NOVARTIS

Full Novartis CTRD Results Template

Sponsor Novartis
Generic Drug Name Vildagliptin
Therapeutic Area of Trial Type 2 diabetes
Approved Indication Type 2 diabetes
Protocol Number CLAF237A1103
Title An open-label, randomized and crossover study to assess the effect of co-administration of vildagliptin and voglibose on the steady-state pharmacokinetics/pharmacodynamics in Japanese patients with type 2 diabetes
Phase of Development IV
Study Start/End Dates 10-Feb-2011 (first patient first visit) to 25-Apr-2011 (last patient last visit)
Study Design/Methodology This was an open-label, randomized, 3-treatment, 3-period and 6-way crossover study. A total of 24 Japanese patients with type 2 diabetes were enrolled into the study. The study consisted of a screening period (Day −28 to −2), a baseline (Day −1 of Period 1), 3 treatment periods (Period 1 to 3), and a study completion evaluation on the following day after the last drug administration. Each period had a 3-day treatment.

Centres

1 center in Japan

Publication

Not applicable.

Outcome measures

Primary outcome measures(s)

PK: Serial PK blood samples were collected on Day 3 following administration of study drug for 3 days. The plasma concentration of vildagliptin was investigated. The primary PK parameters were Cmax,ss and AUCtau in the study.

Secondary outcome measures(s)

PD: The PD parameters: plasma DPP-4 activity, GLP-1 (active in plasma), blood glucose (plasma), Insulin (serum) and glucagon (plasma) were evaluated in this study. The PD blood samples were collected on Day 3 following administration of study drug for 3 days.

Safety: Safety assessments included adverse events (AEs) and serious adverse events (SAEs) collection, with their severity and relationship to study drug, and pregnancies, regular monitoring of hematology, blood chemistry (with blood glucose measured in different time points), urinalysis, and regular assessments of vital signs, ECG evaluations, physical condition and body weight.

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

Study treatment sequences are presented in the below table:

Treatment sequence	Period 1	Period 2	Period 3
1 (N=4)	A	B	C
2 (N=4)	A	C	B
3 (N=4)	B	C	A
4 (N=4)	B	A	C
5 (N=4)	C	A	B
6 (N=4)	C	B	A

Treatment A was 50 mg vildagliptin b.i.d. for 3 days, Treatment B was 0.2 mg voglibose t.i.d. for 3 days and Treatment C was 50 mg vildagliptin b.i.d. and 0.2 mg voglibose t.i.d. for 3 days. On Day 3, the evening dose was not to be administered.

Statistical Methods

Descriptive statistics were used to assess the safety and tolerability endpoints. Summary tables with the number, percentage, and severity of AEs were provided to assess safety and tolerability per treatment, patient and visit/time. The number and percentage of subjects with AEs was tabulated by body system and preferred term with a breakdown by treatment group.
Summary statistics were provided for all PK parameters and the 2 samples Wilcoxon test was used for the comparison of Tmax. The following PK parameters of vildagliptin were also investigated using non-compartmental method(s): Tmax, T1/2, Lambda_z (kel), CL/F, Vz/F, as well as the primary parameter Cmax,ss , AUCtau. Descriptive statistics were used to investigate the effects on the PK parameters of LAY151 and BQS867. The following PK parameters were

determined using non-compartmental method(s): Cmax,ss , AUCtau, Tmax, T1/2, Lambda_z (kel).
DPP-4, GLP-1, glucose, insulin and glucagon plasma/serum levels were measured as the PD variables. The plasma/serum concentrations of these variables were plotted versus time and the PD responses were to be explored by inspecting the graphical representations.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Diabetic patients with inadequately controlled on diet therapy and exercise therapy (HbA1c in the range 6.5 to 10.0% inclusive by NGSP)

Exclusion Criteria:

- Fasting plasma glucose ≥ 270 mg/dL A history of Type 1 diabetes or secondary forms of diabetes Treatment of anti-diabetic agents including GLP-1 analogues within 8 weeks or insulin within 6 months prior to screening.

Other protocol defined inclusion/exclusion criteria applied.

Participant Flow

A total of 24 patients were randomized and treated (4 patients in each of the 6 cohorts). There was no discontinuation in this study.

Patients disposition - n of patients

	Treat. Sequence 1	Treat. Sequence 2	Treat. Sequence 3	Treat. Sequence 4	Treat. Sequence 5	Treat. Sequence 6	Total
	N=4	N=4	N=4	N=4	N=4	N=4	N=24
Patients							
Randomized	4	4	4	4	4	4	24
Treated	4	4	4	4	4	4	24
Completed	4	4	4	4	4	4	24
Discontinued	0	0	0	0	0	0	0

Baseline Characteristics

Demographic summary by treatment sequence (Safety analysis set)

		Treat. Sequence 1	**Treat. Sequence 2**	**Treat. Sequence 3**	**Treat. Sequence 4**	**Treat. Sequence 5**	**Treat. Sequence 6**	**Total**
		N=4	**N=4**	**N=4**	**N=4**	**N=4**	**N=4**	**N=24**
Age (years)	Mean (SD)	44.0 (2.16)	56.3 (7.72)	59.8 (4.65)	54.8 (6.99)	52.5 (7.55)	55.8 (6.40)	53.8 (7.44)
	Median	43.5	57.0	60.5	54.0	53.0	55.5	53.5
	Range	42-47	47-64	54-64	48-63	43-61	49-63	42-64
Gender – n(%)	Male	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	24 (100)
Ethnicity – n(%)	Japanese	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	24 (100)
Weight (kg)	Mean (SD)	87.10 (10.39)	77.20 (12.87)	77.35 (11.45)	75.58 (10.66)	70.93 (7.73)	70.95 (10.55)	76.52 (10.98)
	Median	90.35	81.95	74.0	75.65	70.55	68.60	76.95
	Range	72.0-95.7	58.2-86.7	68.0-93.4	65.0-86.0	63.8-78.8	60.9-85.7	58.2-95.7
Height (cm)	Mean (SD)	180.63 (4.87)	172.53 (7.80)	172.48 (9.22)	175.38 (6.10)	164.98 (1.93)	172.00 (6.81)	173.00 (7.49)
	Median	181.85	170.15	169.75	173.75	165.10	172.75	170.60
	Range	173.7-185.1	166.0-183.8	164.6-185.8	169.9-184.1	162.5-167.2	164.7-177.8	162.5-185.8
BMI (kg/m^2)	Mean (SD)	26.58 (2.11)	25.85 (3.99)	25.83 (1.22)	24.55 (3.68)	26.03 (3.05)	23.85 (2.29)	25.45 (2.73)
	Median	26.80	26.05	25.90	23.55	25.45	23.10	24.85
	Range	23.8-28.9	21.1-30.2	24.5-27.0	21.4-29.7	23.4-29.8	22.1-27.1	21.1-30.2
Duration of diabetes	Mean (SD)	68.3 (69.49)	45.0 (17.98)	74.3 (15.39)	49.5 (19.23)	40.3 (17.90)	91.3 (41.52)	61.4 (36.9)
(months)	Median	56.6	45.0	73.5	46.5	40.0	77.5	59.5
	Range	4-156	23-67	57-93	33-72	21-60	60-150	4-156
HbA1c (%)	Mean (SD)	7.83 (0.67)	6.98 (0.46)	8.08 (0.56)	8.05 (0.71)	7.80 (0.37)	7.50 (0.95)	7.70 (0.69)

	Median	7.55	6.95	7.85	8.25	7.80	7.35	7.70
	Range	7.4-8.8	6.5-7.5	7.7-8.9	7.1-8.6	7.4-8.2	6.6-8.7	6.5-8.9
FPG (mg/dL)	Mean (SD)	171.5 (35.14)	163.3 (15.90)	193.0 (30.69)	178.3 (34.60)	179.0 (55.23)	172.8 (33.18)	176.3 (33.18)
	Median	170.5	160.0	199.5	185.0	167.5	164.0	170.5
	Range	132-213	148-185	154-219	132-211	130-251	143-220	130-251

Treatment sequence 1: A // B // C, 2: A // C // B, 3: B // C // A, 4: B // A // C, 5: C // A // B, 6: C // B // A.

Treatment A: 50 mg vildagliptin b.i.d. for 3 days.

Treatment B: 0.2 mg voglibose t.i.d. for 3 days.

Treatment C: 50 mg vildagliptin b.i.d. and 0.2 mg voglibose t.i.d. for 3 days.

Note: Duration of diabetes: Difference between screening and diagnosis dates (from medical history evaluations).

HbA1c(Glycosylated hemoglobin) and FPG(Fasting plasma glucose) are taken from screening laboratory evaluations.

Outcome measures

Primary Outcome Result(s)

Summary statistics for plasma PK parameters of vildagliptin for the primary PK parameters

Treatment	Statistic	Cmax,ss (ng/mL)	AUCtau (hr*ng/mL)
A	n	24	24
	Mean (SD)	308 (60.0)	1130 (223)
	CV% mean (%)	19.5	19.7
	Geo-mean	303	1110
	CV% geo-mean (%)	19.1	19.5
	Median	314	1090
	[Min; Max]	[220;454]	[796;1560]
C	N	24	24
	Mean (SD)	202 (35.5)	869 (166)
	CV% mean (%)	17.6	19.1
	Geo-mean	199	854
	CV% geo-mean (%)	17.8	18.9
	Median	193	827
	[Min; Max]	[135;273]	[628;1300]

Treatment A: 50 mg vildagliptin b.i.d. for 3 days;

Treatment C: 50 mg vildagliptin b.i.d. and 0.2 mg voglibose t.i.d. for 3 days;

CV% mean = coefficient of variation (%)=sd/mean*100;

CV% geo-mean=(sqrt(exp(variance for log transformed data)-1)*100.

Geometric mean ratio and 90% confidence intervals for the PK parameters of vildagliptin

	Adjusted geo-mean*		Geo-mean ratio*		
PK parameter	Test	Reference	Estimate C/A	Lower 90% CL	Upper 90% CL
Cmax,ss [ng/mL]	198.9	302.8	0.66	0.62	0.70
AUCtau [hr*ng/mL]	854	1111	0.77	0.73	0.81

Notes: * back-transformed from log scale.

Treatment A: 50 mg vildagliptin b.i.d. for 3 days.

Treatment C: 50 mg vildagliptin b.i.d. and 0.2 mg voglibose t.i.d. for 3 days.

Secondary Outcome Result(s)

PD Result
Geometric mean ratio and 90% confidence intervals for PD parameters

PD parameter	PD variable	C vs. A	C vs. B	A vs. B
DPP-4 Percent inhibition	Emax (%)	0.99 [0.83,1.18]	14.28 [11.92,17.11]	14.42 [12.04,17.28]
	AUE0-12hr (hr*%)	1.00 [0.78,1.28]	59.46 [46.41,76.19]	59.42 [46.38,76.14]
GLP-1	Emax (pM)	1.46 [1.26,1.70]	3.02 [2.60,3.50]	2.06 [1.78,2.40]
	Adj. AUE0-4hr (hr*pM)	1.63 [1.30,2.03]	4.03 [3.22,5.05]	2.48 [1.98,3.11]
	AUE0-4hr (hr*pM)	1.53 [1.31,1.78]	3.57 [3.06,4.16]	2.33 [2.00,2.72]
Glucose	Emax (mg/dL)	0.85 [0.83,0.89]	0.87 [0.84,0.90]	1.02 [0.98,1.06]
	Adj. AUE0-4hr (hr*mg/dL)	0.68 [0.62,0.76]	0.76 [0.69,0.85]	1.12 [1.00,1.24]
	AUE0-4hr (hr*mg/dL)	0.89 [0.86,0.92]	0.89 [0.86,0.92]	1.00 [0.96,1.04]
Insulin	Emax (uU/mL)	0.85 [0.75,0.97]	0.99 [0.87,1.12]	1.16 [1.02,1.31]
	AUE0-4hr (hr*uU/mL)	0.83 [0.73,0.96]	1.01 [0.88,1.15]	1.21 [1.05,1.39]
Glucagon	Emax (pg/mL)	0.96 [0.92,1.00]	0.91 [0.87,0.95]	0.95 [0.91,0.99]
	AUE0-4hr (hr*pg/mL)	1.01 [0.98,1.05]	0.91 [0.88,0.94]	0.89 [0.87,0.92]

Results are obtained by back-transformation from log scale.
Treatment A: 50 mg vildagliptin b.i.d. for 3 days.
Treatment B: 0.2 mg voglibose t.i.d. for 3 days.
Treatment C: 50 mg vildagliptin b.i.d. and 0.2 mg voglibose t.i.d. for 3 days.

Model: The log transformed PD parameter data was analyzed using a linear model with sequence, period and treatment as fixed factors and patient nested within sequence as random factor.

Safety Results

There were no adverse events reported in this study.

Other Relevant Findings

Not applicable.

Date of Clinical Trial Report 26-Jan-2012 (content final)
Date Inclusion on Novartis Clinical Trial Results Database 10-Apr-2012
Date of Latest Update Not applicable.