)	0(0.0)
Nasopharyngitis	1(2.1)	0(0.0)	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Total subjects	15(31.2)	4(50.0)	5(62.5)	3(37.5)	3(12.5)	5(55.6)

* Nine (9) patients with T2DM are a subset of the 24 renal impairment patients

Serious Adverse Events and Deaths

No subjects experienced SAEs or severe adverse events during the study. No deaths occurred during the study.

Other Relevant Findings

None

Date of Clinical Trial Report

22 Oct 2009

CSR finalization date

Date Inclusion on Novartis Clinical Trial Results Database

30 April 2010

Date posted to the CTRD

Date of Latest Update

30 April 2010

Date of most recent update (ie, template was modified to include publication information)