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ScienceDirect
Diabetes Research and Clinical Practice 76 (2007) 132–138
DIABETES RESEARCH AND CLINICAL PRACTICE
www.elsevier.com/locate/diabres

Efficacy and tolerability of vildagliptin monotherapy in drug-naïve patients with type 2 diabetes☆

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Received 25 September 2006; accepted 14 December 2006
Available online 12 January 2007

Abstract

This 24-week, double-blind, randomized, multicenter, placebo-controlled, parallel-group study performed in 354 drug-naïve patients with type 2 diabetes (T2DM) assessed efficacy and tolerability of vildagliptin (50 mg qd, 50 mg bid, or 100 mg qd). The primary assessment was change from baseline to endpoint in hemoglobin A1c (A1C), comparing vildagliptin to placebo by ANCOVA. Baseline A1C averaged 8.4% and the between-treatment difference (vildagliptin-placebo) in adjusted mean change (AMΔ) in A1C was $-0.5 \pm 0.2\%$ ($P = 0.011$), $-0.7 \pm 0.2\%$ ($P < 0.001$), and $-0.9 \pm 0.2\%$ ($P < 0.001$) in patients receiving vildagliptin 50 mg qd, 50 mg bid, or 100 mg qd, respectively. Baseline FPG averaged 10.5 mmol/L; the between-treatment difference in AMΔ FPG was -0.6 ± 0.4 mmol/L in patients receiving vildagliptin 50 mg qd and -1.3 ± 0.4 mmol/L ($P = 0.001$) in both groups receiving 100 mg daily. Relative to baseline, body weight did not change significantly in any of the three vildagliptin groups and decreased by 1.4 ± 0.4 kg in the placebo group. Adverse events (AEs) occurred with similar frequency in each group: 55.8%, 59.3%, 59.3%, and 57.6% of patients receiving vildagliptin 50 mg qd, 50 mg bid, 100 mg qd, or placebo, respectively, experienced an AE. No confirmed hypoglycemia was reported.

Conclusion: Vildagliptin is effective and well-tolerated in drug-naïve patients with T2DM and 100 mg vildagliptin provides similar clinical benefit whether given as single or in divided doses.

Keywords: Dipeptidyl peptidase-4; A1C; GLP-1; Incretin hormones

1. Introduction

Vildagliptin is a potent and selective DPP-4 inhibitor that improves islet function by increasing pancreatic α- and β-cell responsiveness to glucose [1,2]. In two 12-week studies [3,4] and one recent 24-week study [5] vildagliptin was found to decrease A1C without weight gain and with minimal hypoglycemia. The present 24-week, multicenter, double-blind, randomized, placebo-controlled clinical trial was conducted to further ascertain the efficacy and tolerability of vildagliptin, and to evaluate the dose–response of vildagliptin monotherapy in drug-naïve patients with type 2 diabetes (T2DM). Vildagliptin dose regimens of 50 mg qd, 50 mg bid, and 100 mg qd were selected and compared to placebo. This would allow determination of whether vildagliptin exhibits dose-related efficacy and whether bid dosing is necessary to obtain maximum efficacy of a 100 mg daily dose.

☆ This trial (NCT00120536) is registered with ClinicalTrials.gov.

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doi:10.1016/j.diabres.2006.12.009

2. Material and methods

2.1. Study design

This was a 24-week, double-blind, randomized, placebo-controlled, parallel-group study conducted at 98 centers in the US (88), India (4), and Slovakia (6). Each patient attended one screening visit (Week-2), during which inclusion/exclusion criteria were assessed. Eligible patients were randomized at Visit 2 (baseline) week 0 to receive vildagliptin 50 mg qd, 50 mg bid, 100 mg qd, or placebo in a 1:1:1:1 ratio. Efficacy and tolerability were assessed during 5 additional visits at Weeks 4, 8, 12, 16, and 24 of treatment. First patient first visit took place on 29-June-2005, and final patient final visit took place on 14-July-2006.

2.2. Study population

The study enrolled patients who were diagnosed with T2DM and had A1C of 7.5–10.0% at the screening visit while receiving no pharmacologic treatment. Patients who had taken no oral antidiabetic drug (OAD) for at least 12 weeks prior to screening and no OAD for >3 consecutive months at any time in the past were considered to be representative of a drug-naïve population. Male and female (non-fertile or of childbearing potential using a medically approved birth-control method) patients aged 18–80 years, inclusive, with a BMI of 22–45 kg/m^2, inclusive, and with FPG <15 mmol/L were eligible to participate.

Patients were excluded if they had a history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 months. Congestive heart failure, NYHA Class III or IV, and liver disease such as cirrhosis or chronic active hepatitis also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: ALT or AST greater than three times the upper limit of normal (ULN), direct bilirubin >1.3 times the ULN, serum creatinine levels >220 μmol/L, clinically significant abnormal thyroid stimulating hormone, or fasting triglycerides (TG) >7.9 mmol/L.

2.3. Study assessments

A1C, FPG, body weight, and vital signs were measured at each study visit. Standard hematology and biochemistry laboratory assessments were made at each visit except those at Weeks 8 and 16. Fasting lipid profiles (TG; total, LDL, HDL, non-HDL, and VLDL cholesterol) were measured and ECGs were performed at screening and at Weeks 0, 12, and 24.

All adverse events (AEs) were recorded and assessed as to severity and possible relationship to study medication. Patients were provided with glucose monitoring devices and supplies and instructed on their use. Confirmed hypoglycemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose (SMBG) measurement <3.1 mmol/L plasma glucose equivalent. Instances of SMBG measurement <3.1 mmol/L plasma glucose equivalent without accompanying symptoms were recorded as asymptomatic low blood glucose. Severe hypoglycemia was defined as any episode requiring the assistance of another party.

All laboratory assessments were made by a central laboratory (Covance-US, Indianapolis, IN). A1C was measured with an ion exchange HPLC method and all assays were performed with standardized and validated procedures according to Good Laboratory Practice.

The primary efficacy variable was the change from baseline in A1C at study endpoint in the intention-to-treat (ITT) population (defined as those who received at least one dose of study medication and had a baseline and least one post-baseline A1C assessment) using last observation carried forward (LOCF) for patients who discontinued early. Secondary efficacy parameters included FPG, fasting plasma lipids, and body weight. Changes from baseline in primary and secondary endpoints were analyzed using an ANCOVA model with treatment and pooled center as the classification variables and baseline as the covariate. Analyses were conducted using two-sided tests and a significance level of 0.05. For A1C and FPG, multiple testing was adjusted for using Hochberg's multiple testing step-up procedure to maintain an overall two-sided significance level of 0.05 [6].

2.4. Ethics and good clinical practice

All participants provided written informed consent. The protocol was approved by the independent ethics committee/institutional review board at each study site and the study was conducted in accordance with the Declaration of Helsinki.

3. Results

3.1. Patients studied

A total of 354 patients were randomized and 340 patients comprised the ITT population. Table 1 summarizes the demographic and baseline metabolic characteristics and disposition of patients in the randomized population. The groups were well balanced at baseline, with a mean age, BMI, A1C, and FPG of ∼51 years, 32.2 kg/m^2, 8.4%, and 10.6 mmol/L, respectively. Approximately 54% of patients were Caucasian, and there was a substantial representation of Asian, Hispanic, and black races/ethnicities. Patients had been diagnosed on average approximately 2 years prior to enrollment.

The study was completed by the lowest percentage of patients in the placebo group and by the highest percentage of patients in the vildagliptin 100 mg qd treatment group. A higher percentage of patients receiving placebo (than any active treatment group) discontinued due to an unsatisfactory therapeutic effect.