Sponsor

Novartis

Generic Drug Name

Vildagliptin (LAF237)

Therapeutic Area of Trial

Type II Diabetes Mellitus

Approved Indication

Indicated for treatment of Type II Diabetes Mellitus

Study Number

CLAF237A2224

Title

An open-label, multiple dose study to assess the steady-state skin concentrations and pharmacokinetics of vildagliptin 50 mg BID for 10 days in healthy subjects and patients with type 2 diabetes

Phase of Development

Phase II

Study Start/End Dates

19 Feb 2008 to 03 Dec 2008

Study Design/Methodology

This was an open-label, multiple-dose study. Subjects participated in a 21-day screening period, a 1-day baseline period, a single treatment period (10 days duration) and an end-of study (EOS) evaluation. Subjects were admitted to the study center on Day -1 for verification of inclusion/exclusion criteria, baseline assessments, and subsequent randomization and were domiciled from Day -1 through Day 11. Each subject received LAF237 (LAF237) 50 mg orally BID (every 12 hours) during the 10-day treatment period, with the last dose administered on the morning of Day 10.

Two punch (4-6 mm diameter) full-thickness skin biopsy samples of the upper arm or lower leg were collected on Day 10. The first skin biopsy sample was taken before the morning dose administration (approximately 12 hours post-Day 9 evening dose and within 30 minutes pre-Day 10 morning dose). The second skin biopsy sample was taken 2 hours ± 10 minutes post-morning dose on Day 10 for the measurement of steady-state skin tissue concentrations of LAF237, LAY151, and BQS867.

Centers

Single center in the United States.

Publication

None.

Objectives

Primary objective(s)

- To assess the skin concentration of LAF237 and its two metabolites, LAY151 and LAF237-O-glucuronide (BQS867) as compared to plasma concentration after 50 mg BID (every 12 hours) dosing of LAF237 for 10 days in healthy subjects (Cohort 1) and patients with type 2 diabetes mellitus (Cohort 2) at steady state.

Secondary objective(s)

To evaluate the safety, tolerability, and pharmacokinetics of LAF237 after 10 days of 50 mg BID treatment in both Cohorts 1 and 2.

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

Vildagliptin (LAF237) 50 mg dose, orally administered every 12 hours.

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

None.

Criteria for Evaluation

Primary variables

Skin samples were collected to determine the steady-state concentration of LAF237 and its metabolites (LAY151 and BQS867) in skin after 10 treatment days.

Secondary variables

Pharmacokinetics: LAF237 and its major metabolites (LAY151 and BQS867) concentrations were measured in PK plasma, urine, and skin samples. PK blood samples were collected prior to the morning dose on Day 10 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post morning dose. PK pooled urine sample was collected 0-12 hours post-Day 10 morning dose.

Safety and tolerability: Safety assessments consisted of collecting all AEs and SAEs (with their severity and relationship to study drug), and pregnancies. They included the regular monitoring of hematology, blood chemistry (including HbA1c and anti-GAD for T2DM patients only) and urine performed at the study center and regular assessments of vital signs, physical condition, wound assessment, and body weight.

Pharmacodynamics: DPP-IV samples were collected on Day -1 for baseline activity and Day 10 at pre-dose, 0.5, 2, 8, 10, and 12 hours post-dose.

Statistical Methods

Pharmacokinetics: All subjects with evaluable PK (blood, urine, and skin biopsy) data were included in the PK data analysis. Descriptive statistics for pharmacokinetic parameters included mean, standard deviation (SD), and coefficient of variation (CV), minimum, and maximum. When a geometric mean was presented it was stated as such. Since Tmax is generally evaluated by a nonparametric method, median values and ranges were given for this parameter.

The steady state skin concentrations of LAF237 and its two metabolites (LAY151 and BQS867) were summarized by time for each cohort using descriptive statistics. To explore the effects of race and gender, the skin concentration data were also summarized by race and gender.

Additionally, plasma and urine concentrations at each timepoint on Day 10 as well as all PK parameters for each analyte were summarized by cohort.

Safety: All subjects who received at least one dose of study drug were included in the safety and tolerability evaluation. Safety and tolerability data were summarized using descriptive statistics.

Study Population: Inclusion/Exclusion Criteria and Demographics

All subjects must have met the following criteria:

- Non-smoking Caucasian and Blacks of African descent between 30 and 65 years of age (inclusive)
- Females of childbearing potential: must use 2 acceptable methods of contraception from screening and for the duration of the study through study completion.
- Females of non-childbearing potential: postmenopausal with no regular menstrual bleeding for at least 1 year prior to initial dosing; surgically sterilized females must have had the procedure at least 6 months prior to initial dosing
- Comply with dietary recommendations throughout the study
- CPK $\leq$ 1.5 x ULN at screening and baseline
- Met vital signs of the following criteria at screening and baseline:
  - oral body temperature between 35.0-37.5 °C
  - systolic blood pressure 90-140 mm Hg (for patients with T2DM 90-140 mmHg)
  - diastolic blood pressure 50-90 mm Hg (for patients with T2DM 50-100 mmHg)
  - pulse rate 40 - 90 bpm

Additional inclusion criteria per cohort:

Cohort 1

- Healthy subjects, as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at Screening.
- Fasting plasma glucose is <5.5 mM (<100 mg/dL at baseline)
- Weight of at least 50 kg and a body mass index within 22 to 35 kg/m^2.

Cohort 2

- Type 2 diabetics (diagnosed at least 3 months prior to screening) stabilized on metformin and/or sulfonylurea (stable dose for at least 4 week)
- Weight of at least 50 kg and a body mass index within 22 to 40 kg/m^2
- HbA1c in the range ≤8% at screening
- Fasting plasma glucose of ≤11.5 mmol/L (≤210 mg/dL) at screening confirmed by a second FPG measurement of ≤11.5 mmol/L (≤210 mg/dL) during the screening period or at baseline

Exclusion criteria

Subjects who met any of the following criteria were excluded from the study.

- Requirement for insulin within the previous 3 months
- Significant unstable concomitant disease or complications of diabetes
- Any severe hypoglycemic episode within 3 months of screening, acute infection(s) which may affect blood glucose control within 4 weeks prior to screening
- Significant illness within two (2) weeks prior to initial dosing and/or acute infection(s) which may affect blood glucose control within 4 weeks prior to screening
- Evidence of clinically significant diabetic organ disease (renal, retinal, neurological, vascular) or complications (e.g., symptomatic autonomic neuropathy or gastroparesis) that would preclude study participation
- Glomerular filtration rate (estimated by Cockcroft-Gault formula) <60 mL/min.
- Fasting triglycerides >5.1 mmol/L (>450 mg/dL) within 4 weeks prior to screening
- Treatment with systemic steroids and/or on an unstable dosage of thyroid hormone
- Hyperkeratosis

- History of:
  - Type 1 diabetes mellitus, diabetes as a result of pancreatic injury, or secondary forms of diabetes (e.g., Cushing's syndrome, acromegaly)
  - ketoacidosis and/or lactic acidosis
  - peripheral vascular disease
  - coagulation abnormalities or use of medication likely to affect wound healing or clotting (PT/PTT and INR should be within normal reference ranges at screening)
  - clinically significant ECG abnormalities and/or prolonged QT_c interval > 460 msec
  - primary or secondary connective tissue diseases, skin disease or skin ulcer/ischemic ulcer
  - malignancies including any form of skin cancer
  - chronic pain, fibromyalgia, regional complex pain syndrome, or paresthesias.
  - migraine, cluster or vascular headaches.
- Any of the following within the 6 months prior to study start: myocardial infarction, coronary artery bypass surgery, unstable angina, stroke, congestive heart failure New York Heart Association class III or IV
- Use of class Ia, Ib, Ic or III anti-arrhythmic.
- Recent (within the last 3 years) and/or recurrent history of acute or chronic bronchospastic disease
- Family history and/or evidence of keloid formation following surgery or trauma.
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study.

Number of Subjects

	Cohort 1 Healthy subjects	**Cohort 2 Patients with T2DM**
Planned N	16	16
Randomised n	16	6
Intent-to-treat population (ITT) n (%)	16	6
Completed n (%)	16	6
Withdrawn n (%)	0	0
Withdrawn due to adverse events n (%)	0	0
Withdrawn due to lack of efficacy n (%)	0	0
Withdrawn for other reasons n (%)	0	0

Demographic and Background Characteristics

	Cohort 1 Healthy subjects	Cohort 2 Patients with T2DM
N (ITT)	16	6
Females : males	6 : 10	0 : 6
Mean age, years (SD)	39.6 (6.58)	54.3 (9.77)
Mean weight, kg (SD)	80.63 (6.796)	104.1 (17.83)
Race White n (%) Black n (%)	 7 (43.8%) 9 (56.3%)	 3 (50.0%) 3 (50.0%)
Characteristics relevant to study population mean fasting glucose (SD)	84 (6.88)	161.2 (46.16)

Primary Objective Result(s)

Summary of skin and skin/plasma concentration ratios following LAF237 50 mg BID on day 10:

		T = 0 hrs (ng/mL)	T =2 hrs (ng/mL)	Skin/plasma ratio (T = 0)	Skin/plasma ratio (T = 2)
LAF237	Healthy subjects	83.7 (96.2)	148.4 (92.1)	7.5 (6.8)	0.7 (0.5)
	Patients with T2DM	41.8 (25.6)	92.5 (31.2)	7.7 (6.6)	0.6 (0.3)
BQS867	Healthy subjects	---	6.1 (13.1)*	---	0.06 (0.13)
	Patients with T2DM	---	---	---	---
LAY151	Healthy subjects	301.6 (94.6)	297.4 (102.9)	1.7 (0.4)	1.5 (0.5)
	Patients with T2DM	246.5 (101.6)	256.5 (53.9)	1.3 (0.6)	1.3 (0.3)

Secondary Objective Result(s)

Summary of the mean (SD) PK parameters for LAF237 on Day 10 following administration of LAF237 50 mg BID for 10 days

Population	Cmax (ng/mL)	AUC(0-τ) (ng*hr/mL)	Tmax (hr)	T1/2 (hr)	CLR (L/hr)	CL/F (L/hr)	Vz/F (L)
Healthy subjects	270.3 (45.7)	955.7 (193.8)	1.5 (0.5-3.0)	2.4 (0.7)	11.3 (2.1)	52.5 (9.2)	181.9 (70.5)
Patients with T2DM	258.3 (73.8)	788.7 (202.8)	1.0 (0.5-2.0)	1.9 (0.2)	13.5 (3.7)	65.1 (13.7)	183.3 (47.5)

Safety Results

Adverse Events by System Organ Class

	Cohort 1 Healthy subjects LAF237 50 mg (n=16) n (%)	Cohort 2 Patients with T2DM LAF237 50 mg (n=6) n (%)	All subjects (n=22)
Subjects/Patients with AE(s)	6 (37.5)	4 (66.7)	10 (45.5)
Gastrointestinal disorders			
TOTAL	3 (18.8)	2 (33.3)	5 (22.7)
Constipation	0 (0.0)	1 (16.7)	1 (4.5)
Diarrhoea	0 (0.0)	1 (16.7)	1 (4.5)
Flatulence	3 (18.8)	0 (0.0)	3 (13.6)
Stomach discomfort	0 (0.0)	1 (16.7)	1 (4.5)
Toothache	0 (0.0)	1 (16.7)	1 (4.5)
Infections and infestations			
TOTAL	0 (0.0)	1 (16.7)	1 (4.5)
Peri-rectal abscess	0 (0.0)	1 (16.7)	1 (4.5)
Musculoskeletal and connective tissue disorders			
TOTAL	1 (6.3)	0 (0.0)	1 (4.5)
Muscle twitching	1 (6.3)	0 (0.0)	1 (4.5)
Nervous system disorders			
TOTAL	4 (25.0)	1 (16.7)	5 (22.7)
Dizziness	1 (6.3)	0 (0.0)	1 (4.5)
Headache	4 (25.0)	1 (16.7)	5 (22.7)
Psychiatric disorders			
TOTAL	1 (6.3)	0 (0.0)	1 (4.5)
Abnormal dreams	1 (6.3)	0 (0.0)	1 (4.5)
Renal and urinary disorders			
TOTAL	1 (6.3)	0 (0.0)	1 (4.5)
Urine odor abnormal	1 (6.3)	0 (0.0)	1 (4.5)
Skin and subcutaneous tissue disorders			
TOTAL	1 (6.3)	1 (16.7)	2 (9.1)
Dry skin	1 (6.3)	1 (16.7)	2 (9.1)

Arranged alphabetically.
A subject with multiple occurrences of an adverse event is counted only once in the AE category.
A subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied; n = number of subjects with at least one AE in the category
Only adverse events occurring at or after first drug intake are included.

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

	Cohort 1 Healthy subjects	Cohort 2 Patients with T2DM
	N=16	N=6
Headache	4 (0.25)	1 (0.167)
Flatulence	3 (0.188)	0 (0.0)
Dry skin	1 (0.063)	1 (0.167)

Serious Adverse Events and Deaths

	Cohort 1 Healthy subjects	Cohort 2 Patients with T2DM
No. (%) of subjects studied	16	6
No. (%) of subjects with AE(s)	6 (0.375)	4 (0.667)
Number (%) of subjects with serious or other significant events	n (%)	n (%)
Death	0 (0.0)	0 (0.0)
SAE(s)	0 (0.0)	0 (0.0)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)

Date of Clinical Trial Report

06 November 2009

Date Inclusion on Novartis Clinical Trial Results Database

03 December 2009

Date of Latest Update